44 International Dexeus Forum

Update in Obstetrics, Gynaecology and Reproductive Medicine

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BARCELONA

Random Start Ovarian Stimulation

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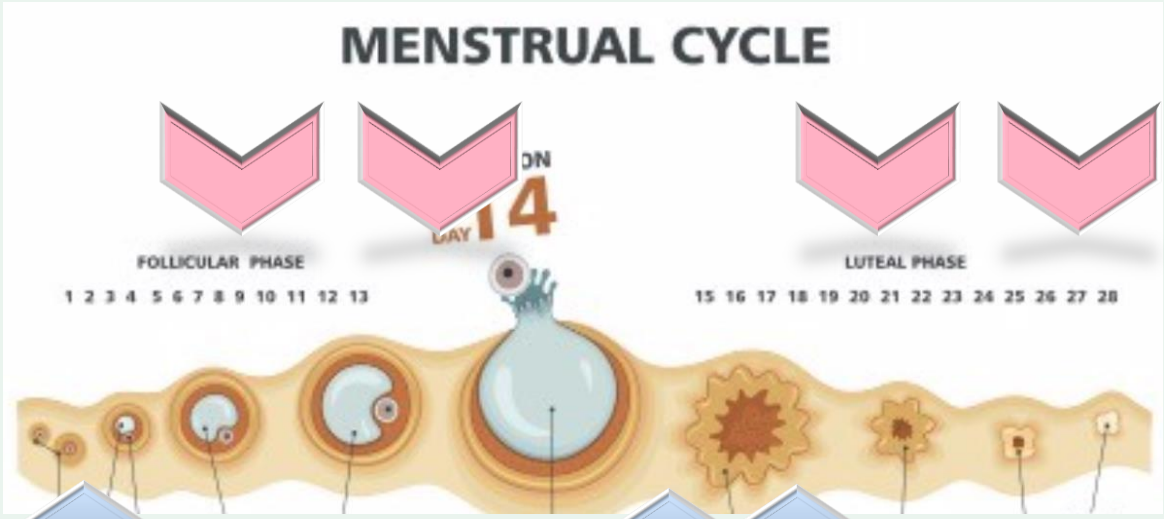
Disclosure of Conflict of Interest (List)	
MSD (Research grants)	

the theoretical concept

Random start



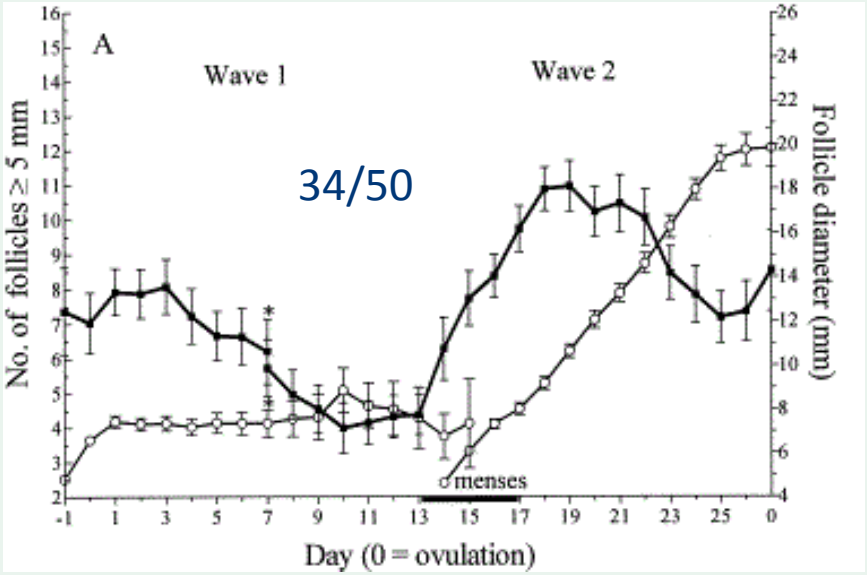
Freeze all

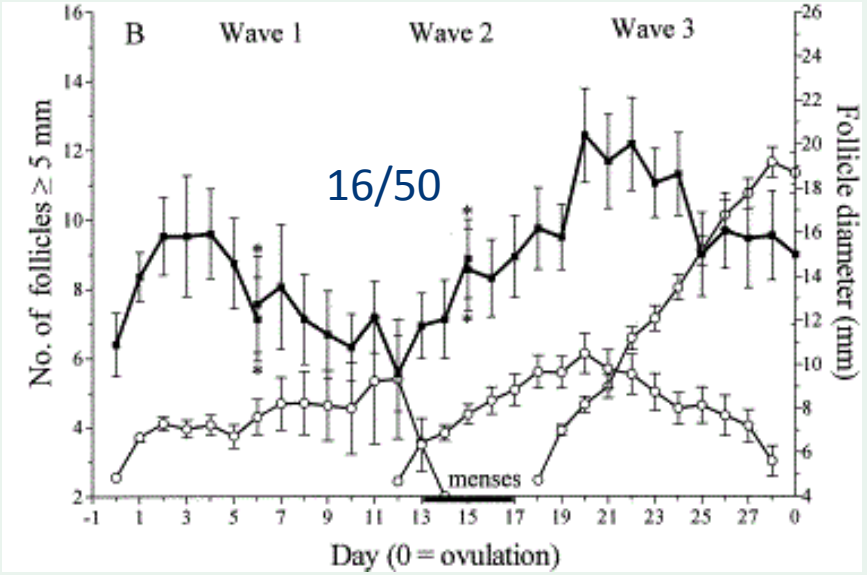
Conventional OS

Luteal phase OS

Freeze all

physiologic follicular waves





- 2 or 3 follicular waves within a menstrual cycle
  - the one emerging in the early follicular phase is ovulatory
  - others are anovulatory (role of progesterone)

Baerwald et al. Fertil Steril. 2003

folliculogenesis is a continuous process

1st wave

2nd wave

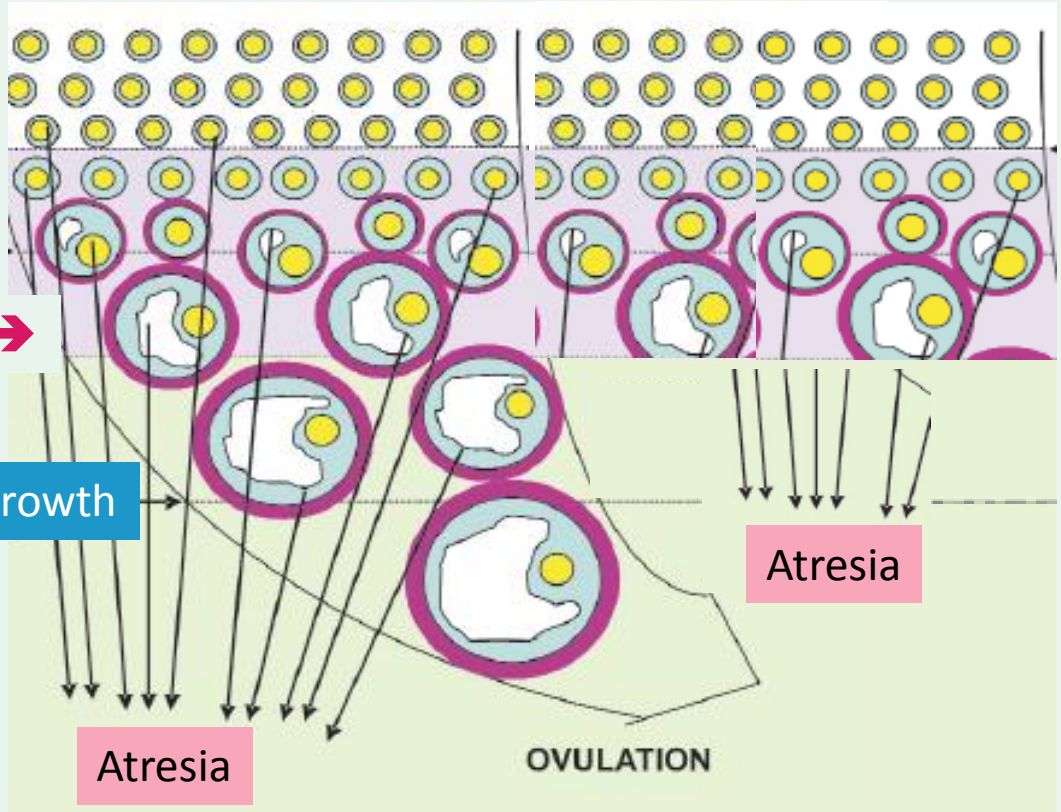
Stock of follicles

Start of foll growth →

Basal growth

FSH-dependent →

Cyclic growth



Continuous recruitment

→ FSH stimulation acts on follicles, irrespective of the cycle day

adapted from **Monniaux et al INRA 2009**

random-start OS concept

- First publication from Turkey **Sonmezer Fertil Steril 2011**
  - Urgent FP in oncologic patients (FSH+letrozole)
  - LH suppression by antagonist
  - 3 patients
  - OS starts at CD11 CD14 or CD17
  - 9 to 17 oocytes, good maturity and fertilization rates
- Luteal start in oncologic patients **Bedoschi JARG 2010 ; Van Wolff FS 2009**
- … and others in urgent FP but little data about clinical outcomes **Cakmak 2013 ; Cafmak 2015 ; Kim 2015 ; Peireira 2016**

not oncologic random-start OS

- Only 2 published studies (retrospective but large)
  - From Asia in 2016 : normal population
  - From USA in 2017 : non medical egg freezing

RBM ONLINE

ELSEVIER

Article

Random-start ovarian stimulation in women desiring elective cryopreservation of oocytes

Nigel Pereira [a,*], *Anna Voskuilen-Gonzalez* [a], *Kolbe Hancock* [b], *Jovana P Lekovich* [a], *Glenn L Schattman* [a], *Zev Rosenwaks* [a]

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[b] *Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY, USA*

- No medical reason
- Women choice: conventional CD2/3 or random start OS
  - Conventional: flexible antagonist protocol 87.5% or agonist flare protocol 12.5%
  - Random start: antagonist (start with FSH)
- Rec-FSH and HMG; triggering HCG or agonist or dual
- Oocyte vitrification

Random-start ovarian stimulation in women desiring elective cryopreservation of oocytes

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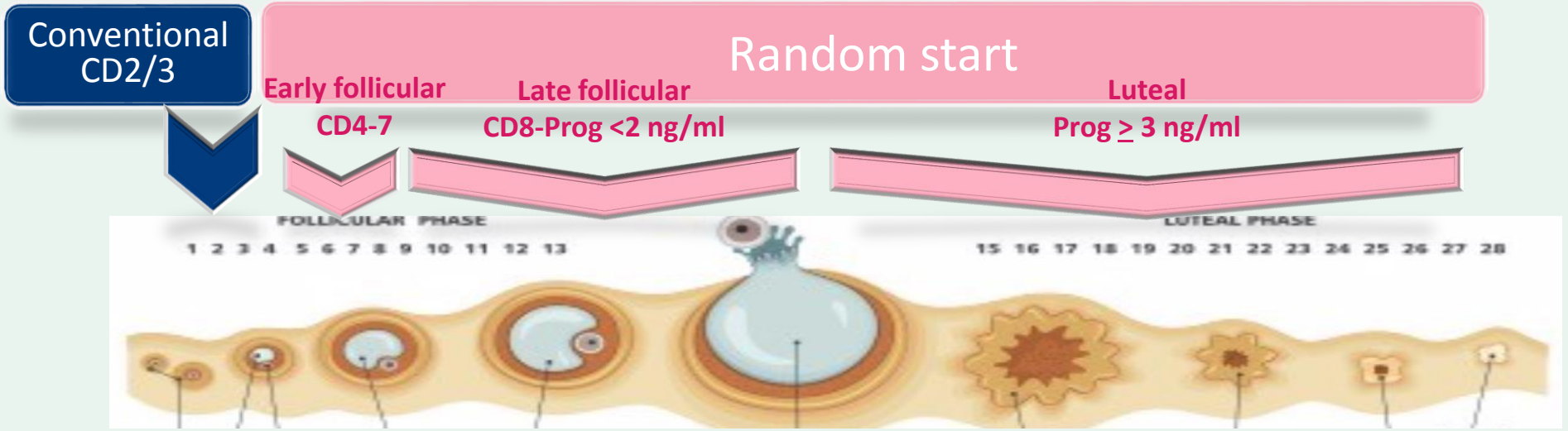

N=859 N=342 N=42 N=59

No difference in demographics and baseline characteristics

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Random-start ovarian stimulation in women desiring elective cryopreservation of oocytes

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Parameter	Control (*n* = 859)	Early follicular (*n* = 342)	Late follicular (*n* = 42)	Luteal (*n* = 59)
Protocol *n* (%)				
GnRH-agonist based	93 (10.8)	55 (16.1)	6 (14.3)	9 (15.3)
GnRH-antagonist based	766 (89.2)	287 (83.9)	36 (85.7)	50 (84.7)
Total stimulation days*	9.5 (8–11)	9.5 (8.5–12)	11.5 (7.5–13.5)	11 (8–12)
Total gonadotrophin dose (IU)*	3155 (2100–4500)	3280 (2180–4700)	4665.5 (3300–5975)	4345 (3100–5650)
Gonadotrophin dose/day (IU/day)*	332.1	345.3	405.7	395.0
Trigger type *n* (%)				
i.m. HCG	197 (22.9)	94 (27.5)	9 (21.4)	15 (25.4)
subcutaneous HCG	449 (52.3)	192 (56.1)	20 (47.6)	29 (49.2)
Dual leuprolide and HCG	152 (17.7)	37 (10.8)	8 (19.1)	11 (18.6)
Pure leuprolide	61 (7.1)	19 (5.6)	5 (11.9)	4 (6.8)
Oestradiol on day of trigger (pg/ml)	1796 (1189–2540)	1781 (1045.5–2583.5)	1804 (1058.5–2661)	1789 (1052–2504)
Oestradiol after day of trigger (pg/ml)	2509 (1619.5–3372.5)	2495.5 (1442.5–3298.5)	2488 (1674–3174.5)	2465 (1309–3174.5)
Cancellation rate *n* (%)	31 (3.6)	12 (3.5)	3 (7.1)	2 (3.4)
Total oocytes retrieved	13.1 (±2.3)	12.7 (±2.7)	13.0 (±3.1)	13.2 (±2.9)
MII oocytes retrieved	11.0 (±3.1)	10.8 (±2.7)	11.1 (±3.0)	10.9 (±3.2)
MII oocytes (%)	84.0	85.0	85.4	82.6
MII oocytes/AFC	0.83	0.84	0.85	0.82

Similar yield of mature oocytes

But longer duration and higher FSH dose

But no information on oocyte quality and competence

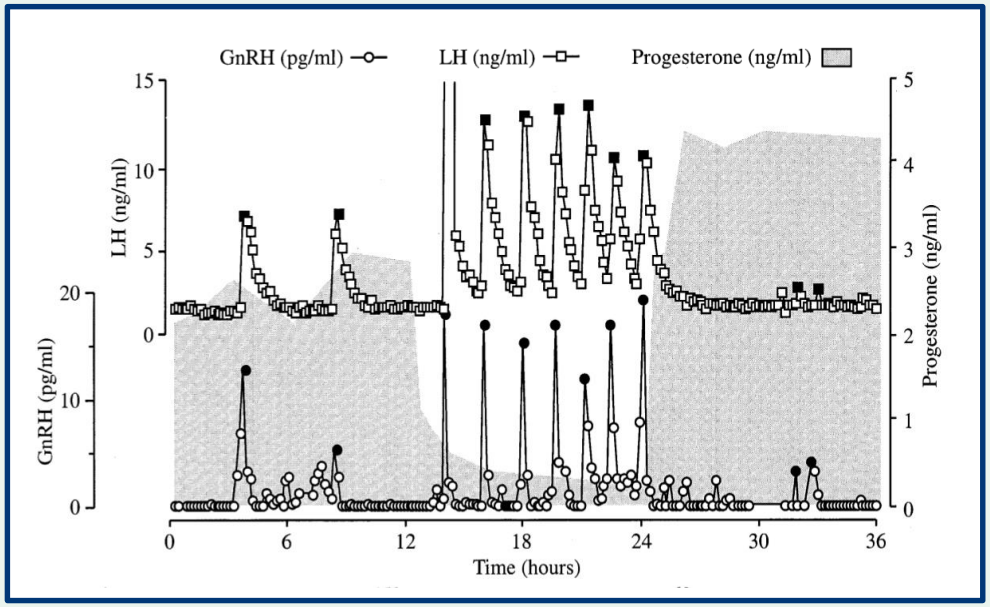
Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection

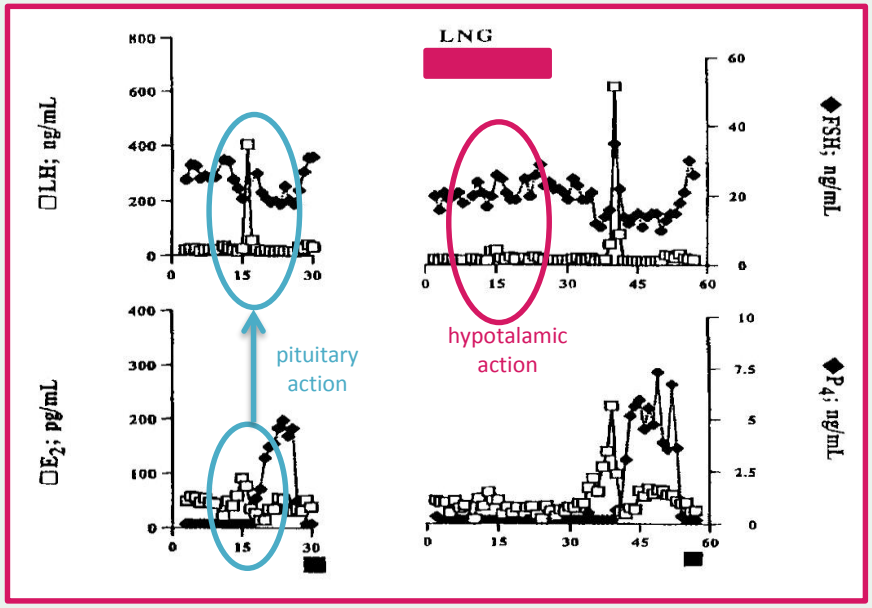
Ningxin Qin, M.M.,[a,b] Qiuju Chen, Ph.D.,[a] Qingqing Hong, M.D.,[a] Renfei Cai, M.D.,[a] Hongyuan Gao, M.D.,[a] Yun Wang, M.D.,[a] Lihua Sun, M.D.,[a] Shaozhen Zhang, M.D.,[a] Haiyan Guo, M.D.,[a] Yonglun Fu, M.D.,[a] Ai Ai, M.D.,[a] Hui Tian, M.D.,[a] Qifeng Lyu, Ph.D.,[a] Salim Daya, MBChB,[c] and Yanping Kuang, M.D.[a]

[a] Department of Assisted Rreproduction, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China; [b] Shanghai JiaoTong University School of Medicine, Shanghai, People's Republic of China; and [c] Newlife Fertility Centre, Mississauga, Ontario, Canada

- No medical reason: long distance from the center, saving time
- Cost saving: use of letrozole and clomiphene citrate → freeze all embryo policy
- Suppression of LH surge with progesterone

progesterone prevents LH surge





- Progesterone modulates LH secretion by decreasing GnRH pulse frequency (hypothalamic action)

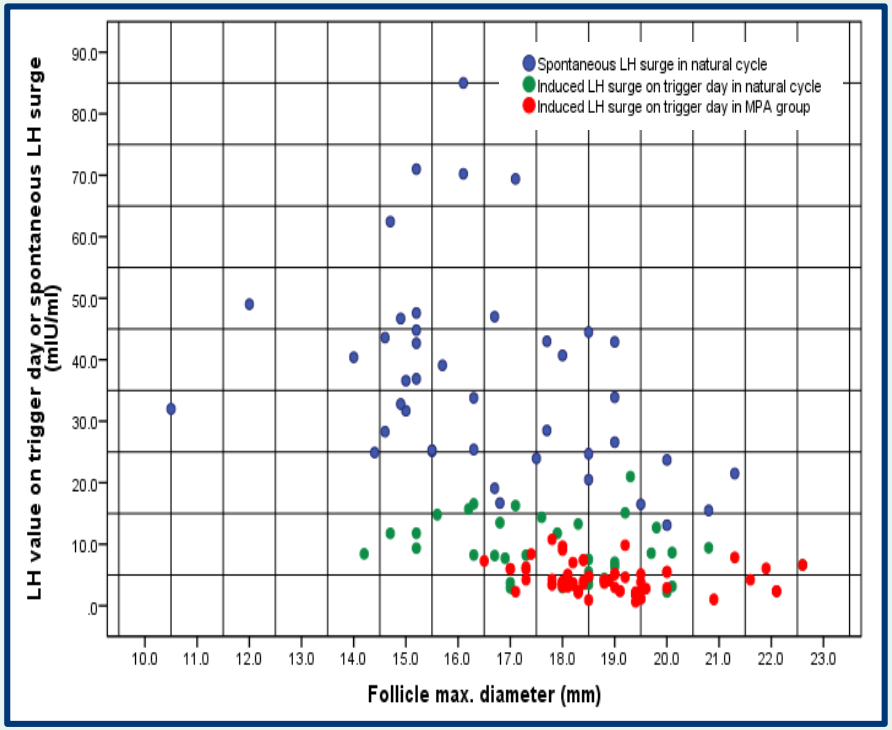
- Levonorgestrel (LNG) inhibits physiologic estradiol induced LH surge
- It's action is reversible

Chabbert-Buffet et al. Steroid 2000; Skinner et al. PNAS 1998

Heikinheimo et al. Contraception 1996

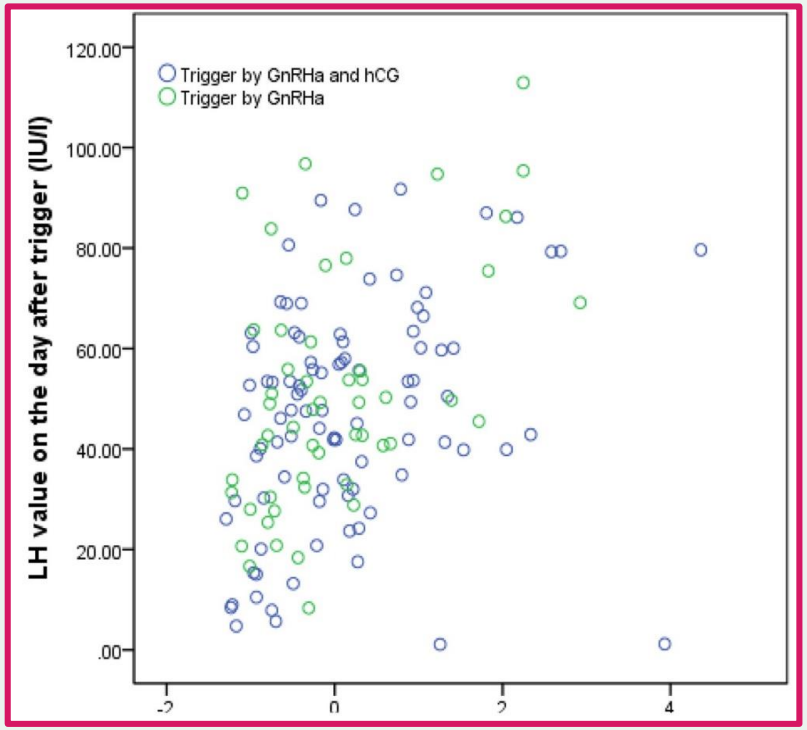
progesterone prevents LH surge

MPA inhibits LH during FSH stimulation



Kuang et al. ESHRE 2015

without impairing response to triggering



Kuang et al. Fertil Steril. 2015

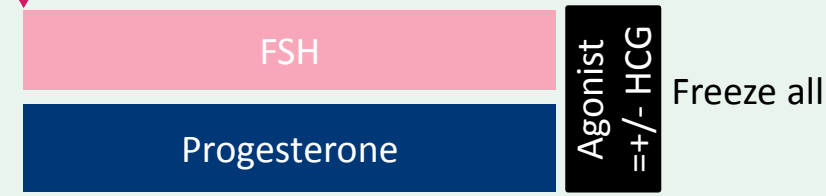
How to use progesterone protocols?

1. ENDOGENOUS PROGESTERONE: luteal phase stimulation (LPS)

CD16-18 prog ≥ 2 ng/ml

2. EXOGENOUS PROGESTERONE : progestin primed ovarian stimulation (PPOS)

CD1-3 (E2 < 50 pg/ml)



How to use progesterone protocols?

1. ENDOGENOUS PROGESTERONE: luteal phase stimulation (LPS)

CD16-18 prog ≥ 2 ng/ml

What results?

- Oocyte donor model (D2 vs D15)
  - Same FSH dose
  - Same number of M2 oocyte
  - Same fertilization rate
  - Same pregnancy rate in recipients
- But some authors (retrospective studies)
  - Used antagonist
  - More FSH needed/ duration longer
  - More oocytes (poor responders)
- No RCT

Martinez FS 2014; Wang Clinical Endocrinol 2015; Li Gynecol Endocrinol 2015

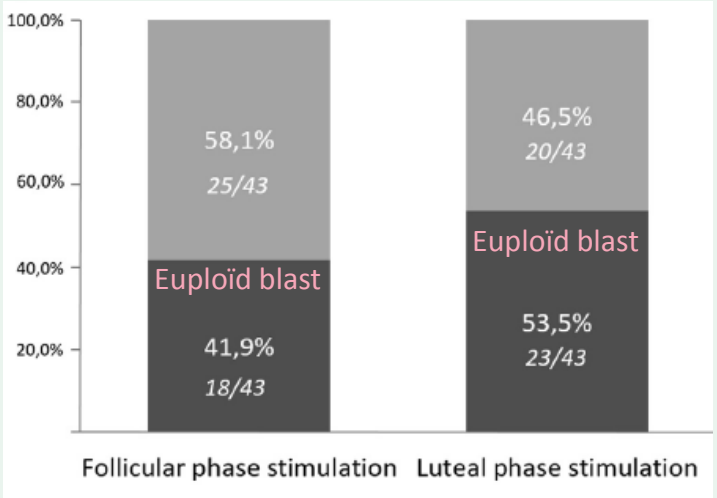
How to use progesterone protocols?

1. ENDOGENOUS PROGESTERONE: luteal phase stimulation (LPS)

CD16-18 prog ≥ 2 ng/ml

Safety?

- Same rate of euploïd blastocystes

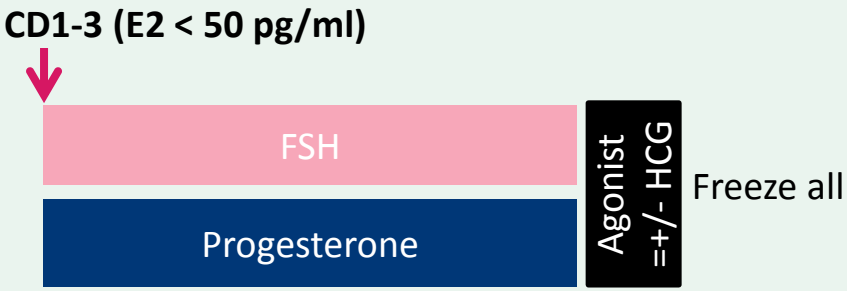


- Same perinatal outcomes
- Same birth defects (N=587)

Ubaldi FS 2016; Chen FS 2015

How to use progesterone protocols?

2. EXOGENOUS PROGESTERONE : progestin primed ovarian stimulation (PPOS)



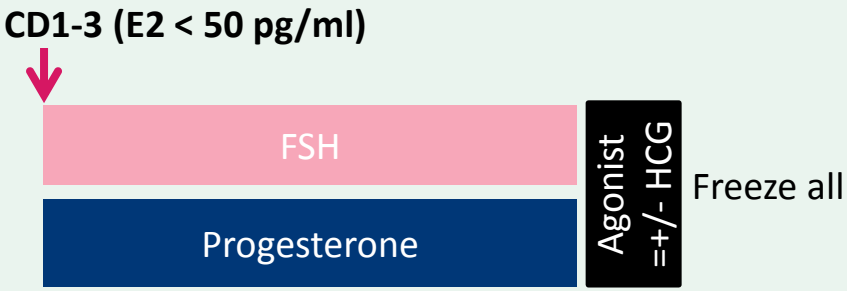
Which progestin?

- Medroxyprogesterone acetate
  - Not hyperandrogenic
  - No interference with endogenous progesterone dosage
  - 4 mg/d or 10mg/d
- Micronized progesterone (oral)
  - 100 mg or 200 mg/d
- Didrogesterone
  - 20 mg/d
  - No interference with endogenous progesterone dosage
- Desogestrel 75 mcg/d

Kuang FS 2015; Zhu Medecine 2015; Zhu FS 2017; Iwami ESHRE 2017; Martinez ASRM 2017

How to use progesterone protocols?

2. EXOGENOUS PROGESTERONE : progestin primed ovarian stimulation (PPOS)



What results?

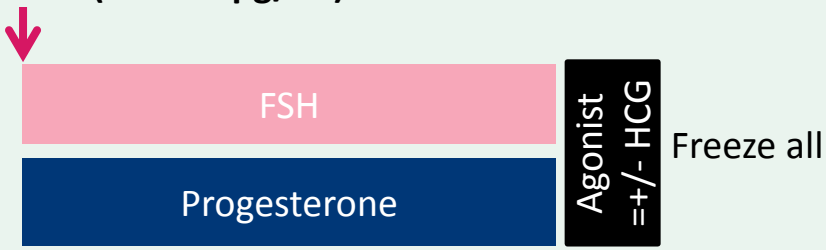
- Oocyte donor model (Corifollitropin)
  - Desogestrel 75 vs antag
  - Same number of M2 oocytes
  - Higher acceptance
- Strong control of LH surge
  - 1.5% LH surge (poor responders)
  - <1% premature ovulation (normo)
  - But 5% LH response non optimal (<20 UI/L) after agonist triggering
- Same number of oocytes
- Same pregnancy/birth rate
- But higher FSH dose/ duration

Martinez ASRM 2017; Chen ASRM 2017; Kuang FS 2015; Wang Medicine 2016; Chen Reprod Biol Endoc 2017; Zhu Medecine 2015 ; Iwami ESHRE 2017

How to use progesterone protocols?

2. EXOGENOUS PROGESTERONE : progestin primed ovarian stimulation (PPOS)

CD1-3 (E2 < 50 pg/ml)



Safety?

- Neonatal outcomes (MPA) N=1931
  - Same birthweight
  - Same gestational age
  - Same congenital malformations

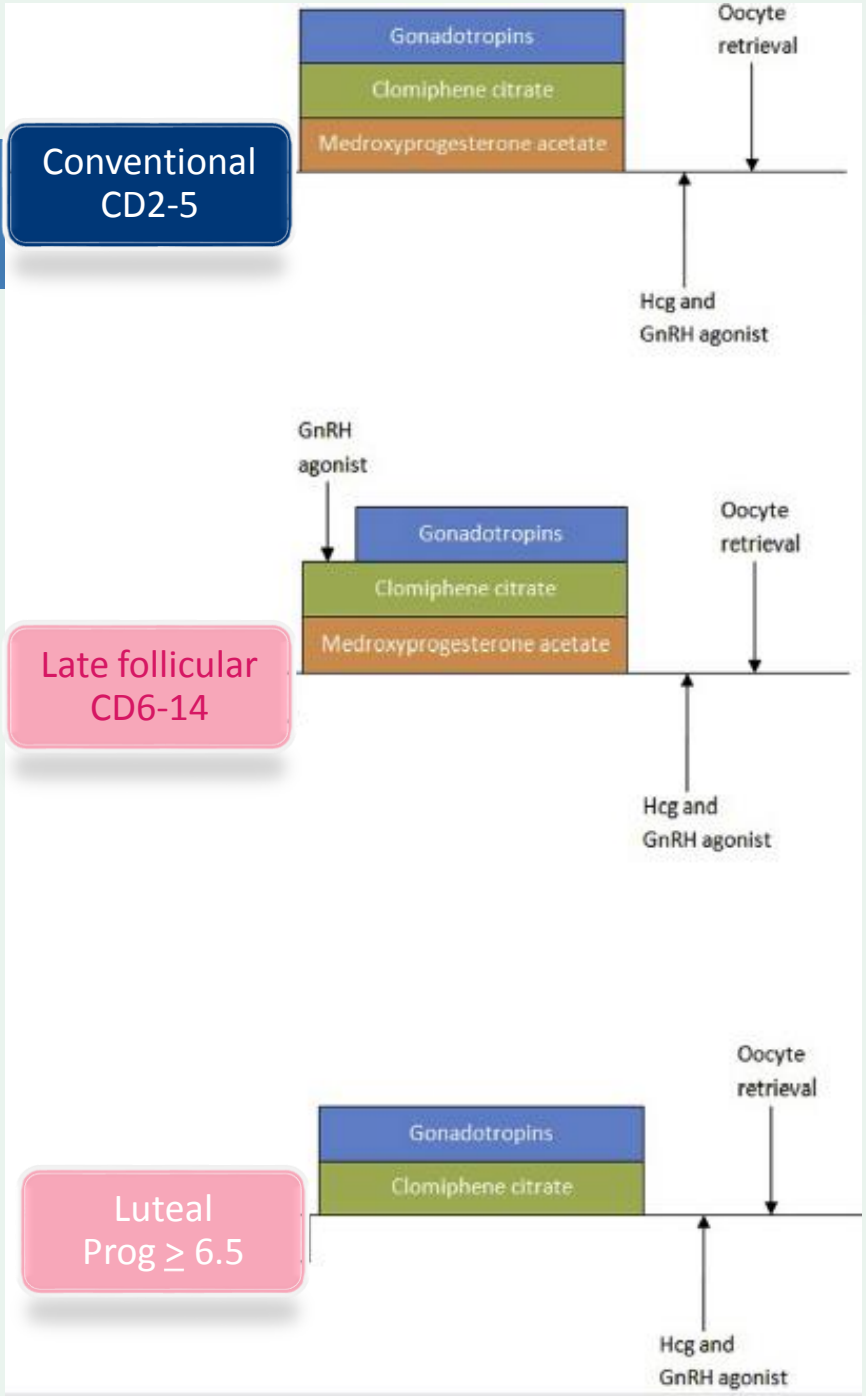
Kuang FS 2015; Zhang ESHRE 2017

random start

Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection

Ningxin Qin, M.M.,[a,b] Qiuju Chen, Ph.D.,[a] Qingqing Hong, M.D.,[a] Renfei Cai, M.D.,[a] Hongyuan Gao, M.D.,[a] Yun Wang, M.D.,[a] Lihua Sun, M.D.,[a] Shaozhen Zhang, M.D.,[a] Haiyan Guo, M.D.,[a] Yonglun Fu, M.D.,[a] Ai Ai, M.D.,[a] Hui Tian, M.D.,[a] Qifeng Lyu, Ph.D.,[a] Salim Daya, MBChB,[c] and Yanping Kuang, M.D.[a]

- Age < 42y, AFC > 3 and FSH < 12
- N = 150
- Freeze all embryos +/-blastocysts
- FET: natural or stimulated cycles with HCG trigger
- No difference in demographics and baseline characteristics



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random start

Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection

Cycle characteristics of controlled ovarian stimulation in the three groups.

Characteristic	Conventional group	Late follicular phase group	Luteal phase group	*P* value
Cycles (n)	50	50	50	
Ovarian stimulation duration (d)	8.9 ± 1.4	11.4 ± 3.1	10.9 ± 3.4	.000
hMG duration (d)	9.0 ± 1.4	10.1 ± 2.7	10.6 ± 3.4	.013
hMG daily dose (IU)	149.2 ± 14.6	155.9 ± 11.9	169.4 ± 28.1	.000
E_2 level on started day (pg/mL)	39.9 ± 21.2	154.4 ± 120.3	141.1 ± 94.9	.000
>10-mm follicles on hCG administration day (n)	9.4 ± 4.7	9.7 ± 6.1	8.7 ± 5.6	.654
>14-mm follicles on hCG administration day (n)	7.2 ± 3.9	6.8 ± 4.6	6.9 ± 5.5	.912
Oocytes retrieved (n)	6.6 ± 3.8	5.9 ± 4.3	5.9 ± 4.2	.633
MII oocytes (n)	5.7 ± 3.6	5.2 ± 3.7	5.2 ± 3.9	.699
Fertilized oocytes (n)	4.9 ± 3.1	4.1 ± 3.0	4.1 ± 3.0	.298
Cleaved embryos (n)	4.8 ± 3.0	4.0 ± 2.9	4.0 ± 3.0	.291
Top-quality embryos on day 3 (n)	2.1 ± 2.0	1.8 ± 1.9	2.3 ± 2.4	.412
Cryopreserved day 3 embryos (n)	2.0 ± 1.8	1.8 ± 1.8	2.3 ± 2.2	.418
Cryopreserved day 5/6 embryos (n)	0.5 ± 0.7	0.4 ± 0.7	0.3 ± 0.5	.229
Total cryopreserved embryos (n)	2.5 ± 2.0	2.1 ± 2.2	2.5 ± 2.5	.589
Oocyte retrieval rate (%)	60.3 (329/546)	51.4 (296/572)	62.3 (294/472)	.152
Mature oocyte proportion (%)	87.2 (287/329)	87.8 (260/296)	88.1 (259/294)	.996
Fertilization rate (%)	85.7 (246/287)	78.8 (205/260)	78.8 (204/259)	.741
Cleavage rate (%)	97.6 (240/246)	97.1 (199/205)	98.0 (200/204)	.998
Proportion of viable embryos per oocyte retrieved (%)	37.9 (127/329)	38.5 (107/296)	43.6 (127/294)	.500
Cancellation rate (%)	10.0 (5/50)	22.0 (11/50)	16.0 (8/50)	.388

random start

Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection

Pregnancy outcomes of frozen-thawed embryos originating from the three groups.

Outcome	Conventional group	Late follicular phase group	Luteal phase group
No. of patients	33	27	30
No. of FET cycles	41	33	36
No. of thawed embryos	75	53	60
No. of viable embryos after thawing	75	53	59
No. of transferred embryos per FET cycle (mean)	1.8	1.7	1.7
Biochemical pregnancy rate per transfer (%)	46.3 (19/41)	48.5 (16/33)	47.2 (17/36)
Clinical pregnancy rate per transfer (%)	41.5 (17/41)	45.5 (15/33)	38.9 (14/36)
Implantation rate (%)	30.7 (23/75)	30.2 (16/53)	27.1 (16/59)
Miscarriage rate (%)	0 (0/17)	13.3 (2/15)	7.1 (1/14)
Ectopic pregnancy rate (%)	0 (0/17)	0 (0/15)	7.1 (1/14)
Heterotopic pregnancy rate (%)	5.9 (1/17)	0 (0/15)	0 (0/14)
Ongoing pregnancy rate (%)	39.0 (16/41)	39.4 (13/33)	33.3 (12/36)

Similar yield of mature oocytes

But longer duration and higher FSH dose

Similar embryo competence with similar ongoing pregnancy rate

random start OS

- Exogenous FSH stimulates follicular growth whatever the menstrual cycle day (continuous recruitment and follicular waves theories)
- Same number of mature oocytes can be yielded independent of the cycle day of FSH start
- Progesterone seems to have no impact on oocyte and embryo quantity and quality
- Progesterone effectively prevent the LH surge during FSH stimulation
- Endogenous and exogenous progesterone are both efficient

- Allow ovarian stimulation with no delay (oncologic patients)
- Allow more flexibility and less injection but need for freeze all
- Follow up of newborns is required
- RCT and medico-economics studies are needed

random start OS for whom?

- No fresh transfer
  - Oocyte donation
  - Oncologic and non oncologic fertility preservation
  - Planned freeze all
    - PCOS/High responders
    - Endometriosis?
    - Low ressource patient (use of CC and progesterone protocole)
- More patient friendly
  - Fewer injections, lower cost (in progesterone protocole)
  - Less logistics constraints (no restriction regarding menstrual cycle day)

- To be determined
  - Need for more FSH? Duration longer?
  - Neonatal outcomes, frozen embryo transfer
  - RCT needed +++

ongoing trial

- Oocyte donors (N = 100)
- Randomization in 5 groups

Groups	Cycle phase	CD	Stimulation
A	Conventional (Control)	1-3	Desogestrel + Corifollitropin +/- FSH after 7 days
B	Early follicular phase (EFP)	4-7	Desogestrel + Corifollitropin +/- FSH after 7 days
C	Late follicular phase (LFP)	7-11	Desogestrel + Corifollitropin +/- FSH after 7 days
D	Ovulatory Phase (OP)	12-15	Desogestrel + Corifollitropin +/- FSH after 7 days
E	Luteal phase (LP)	16-30	Corifollitropin +/- FSH after 7 days

Thank you

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Smr
Société de Médecine de la Reproduction

Geff

EVERYTHING YOU ALWAYS WANTED TO KNOW ABOUT PROGESTERONE*

(*But Were Afraid to Ask)

January 17th, 2019

ESPACE DU CENTENAIRE
54 quai de la Rapée - 75012 Paris, FRANCE

SAVE THE DATE

Online registration available

on www.s-m-r.org

9.00-10.15 → **Progesterone in follicular phase**

- *Deleterious threshold ; is it possible to prevent premature progesterone elevation?*
- *Embryo and endometrial impact*
- *Debate on the importance of progesterone in late follicular phase*

Speakers: *P. Arvis (Rennes), C. Blockeel (Bruxelles), E. Bosch (Valence), H. Fatemi (Abu Dhabi), P. Humaidan (Skive), N. Polyzos (Barcelone)*

10.15-10.45 Coffee break and visit of the exhibition

10.45-12.15 → **Progesterone in luteal phase**

- *What is the most optimal treatment for luteal phase in IVF after either agonist or HCG triggering?*

Speakers: *G. Griesinger (Lübeck), P. Humaidan (Skive), X. Le Chat (Bruges)*

12.15-14.00 Lunch break and visit of the exhibition

14.00-15.30 → **Progesterone and FET**

- *Which treatment? Which timing? Doses adaptation, progesterone as an essential marker*
- *Endometrial receptivity*

Speakers: *C. Blockeel (Bruxelles), I. Cedrin (Bondy), E. Labarta (Valence), C. Simon (Valence)*

15.30-16.00 Coffee break and visit of the exhibition

16.00-16.30 → **Progesterone and ovarian stimulation**

- *What place for progesterone in ovarian stimulation?*

Speaker: *N. Massin (Créteil)*