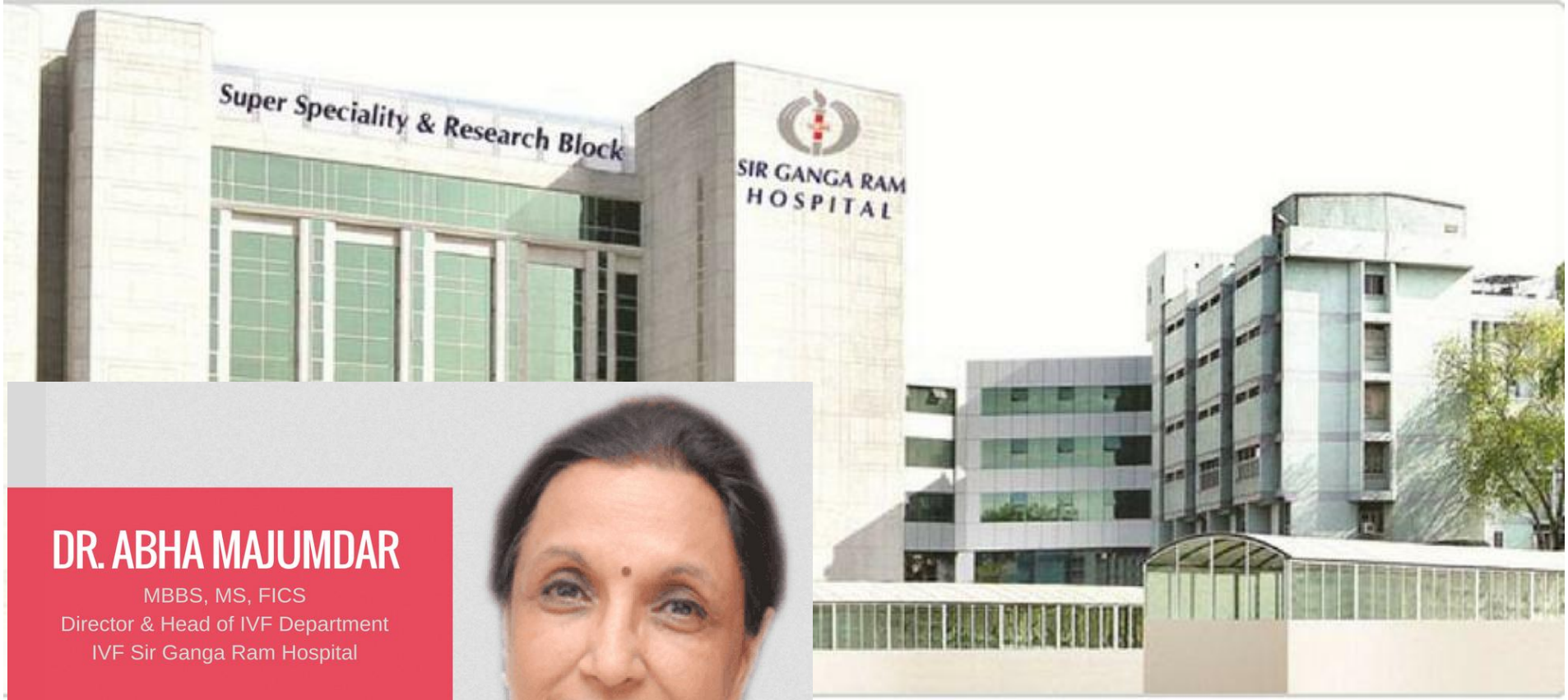
Prof. Abha Majumdar

Director, Center of IVF and Human Reproduction
Sir Ganga Ram Hospital, New Delhi, INDIA

President's Medal for best medical graduate of year1970-75
Award from DMA on Dr. B.C Roy's birthday: outstanding contribution to medicine,1999
Vikas Ratan Award by Nations economic development & growth society 2002
Chitsa Ratan Award by International Study Circle in 2007
Life time Medical excellence award Obs & Gyne by Hippocrates foundation 2014
Abdul Kalam gold medal 2015 & **Rashtriya Gaurav Gold Medal award** 2017 by Global Economic Progress & Research Association.
Distinguished teacher of excellence award for PG medical education by ANBAI & NBE 2017 and **Inspiring Gynecologists of India** by Economic Times 2017.
Felicitated by highest Merck Serono honor award at times healthcare achievers award 2018
Course director for post doctoral **Fellowship in Reproductive Medicine** by NBE, since 2007, IFS since 2014, ISAR 2014 and by FOGSI for basic & advanced infertility training since 2008.
Member of Editorial board of '**IVF Worldwide',** peer reviewer for '**Journal of Human Reproductive Sciences',** and member of advisory board for '**Journal of Fertility Science & Research'.**
Field of interest: Infertility, ART, Reproductive endocrinology, Endoscopic surgery for pelvic resurrection.



DR. ABHA MAJUMDAR

MBBS, MS, FICS
Director & Head of IVF Department
IVF Sir Ganga Ram Hospital

Expertise

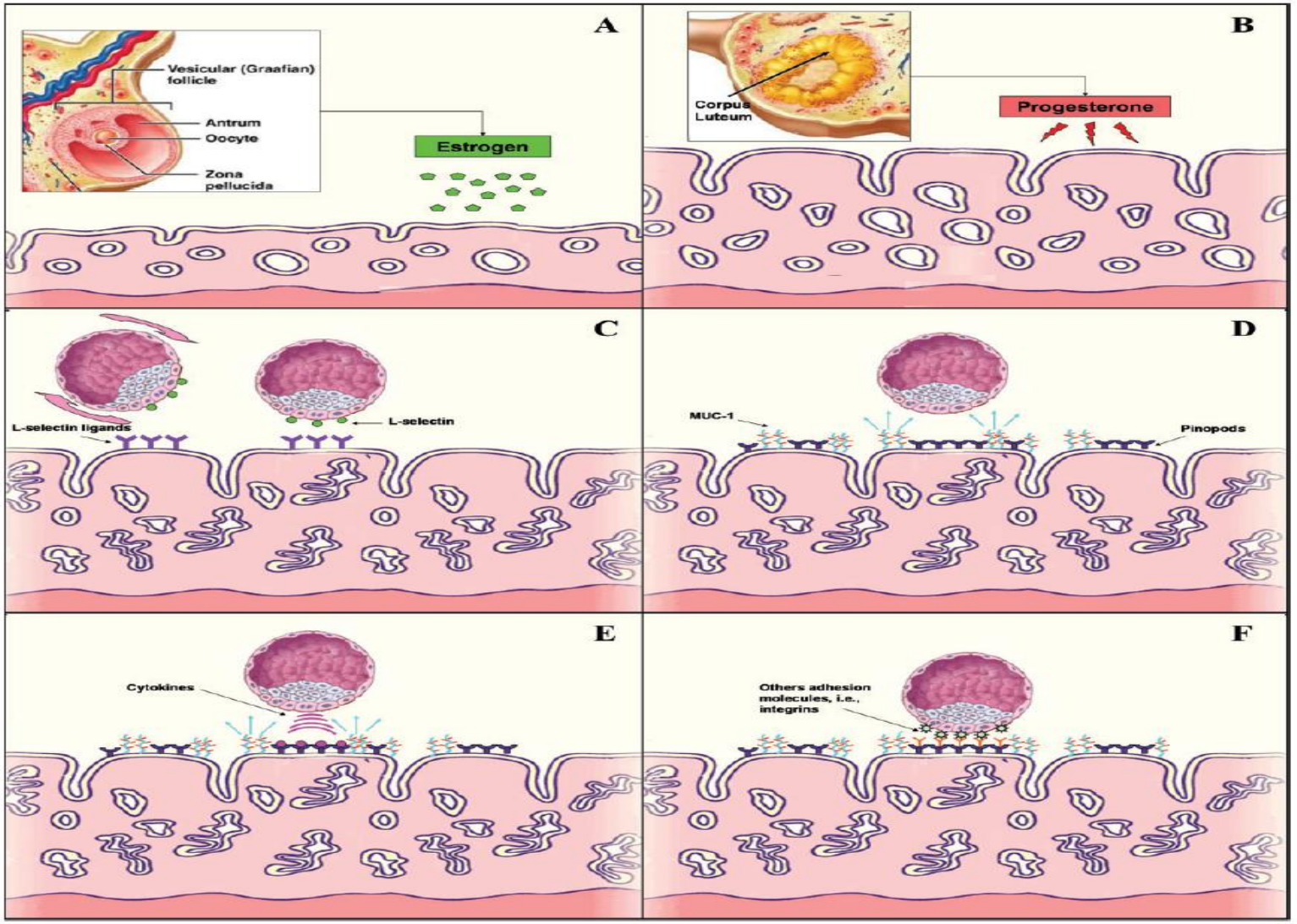
Infertility, assisted reproductive techniques, reproductive endocrinology, endoscopic surgery for pelvic resurrection.

Director
Centre of IVF and Human Reproduction

Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, 110060
Ph: 011 4225 4000/ 011 4225 1800/ 011 4225 1777/ 8375990881
Website: www.ivfgangaram.com

SGRH
IVF SIR GANGARAM HOSPITAL

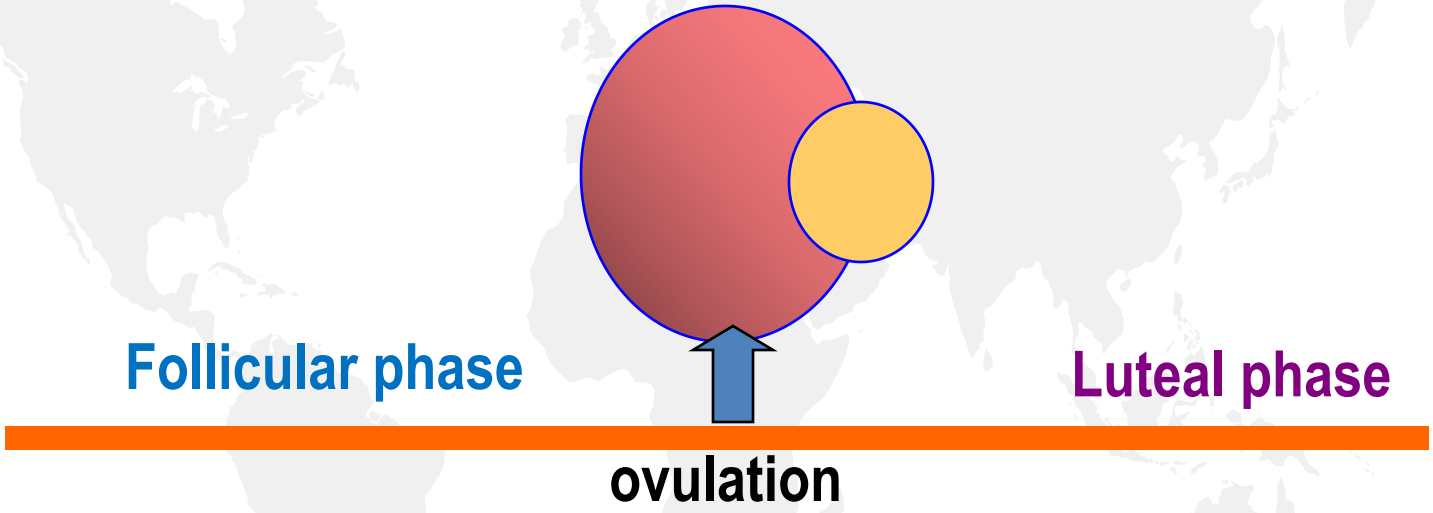
LUTEAL SUPPORT SIMPLIFIED IN IVF



Luteal phase questions

- What is luteal phase?
- What is the function of luteal phase?
- What is luteal phase deficiency?
- When does luteal phase deficiency happen?
- Situations in which luteal support required?
- Simplifying Individualized luteal support?

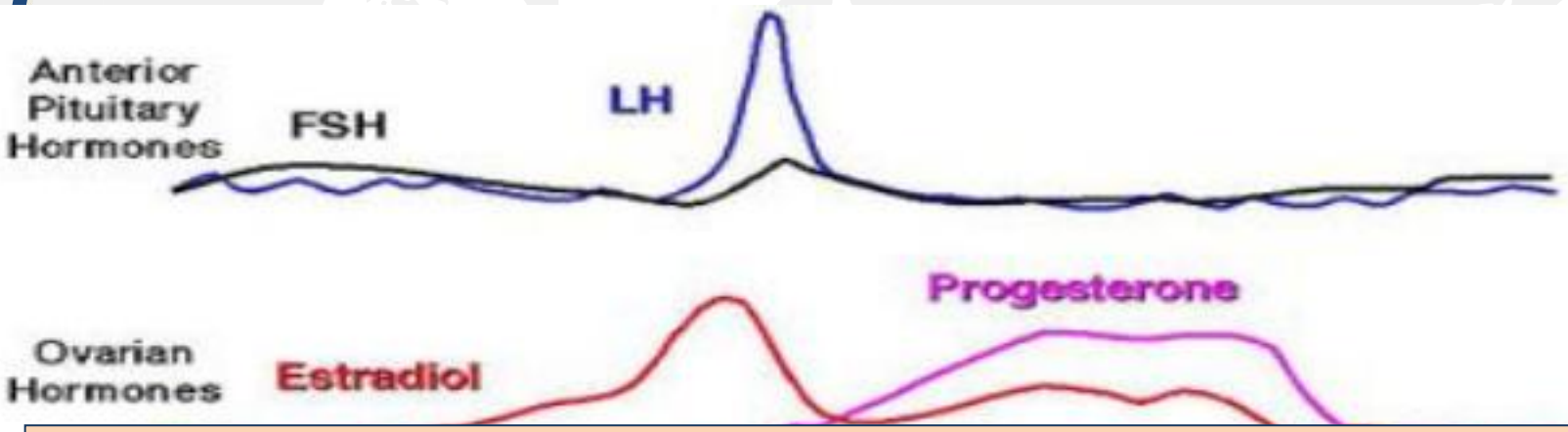
What is luteal phase?



The menstrual cycle

Luteal phase is the period between ovulation and establishment of pregnancy or starting of the next menses.

What is the function of luteal phase?

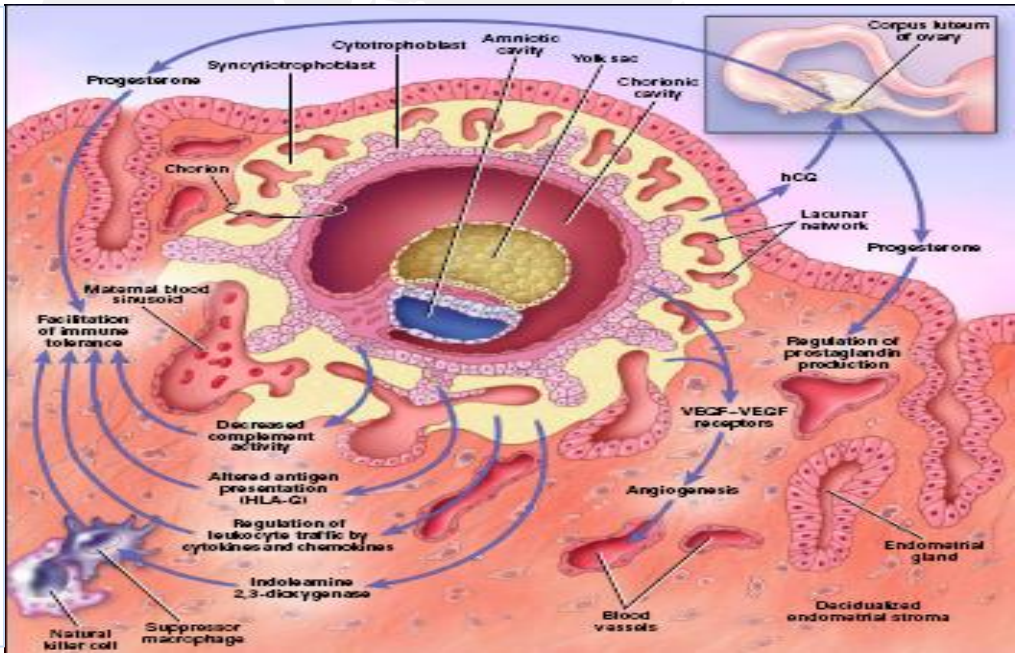


The luteal phase aims at creating a **"window of implantation"** to successfully cause '***implantation of the embryo'*** . The whole purpose of endometrial growth and receptivity is all targeted towards this one ultimate function. Progesterone is the most important regulator of the luteal phase.

What is luteal phase deficiency?

It is defined as luteal phase not capable of implantation or maintenance of pregnancy.

First described by Georgiana Seegar Jones in 1949 as defective progesterone synthesis by corpus luteum, resulting in infertility or early miscarriage.



When does luteal phase deficiency happen?

Natural cycle LPD

3-20% in infertile women

5-60% in women with RPL

Stimulated non IVF cycles

LPD in 50% of cycles

Stimulated IVF cycles with GnRH agonist or antagonist

LPD in all cycles

All frozen embryo transfer cycles on HRT

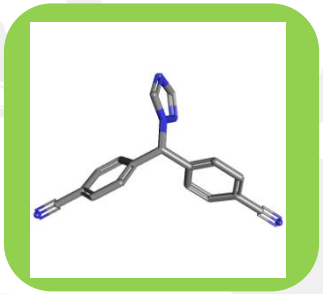
Ubaldi et al., 1997, Macklon and Fauser 2000, Kolibianiskis et al., 2003.

Luteal phase defects in stimulated cycles?

Clomiphene

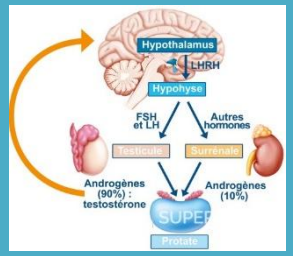
-High luteal E2
-GS asynchrony
-Anti-estrogenic
-E2 receptor down regulated
-lowP4 receptor

Letrozole



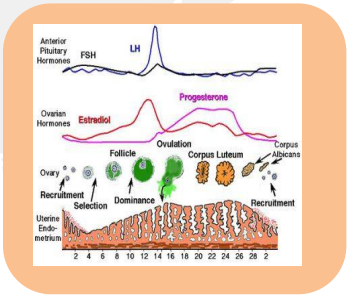
-Low E2 in follicular phase
-Low P4 receptor in luteal phase

Gonadotropin



-Endometrial advancement
-GS dys-synchrony
-Leutolysis in >2 follicles

IVF & analogues



-Pit gnt blocked
-High E2 levels
-Altered EP ratio
-Lysis of multiple CL in LP
- > CL Cytokines

CAN FINAL TRIGGER ALSO CAUSE LPD?

Controlled Ovarian stimulation cycle:

hCG - least LPD

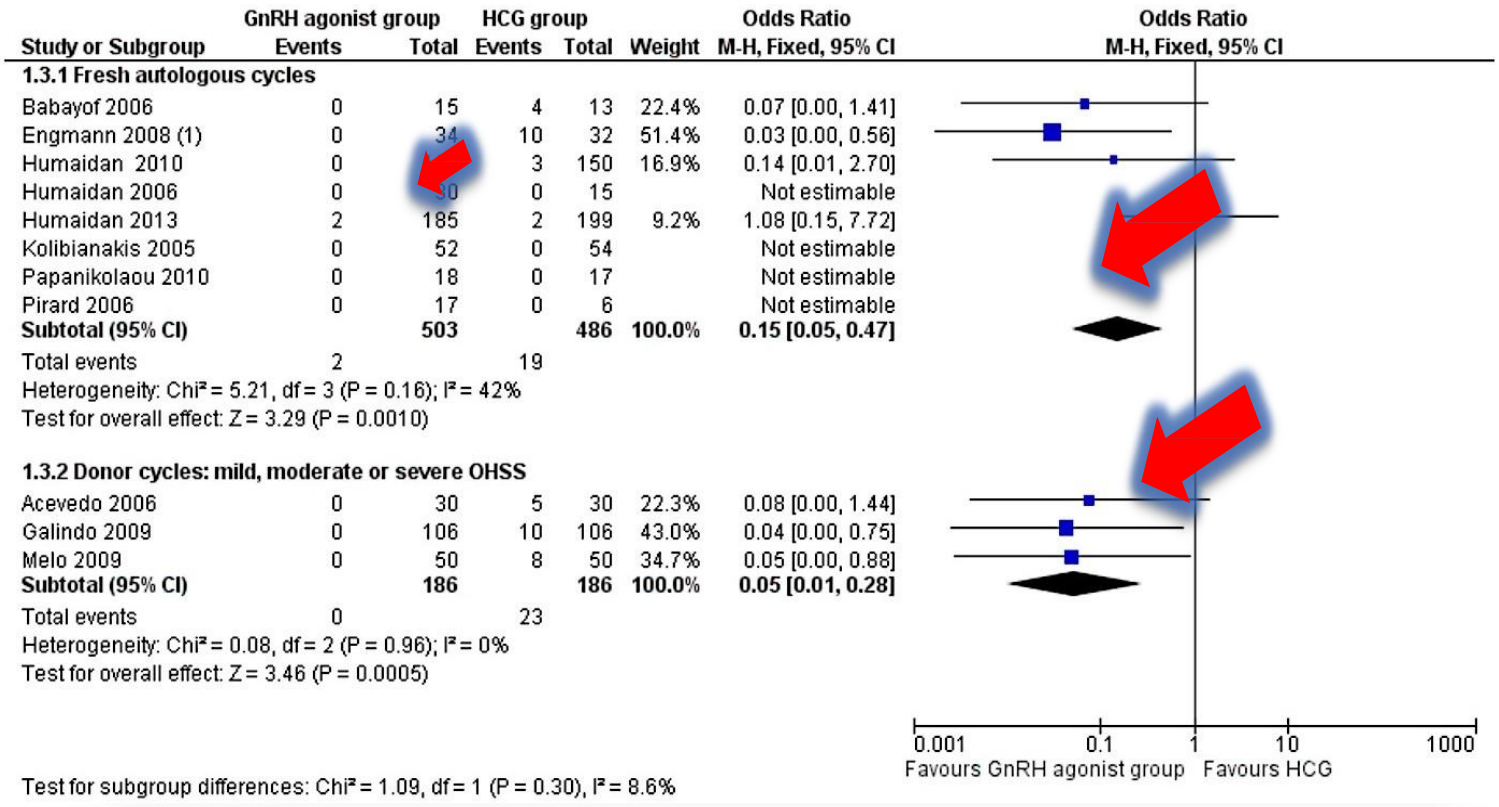
GnRH agonist - profound LPD

No trigger- extreme / complete LPD

YES!! Trigger for final oocyte maturation in a COS cycle for IVF decides occurrence of LPD

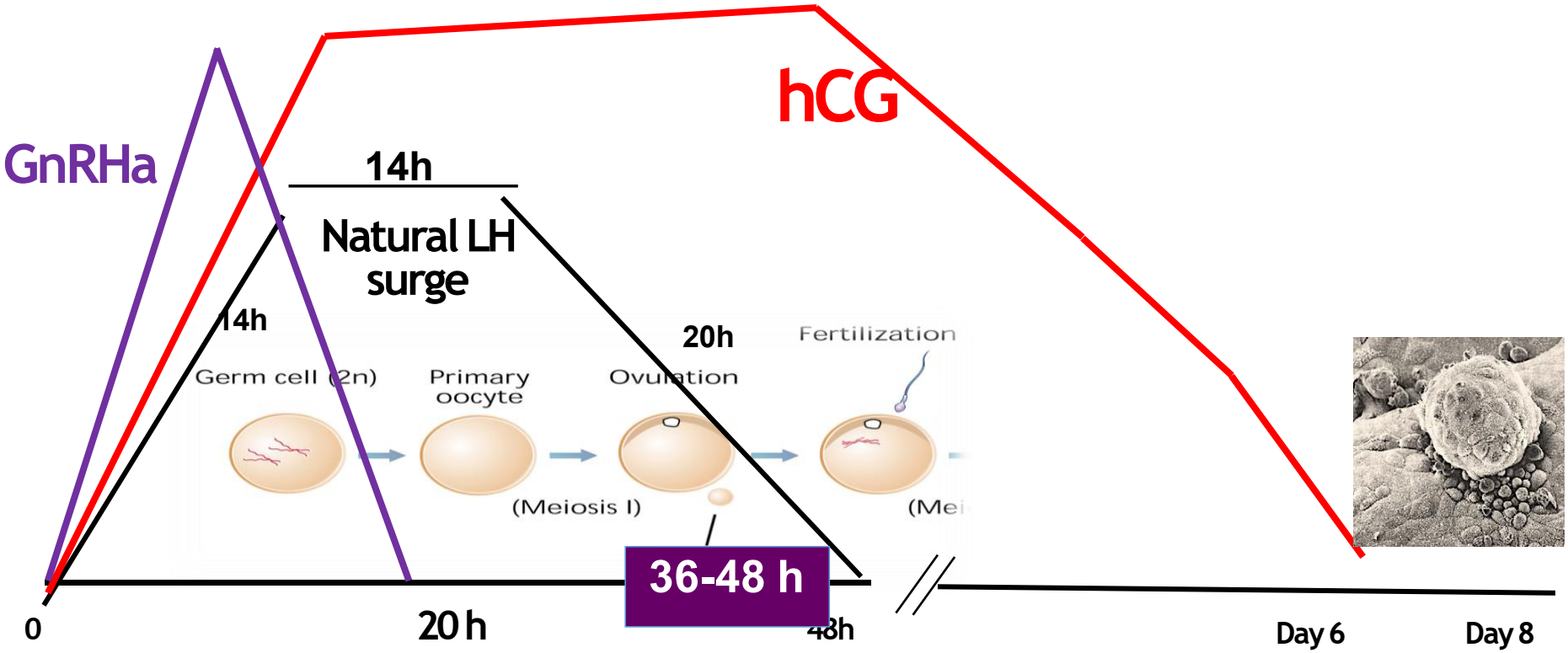
MAIN ADVANTAGE OF GNRH-a only TRIGGER IS PREVENTION OF OHSS

Figure 5. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.2 OHSS incidence per women randomly assigned.

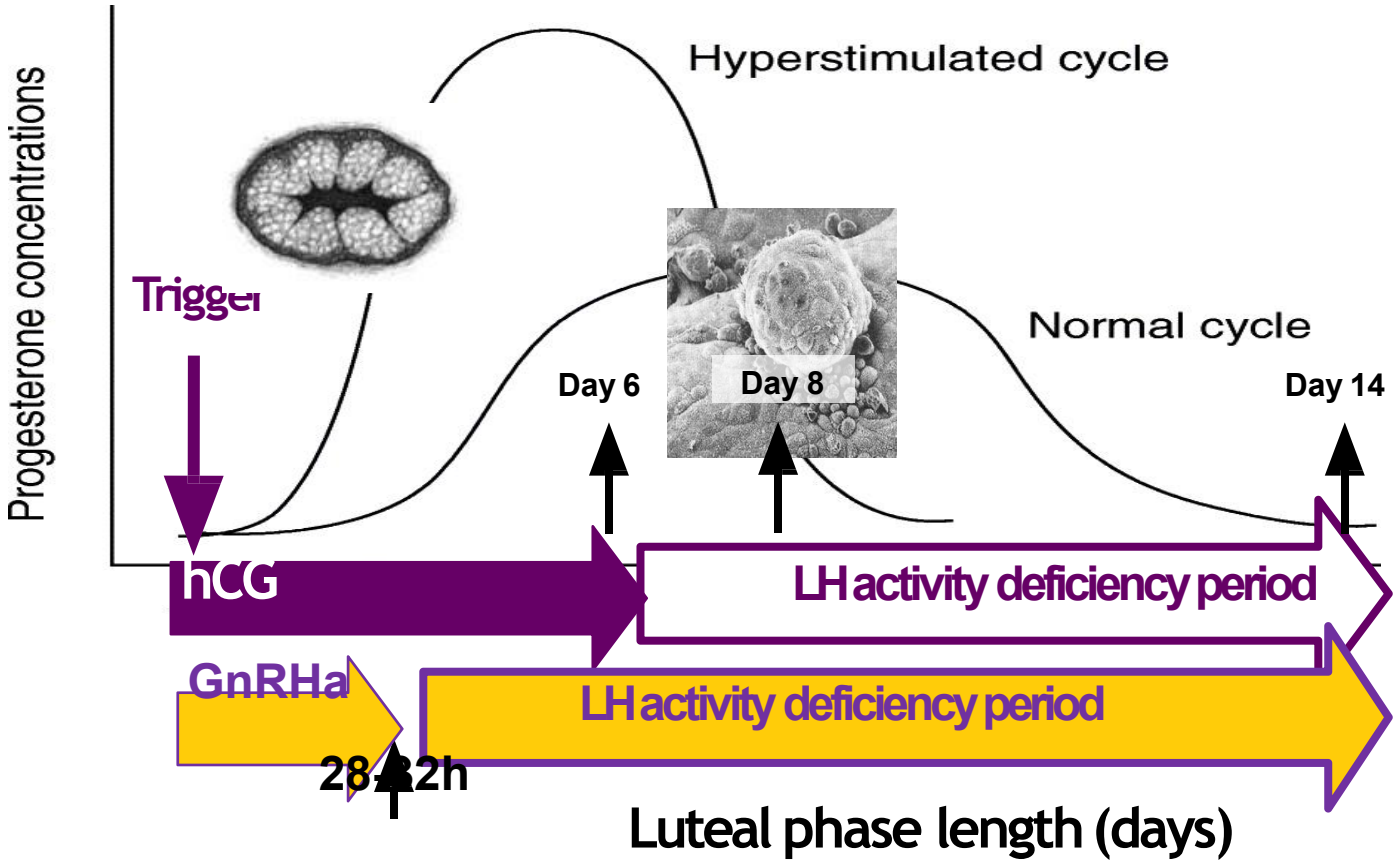


Youssef et al Cochrane Database Syst Rev. 2014 Oct 31;(10):CD008046.

NATURAL LH SURGE vs. hCG vs. GnRH-a TRIGGER



ABNORMAL LUTEAL PHASE OF STIMULATED CYCLES

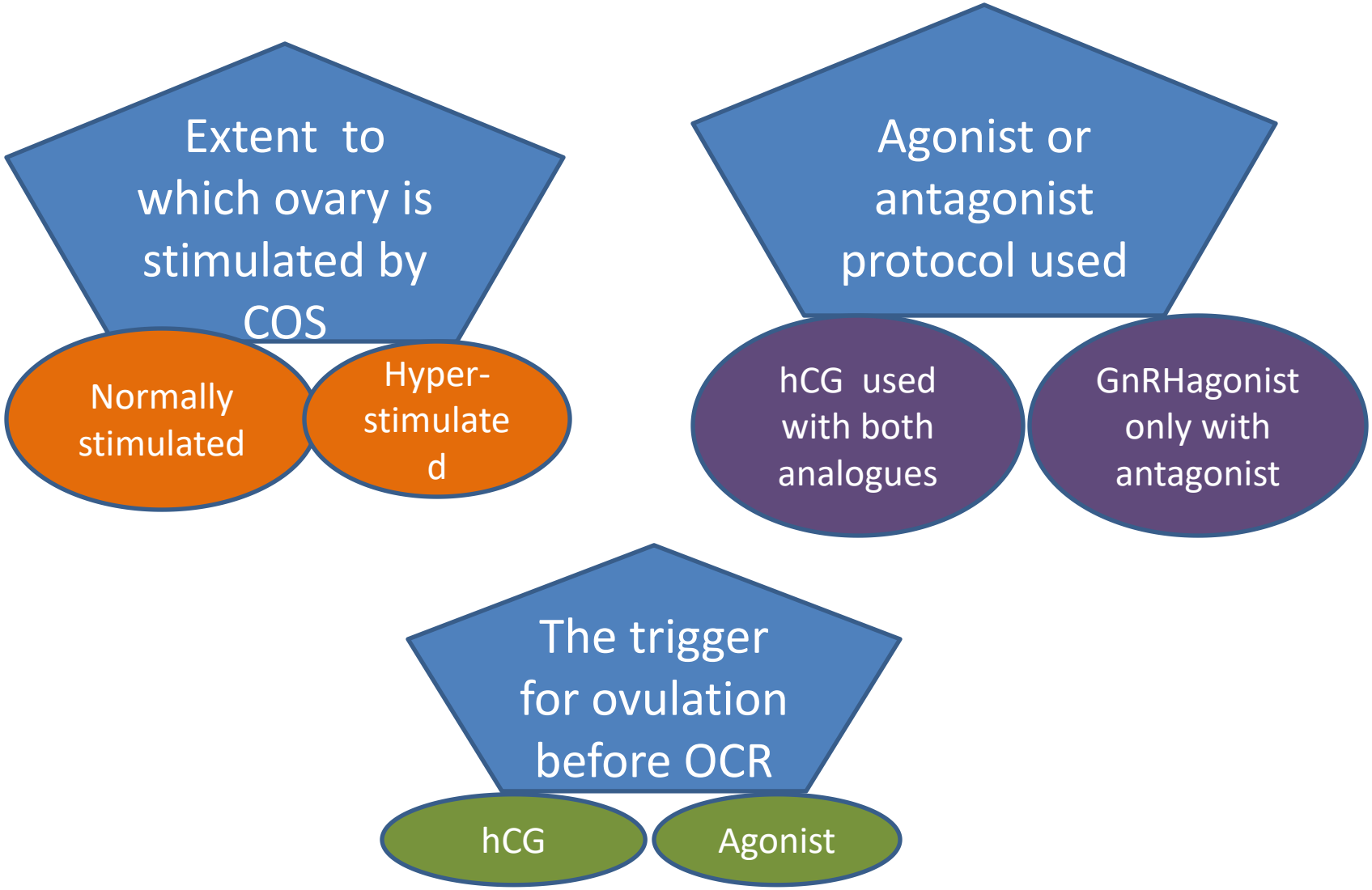


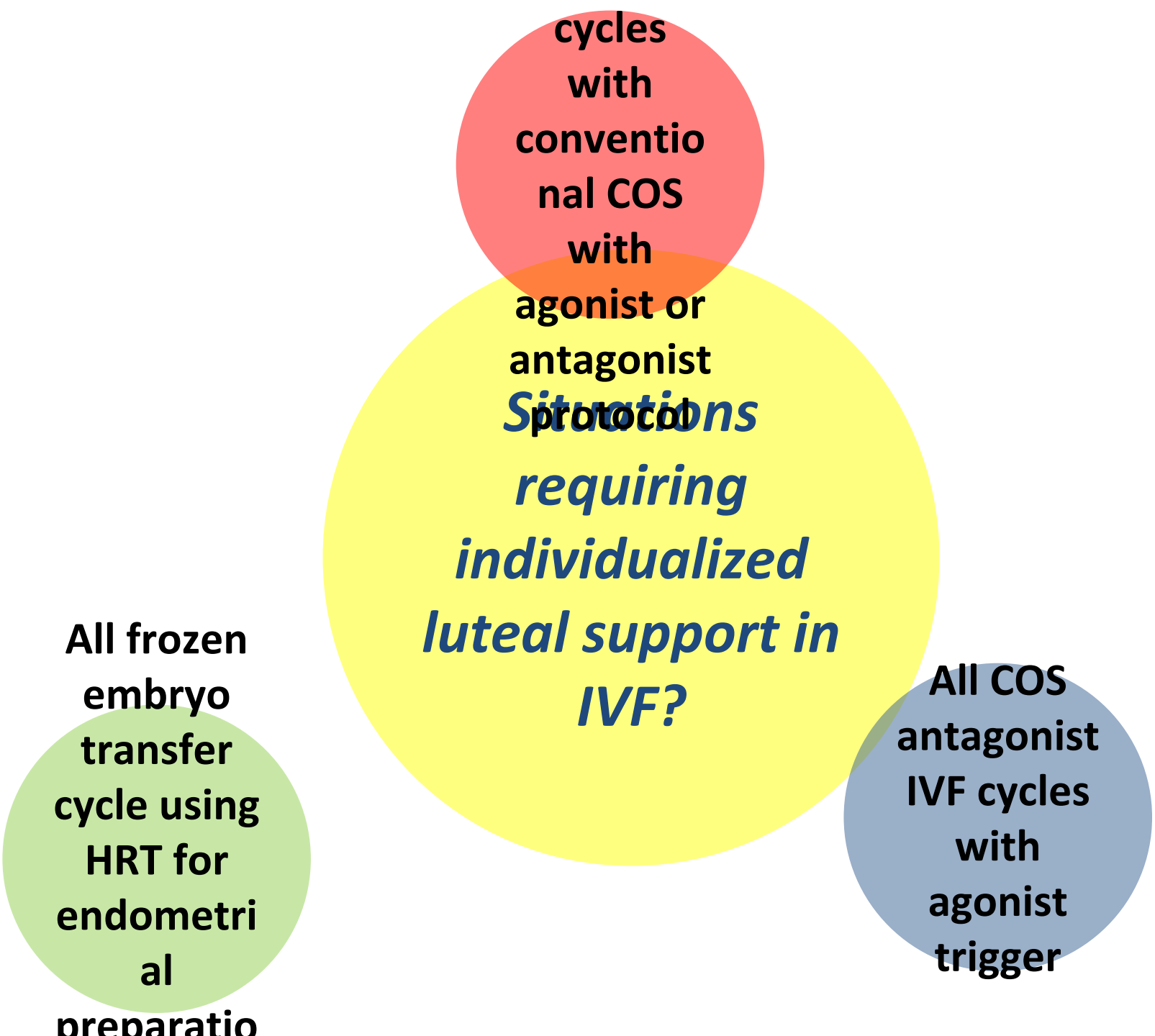
Damewood et al., 1989; Gonen et al., 1990; Itskovitz et al., 1991;
Weissman et al., 1986 ; Bonduelle et al., 1988

Reproductive Outcomes

	GnRHa (2005)	GnRHa + hCG 1500	hCG
Patients, n	55	152	150
Rate of ET, n (%)	48/55 (87)	130/152 (86)	138/150 (92)
Pos. hCG/ET, n (%)	14/48 (29)	63/130 (48)	66/138 (48)
Ongoing PR per pat (%)	3/55 (6)	40/152 (26)	49/150 (33)
Delivery rate per pat (%)	3/55 (6)	36/152 (24)	47/150 (31)
Early PL, n (%)	11/14 (79)	13/63 (21)	11/66 (17)

What decides the luteal support?




cycles with conventio nal COS with agonist or antagonist protocol
Situations requiring individualized luteal support in IVF?
All frozen embryo transfer cycle using HRT for endometri al preparatio
All COS antagonist IVF cycles with agonist trigger

1. All IVF cycles with conventional COS with agonist or antagonist protocol undergoing fresh embryo transfer

COS normal response

Progesterone only
or
combine
hCG 3 doses in 1st week luteal phase

COS hyper-response

Progesterone only
or
combine
Estrogen 2 mg bid full luteal phase

COS normal response

Progesterone
or
combine
Agonist mid luteal 1 to 3 doses only

2. All COS IVF antagonist cycles with agonist trigger and fresh ET to be done

Profound luteolysis after GnRHa triggering necessitates aggressive luteal support to secure reproductive outcome

Small bolus hCG 1500 iu on day of OPU

Penarrubia *et al.*, 1998; Emperaire *et al.*, 2004

Progesterone Day after OPU for 14 days

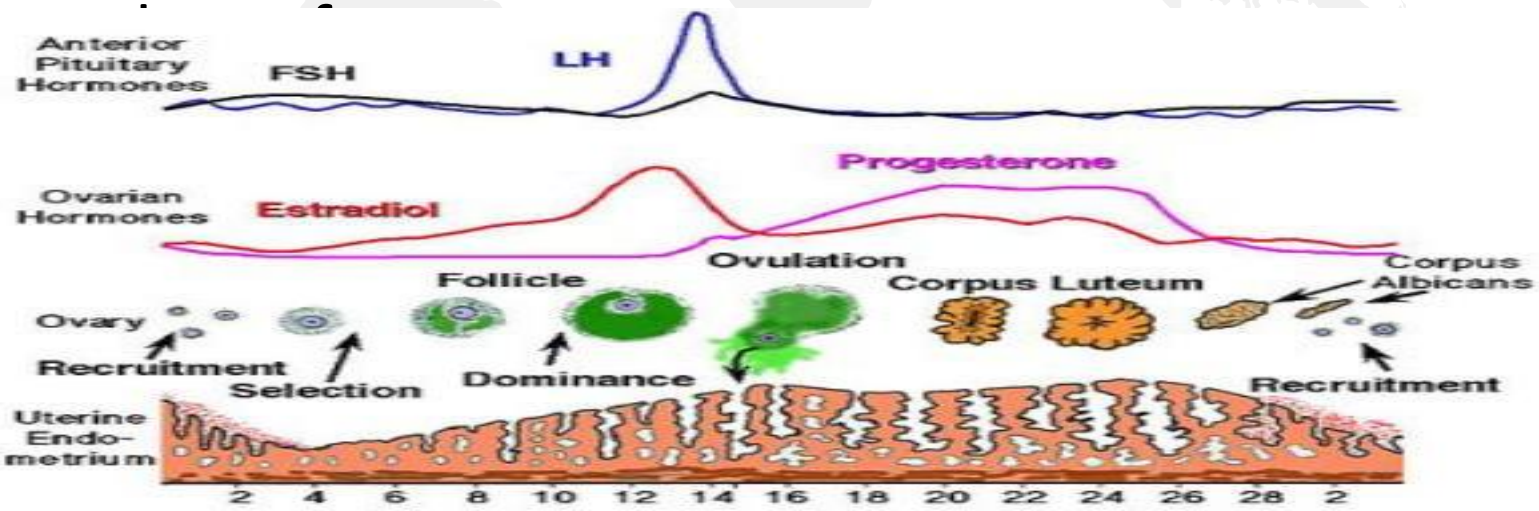
Castillo *et al.*, 2010

Estradiol valerate from day after OPU for 14 days

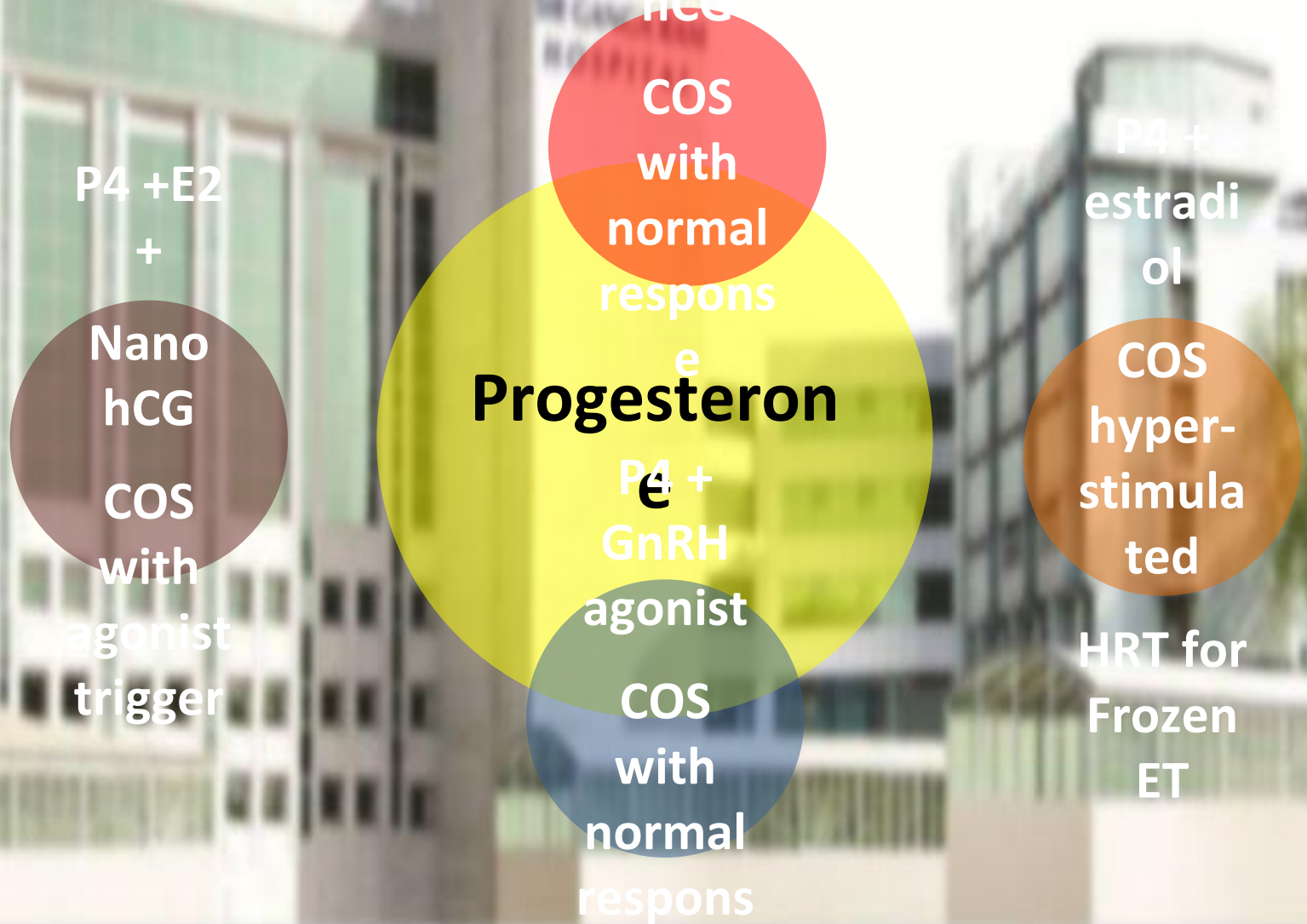
Humaidan *et al.*, 2005

3. Frozen embryo transfer cycle using HRT for endometrial preparation

- Estrogen priming of endometrium to ensure adequate proliferation
- Progesterone administration to create window of implantation for embryo transfer
- Estrogen with progesterone for 14 days



Drugs and combinations for luteal support in stimulated cycles



Progesterone with hCG

Advantages:

1. Corpus luteum can be rescued by hCG
2. hCG stimulates CL to produce progesterone & E2 both. Also produces placental protein 14, integrin α√β3, relaxin to support luteal phase. *(Anthony et al., 1993, Honda et al.,1997, Ghosh et al.,1997*.

Disadvantage: Risk of OHSS increases

Not to be given within 7 days of pregnancy test, as may interfere with pregnancy detection

Progesterone with estrogen

- **Agonadal cycles** (frozen embryo transfer cycles) :

  Supplementation of E2 (6 to 8 mgs/day) with progesterone essential in luteal phase in absence of corpus luteum
- **Hyper-stimulated COS cycles** appear to do better with 2 to 4 mg/d estrogen along with progesterone as luteal support ***(Farhi et al.,2000)***

COS with Antagonist protocol & agonist trigger

Aggressive luteal support to rescue cycle if fresh transfer planned

- Luteal progesterone from the day after OCR
- Estradiol valerate with progesterone
- nano hCG 500u for 3 days or 1500u on day of OCR.

Progesterone with GnRH agonist

Novel method of luteal support with GnRH agonist

- Stimulates pituitary gonadotrops to produce more LH
- Acts directly on endometrium by locally expressed GnRH receptors
- May act on the embryo with doubtful adverse effects

1 mg/day lupride for 2 to 3 days from day 5 or 6 of OCR

Mainly effective in antagonist treated gonadotropin stimulated cycles

Tesarik et al 2006, Pirard et al., 2005,Lambalk and Homburg 2006

Increased live birth rates with GnRH agonist addition for luteal support in ICSI/IVF cycles: a systematic review and meta-analysis

- Six relevant RCTs N = 2012 patients.
- Probability of live birth rate (RD: +16%, 95% CI: +10 to +22%) significantly higher in patients with GnRHa support compared with those who did not.
- Subgroup analysis according to type of GnRH analogue used for LH suppression did not change the effect observed
  - studies in which GnRH agonist was used during ovarian stimulation, RD: +15%, 95% CI: +5 to +23%
  - studies in which GnRH antagonist was used during ovarian stimulation, RD: +19%, 95% CI: +11 to +27%

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Evaluation of the impact of gonadotropin-releasing hormone agonist as an adjuvant in luteal-phase support on IVF outcome

Dattaprasad B Inamdar, Abha Majumdar[1]
Department of Obstetrics and Gynecology, Fellow in Reproductive Medicine, [1]Centre of IVF and Human Reproduction, Sir Ganga Ram Hospital New Delhi, India

Address for correspondence:
Dr. Abha Majumdar, Director, Centre of IVF and Human Reproduction, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi - 110 060, India.
E-mail: abhamajumdar@hotmail.com

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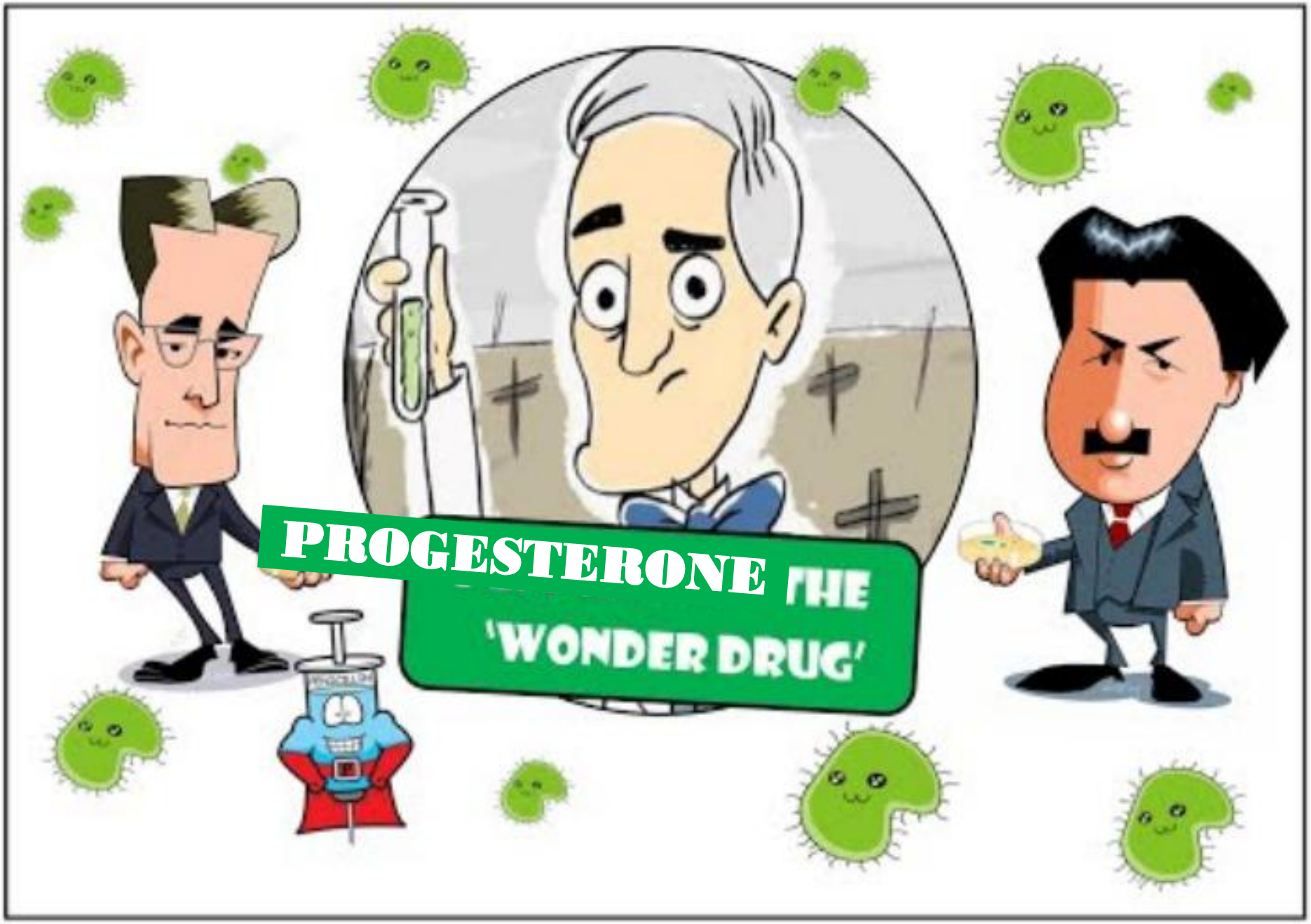
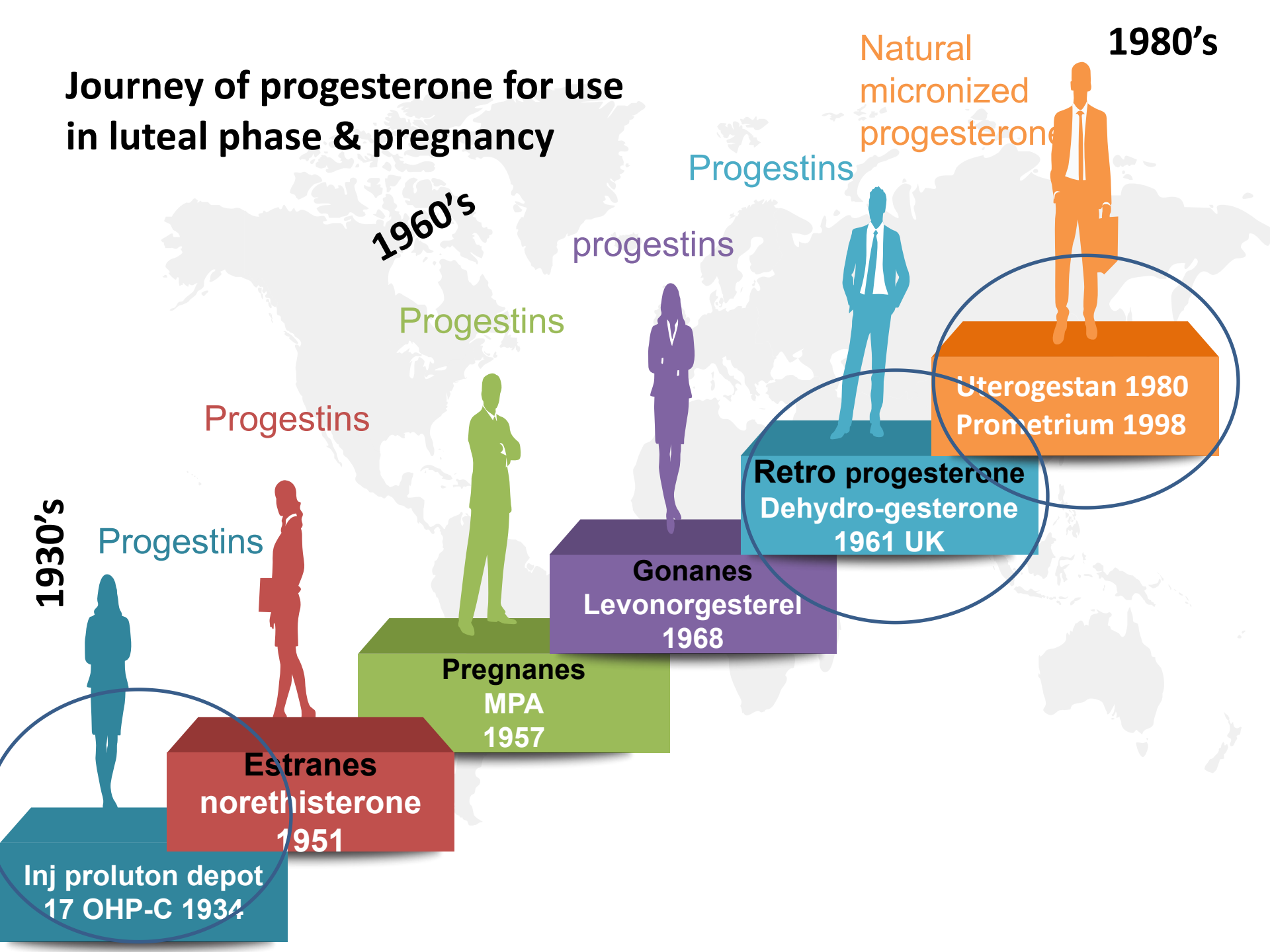
ABSTRACT

OBJECTIVES: To evaluate whether three daily doses of GnRH agonist (Inj. Lupride 1 mg SC) administered 6 days after oocyte retrieval increases ongoing pregnancy rates following embryo transfer (ET) in cycles stimulated with the long GnRH agonist protocol. **SETTINGS AND DESIGN:** Prospective randomized controlled study in a tertiary care center. **MATERIALS AND METHODS:** Four hundred and twenty six women undergoing ET following controlled ovarian stimulation with a long GnRH agonist protocol were included. In addition to routine luteal-phase support (LPS) with progesterone, women were randomized to receive three 1 mg doses of Lupride 6 days after oocyte retrieval. Computer-generated randomization was done on the day of ET. Ongoing pregnancy rate beyond 20th week of gestation was the primary outcome measure. The trial was powered to detect a 13% absolute increase from an assumed 27% ongoing pregnancy rate in the control group, with an alpha error level of 0.05 and a beta error level of 0.2. **RESULTS:** There were 59 (27.69%) ongoing pregnancies in the GnRHa group, and 56 (26.29%) in the control group ($P = 0.827$). Implantation, clinical pregnancy and multiple pregnancy rates were likewise similar in the GnRHa and placebo groups. **CONCLUSIONS:** Three 1 mg doses of Lupride administration 6 days after oocyte retrieval in the long protocol cycles does not result in an increase in ongoing pregnancy rates.

KEY WORDS: GnRH agonist, implantation rate, luteal-phase adjuvant, ongoing pregnancy

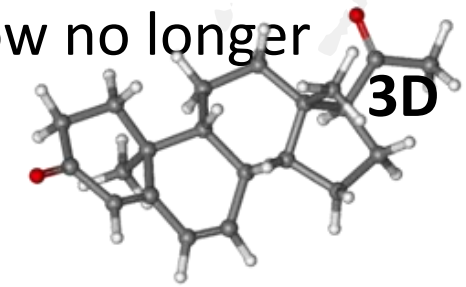

PROGESTERONE THE
'WONDER DRUG'

Journey of progesterone for use in luteal phase & pregnancy



Dydrogesterone

- Synthetic isomer of progesterone & only progestogen used in luteal phase or pregnancy because of its similarity to natural P4 in immuno-modulation
- Can be absorbed orally, (stable molecule made by conversion with ultra violet light)
- Dose: 20mg to 30mg /day orally in 3 divided doses
- 50% higher affinity to progesterone receptors than progesterone its self.
- Does not show as progesterone in blood bioassay.
- Available widely in Europe, UK, Australia, Hong-Kong, and India. Previously marketed in USA but now no longer available there.



Queisser-Luft A. Early Hum Dev. 2009;85:375-7

Oral Natural progesterone

This study evaluated combination of 2 processes which have synergistic effects to influence absorption of progesterone orally.

1. **Micronization**
2. **Suspension in long chain fatty acids**

On the basis of the results of this study, the optimal preparation for the administration of natural progesterone should include micronization of the progesterone particles and dissolution in oils consisting of principally long-chain fatty acids.

Hargrove et al

'Micronized" refers to small particle size of the progesterone (less than 10 micron) as better absorbed (33%)
[1 micron = 0.001 millimeter]

October 1989
Am J Obstet Gynecol

Micronized Progesterone routes and doses

Oral tabs100 -400 mg tid or qid. E[illegible]bility in serum c[illegible]ation due to indivi[illegible]filling and entero-hepatic circulation with too many side effects

I/M inj. P4 once a day in sesame c[illegible]) and 10% v/v benzyl a[illegible]as preserva[illegible]g the oil solution decreases its viscosity

Vaginal soft gel cap 200 -400 BID absorbed by 'first uterine pass effect'- 10 times highe[illegible] concentration in uterus compared to serum.

- Direct diffusion cel[illegible]ell
- Lymphatics vag t[illegible]us
- Vein to artery p[illegible]ystem

Vaginal gel 90[illegible]% oil-in-[illegible]y-carbophil base[illegible]gel adheres to vagina[illegible]m, while emulsion pro[illegible] oily depot to release P4 into aqueous phase and into tissue.

Oral Natural Micronized Progesterone SR

Different methods used to optimize oral use

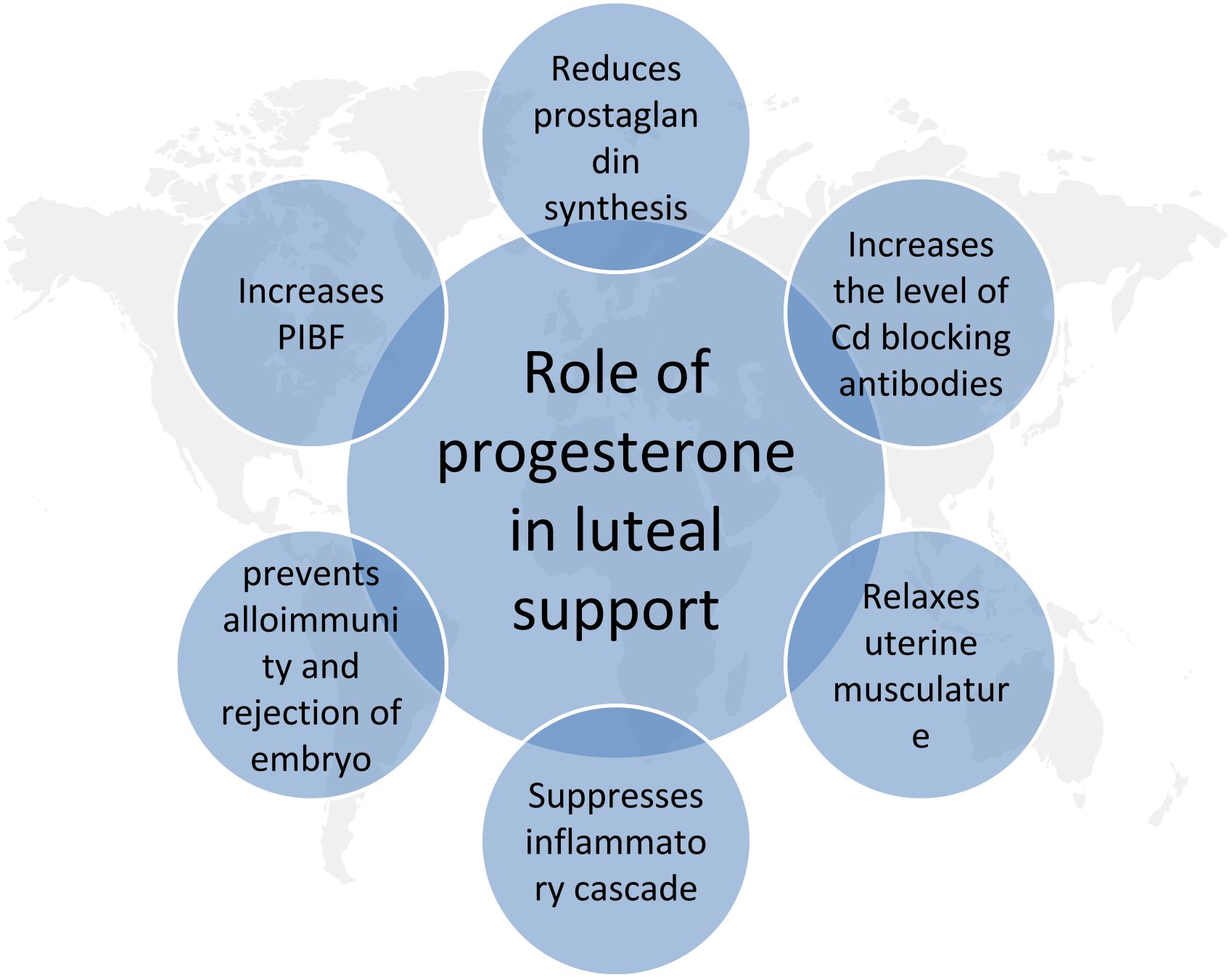
MATrix Sustained Release Technology (Oral NMP* SR)

Dual release tablet (ICAT) (Microgest)

Allows Slow 'SMOOTH' release of progesterone from Intestine over 24 hours offering OD convenience

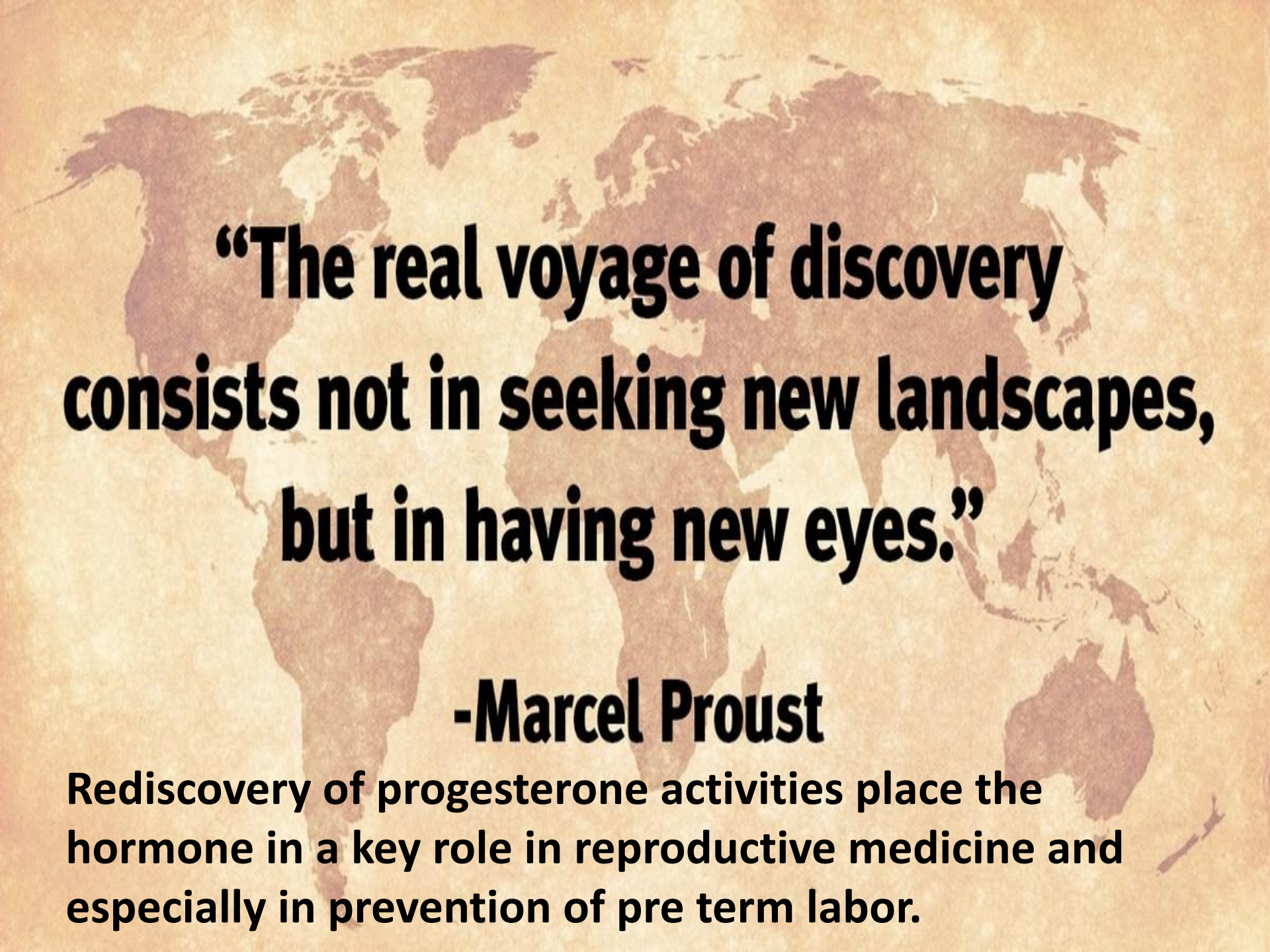
Avoids sudden drug release or 'DOSE DUMPING' thus loss of drug due to hepatic metabolism (33% in 24 hrs vs 4hrs)

MINIMIZES DOSE related central side effects including drowsiness (57% vs 0.6%)


Role of progesterone in luteal support
Reduces prostaglandin synthesis
Increases the level of Cd blocking antibodies
Relaxes uterine musculature
Suppresses inflammatory cascade
prevents alloimmunity and rejection of embryo
Increases PIBF

Take home message

- Progesterone appears to be universally effective in ovulatory as well in non ovulatory cycles for LS
- Vaginal P4 appears most effective route for P4 administration
- Dydrogesterone appears promising if oral drug desired.
- HCG only in mild to moderately stimulated cycles because of risk of OHSS. No role in non ovulatory frozen ET cycles
- Combination of hCG with P is more beneficial in terms of PR
- Combination of estradiol and P appears to favor PR in hyper-stimulated COS cycles
- GnRh agonist for 1 to 3 days in mid luteal phase appears to be effective luteal support in ***antagonist*** cycles
- After GnRHa triger; bolus of small hCG dose on day of OCR, estradiol & P4 through luteal phase appear essential.



Rediscovery of progesterone activities place the hormone in a key role in reproductive medicine and especially in prevention of pre term labor.

2 prospective RCT at IVF SGRH where luteal progesterone with GnRH agonist support used

- N=376 ***IUI cycles with unexplained infertility.*** Prospective RCT
  2 groups: GnRHa with P and hCG with P in COH cycles
  clinical PR 22% vs 6.8% (p-0.001)

Significantly higher clinical PR in agonist co-treatment arm

- N=426 ***IVF cycles with long protocol.*** Prospective RCT
- Study group vs control group
- Ongoing PR 27.69% vs 26.29% (p- 0.827).
- No difference in progesterone plus agonist support vs only progesterone support

B Inamdar, Dattaprasad & Majumdar, Abha. (2012).. Journal of human reproductive sciences. 5. 279-84. 10.4103/0974-1208.106341.