

ENDOCRINE CHARACTERISTICS OF ART CYCLES

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30.04.2014, ANTALYA




INTRODUCTION

- The endocrine control of ovarian function through gonadotropins - Follicular growth and differentiation

- ART- Folliculogenesis, ovulation and luteal phase support

Macklon et al, Endocr Rev 2006 Apr;27(2):170-207

de Ziegler et al, Reprod Biomed Online 2007 Nov;15(5):507-13

Loutradis et al, J Steroid Biochem Mol Biol 2008 Nov;112(1-3):1-4

INTRODUCTION

- *Specific modification of the endocrine environment by the pharmacologic agents used in ART cycles*

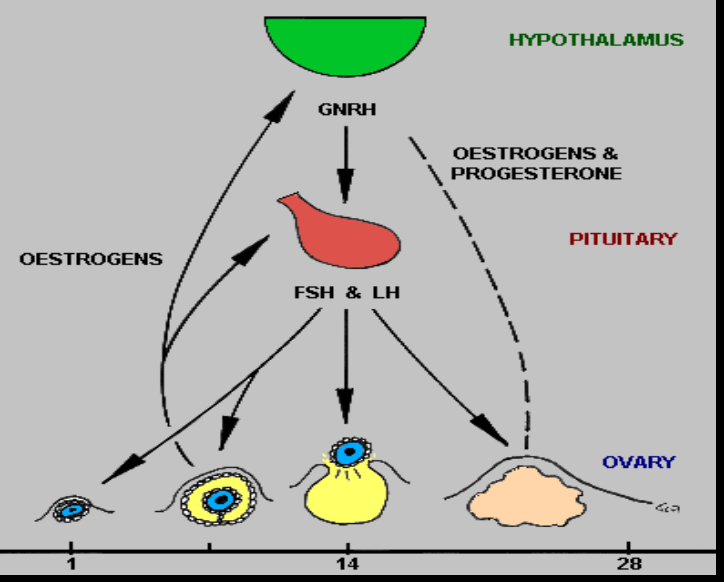
- *The use of hormonal assessments in order to control the ovarian hyperstimulation and predict the cycle outcome*

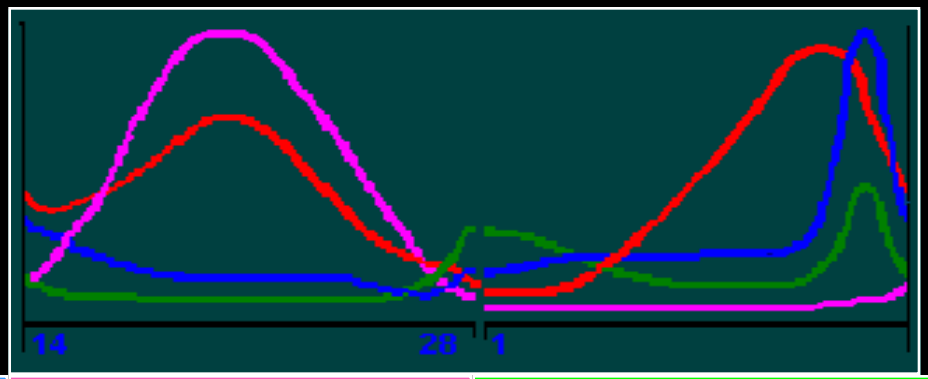
INTRODUCTION

- *Assessment of the required supply of exogenous FSH and LH in ART cycles*

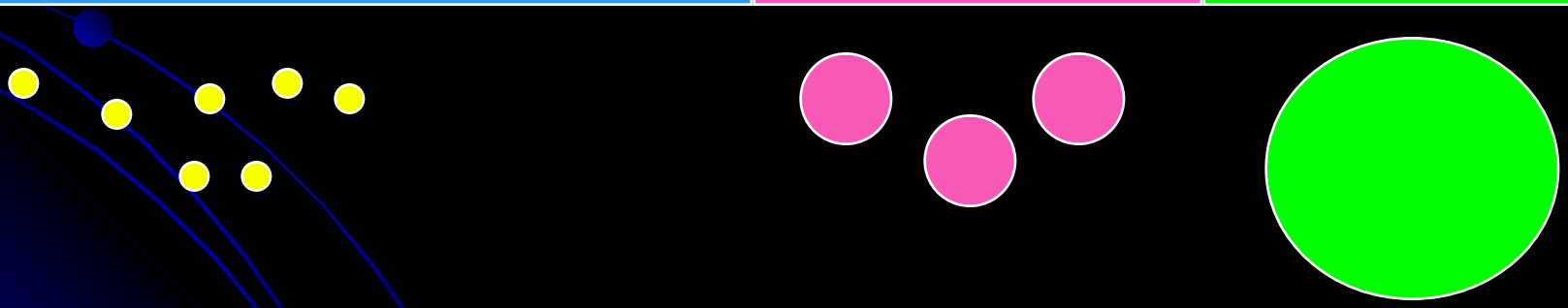
- *Steroid output -Implantation and paracrine/autocrine effects on the cumulus-oocyte unit*

FOLLICULOGENESIS





60 days	14 days	14 days



1mm. → 4-6 mm. → 20 mm.

Gougeon, 1982

PRIMORDIAL GERM CELL

mitosis ↓ 5-20. week

OOGONIUM

1.meiosis ↓

MSF

PRIMARY OOCYTE

(46,XX)

LH SURGE

OVULATION

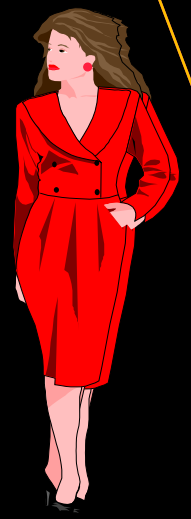
(23,X)

SECONDARY OOCYTE

2.meiosis ↓

FERTILIZATION

HAPLOID OVUM



7.000.000

2.000.000

400.000

PRIMORDIAL FOLLICLE

DEVELOPING FOLLICLES

atresia

RECRUITMENT

(1-4.day)

FOLLICLES DESTINED TO OVULATE

SELECTION

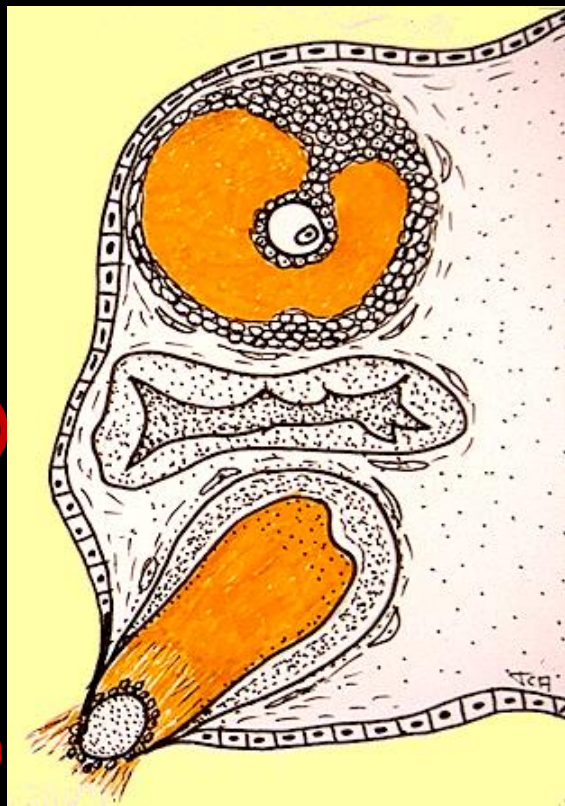
(5-7.day)

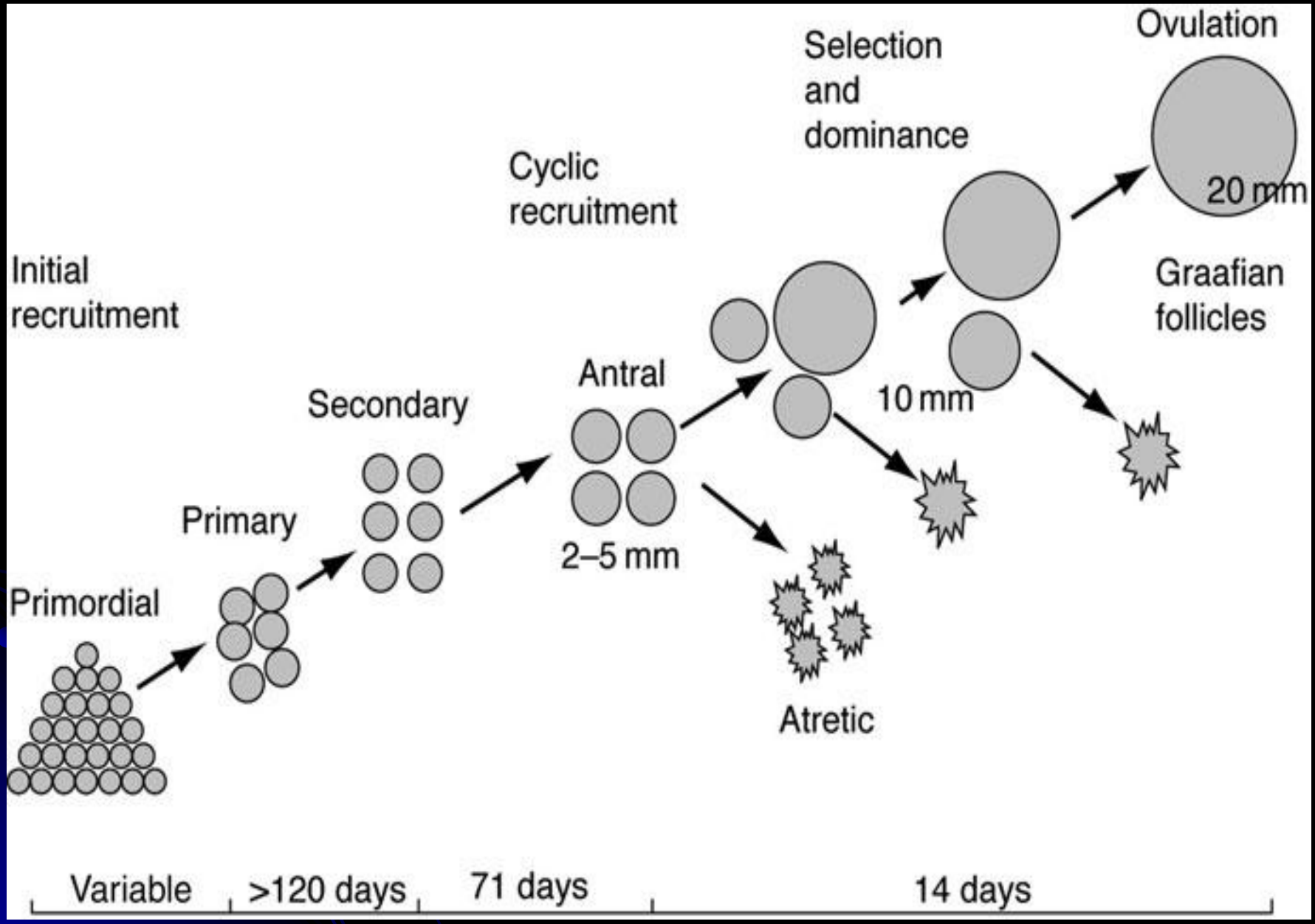
atresia

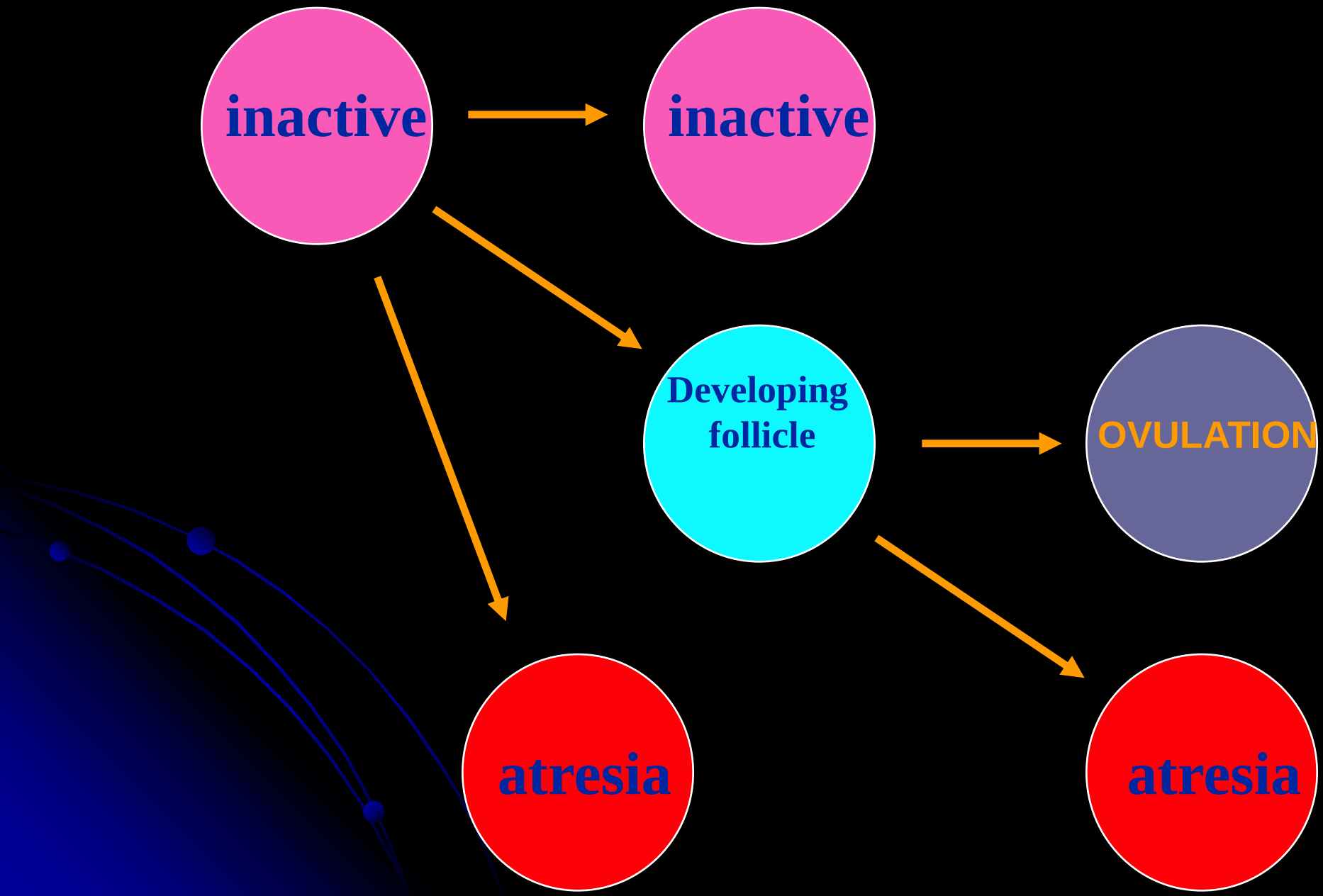
DOMINANT FOLLICLE (8-12. day)

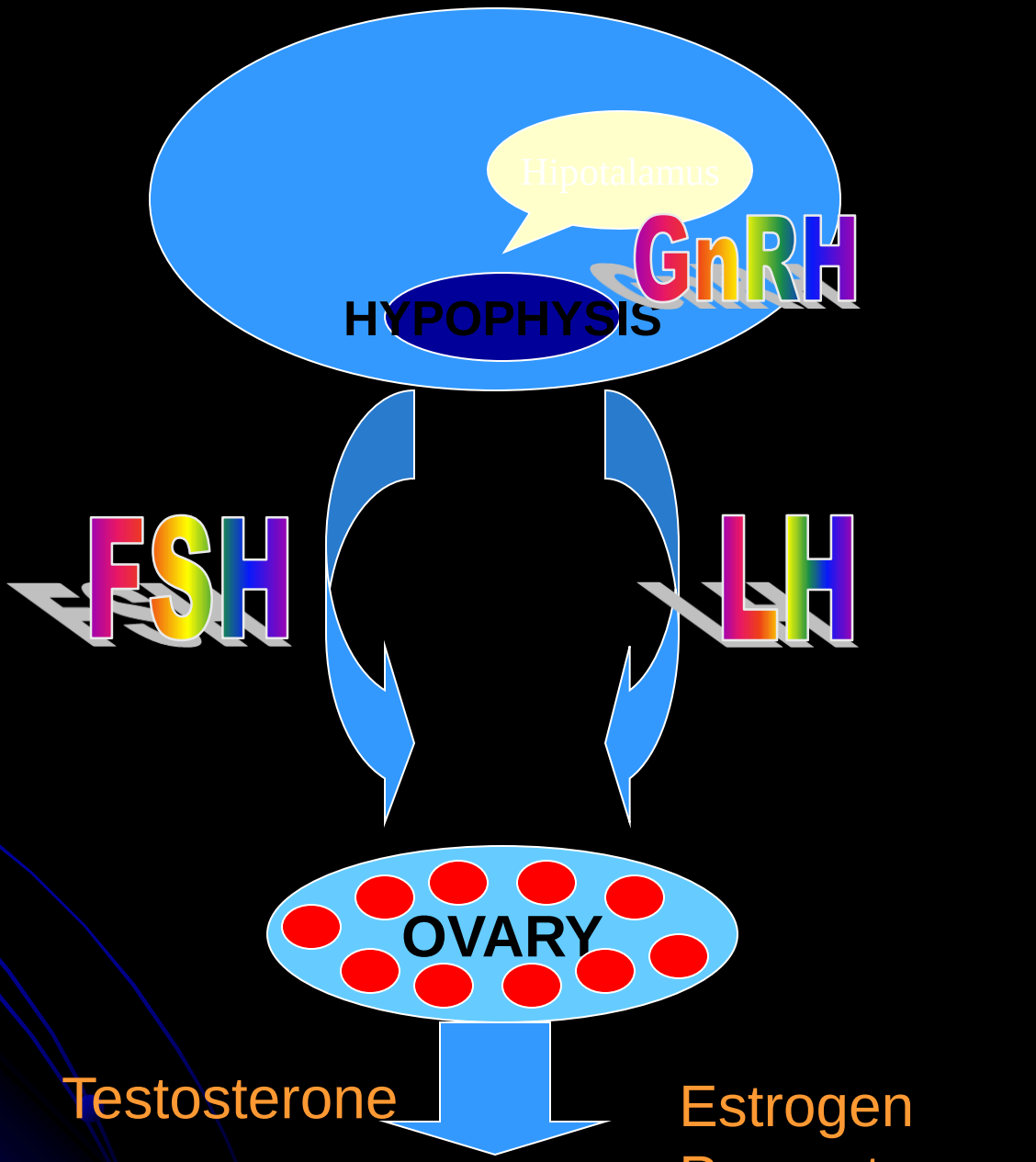
atresia

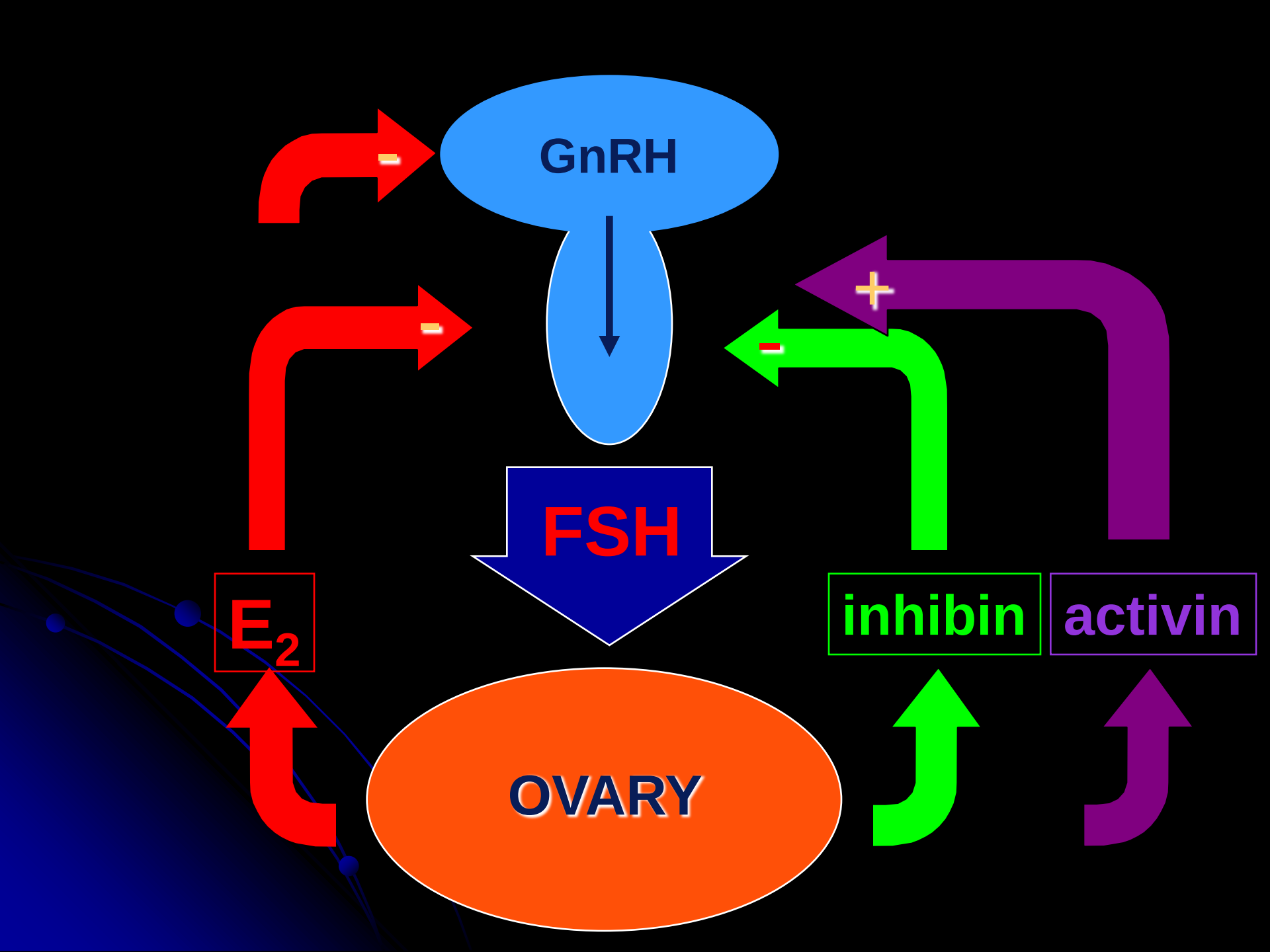
OVULATION (13-15. day)




Ovulation
Selection
and
dominance
Cyclic
recruitment
20 mm
Initial
recruitment
Graafian
follicles
Antral
Secondary
10 mm
Primary
2–5 mm
Primordial
Atretic
Variable
>120 days
71 days
14 days


inactive
inactive
Developing follicle
OVULATION
atresia
atresia

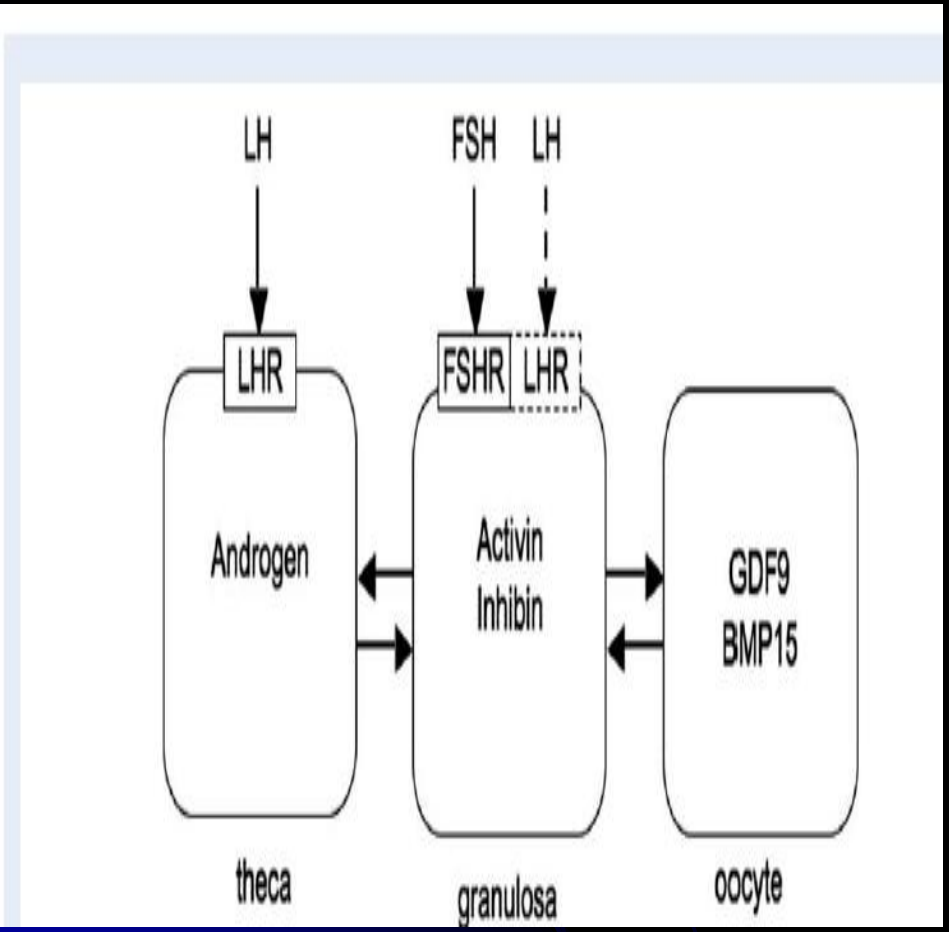

Hipotalamus
GnRH
HYPOPHYSIS
FSH
LH
OVARY
Testosterone
Estrogen
Progesterone


GnRH
-
-
-
+
FSH
E_2
inhibin
activin
OVARY

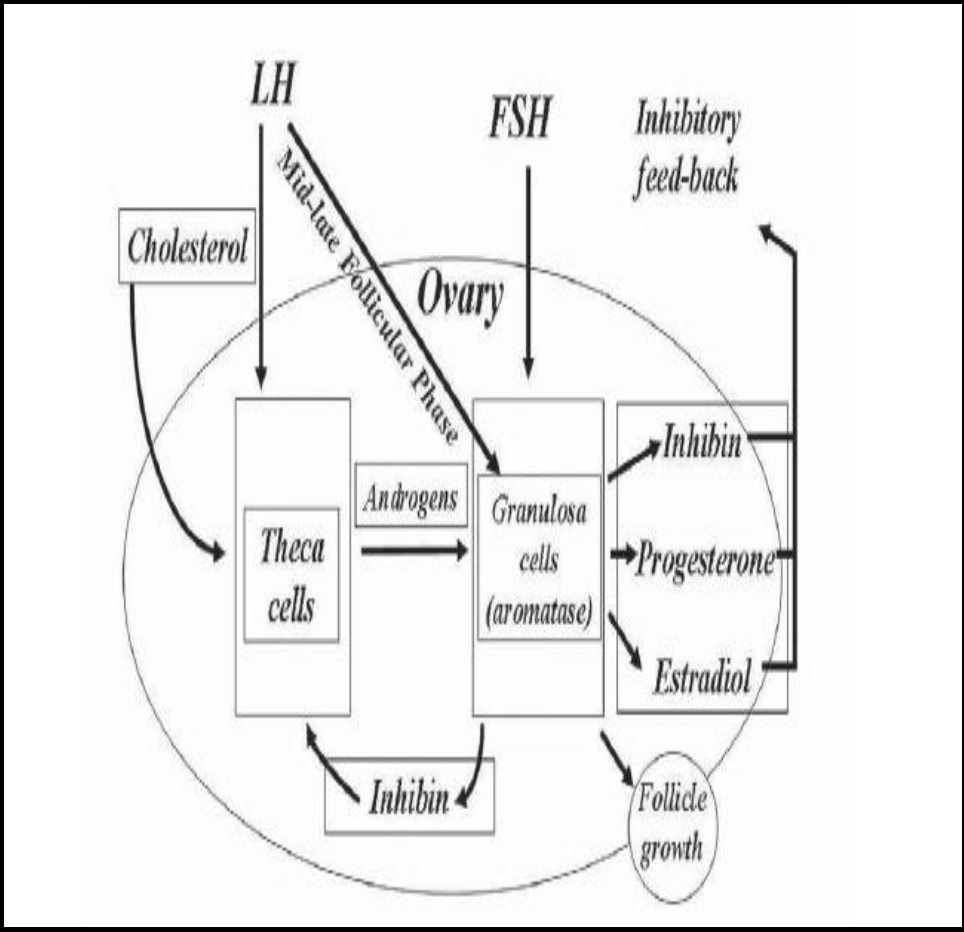
TWO CELL-TWO GONADOTROPIN THEORY

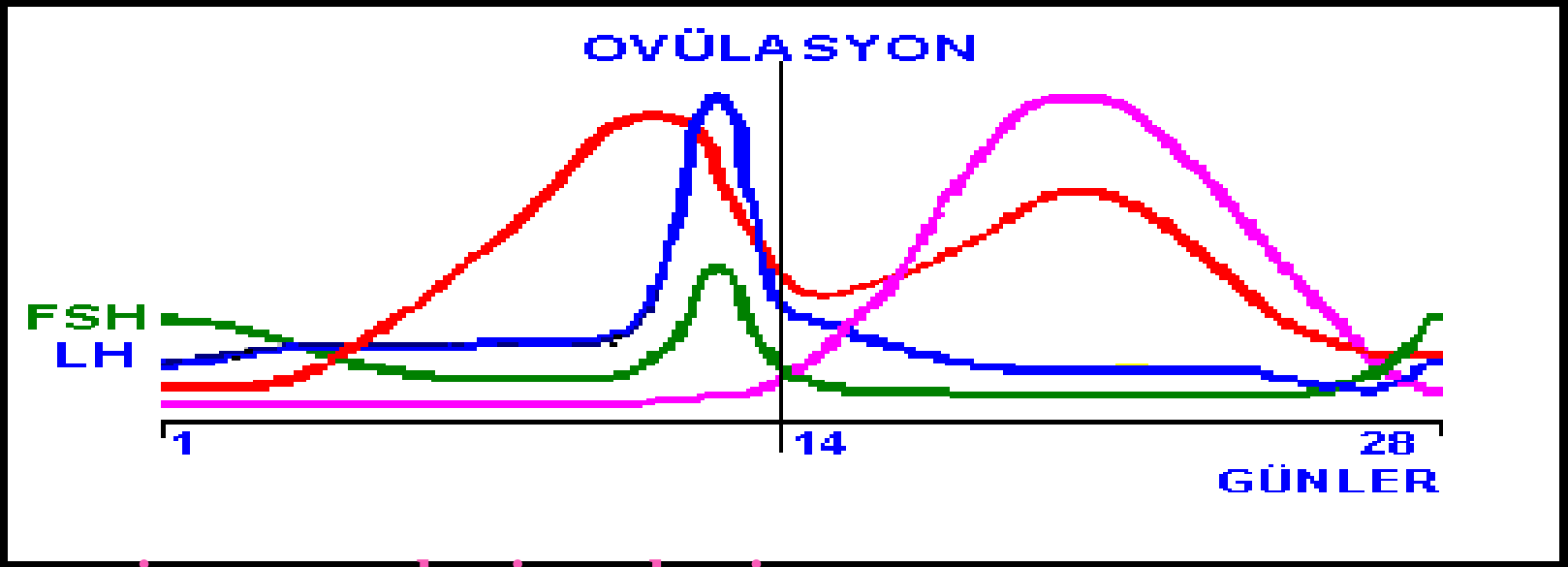
Dorrington and Armstrong, 1979

Hillier SG, Hol Hum Reprod 2009



Vegetti et al, RBM Online 2006





recruitment selection dominance

HORMONE FREE PHASE

GRANULOSA LAYER

THECA

GRANULOSA LAYER

LUTEINISED GRANULOZA CELLS

PRIMARY FOLLICLE

SECONDARY FOLLICLE

TERTIARY FOLLICLE

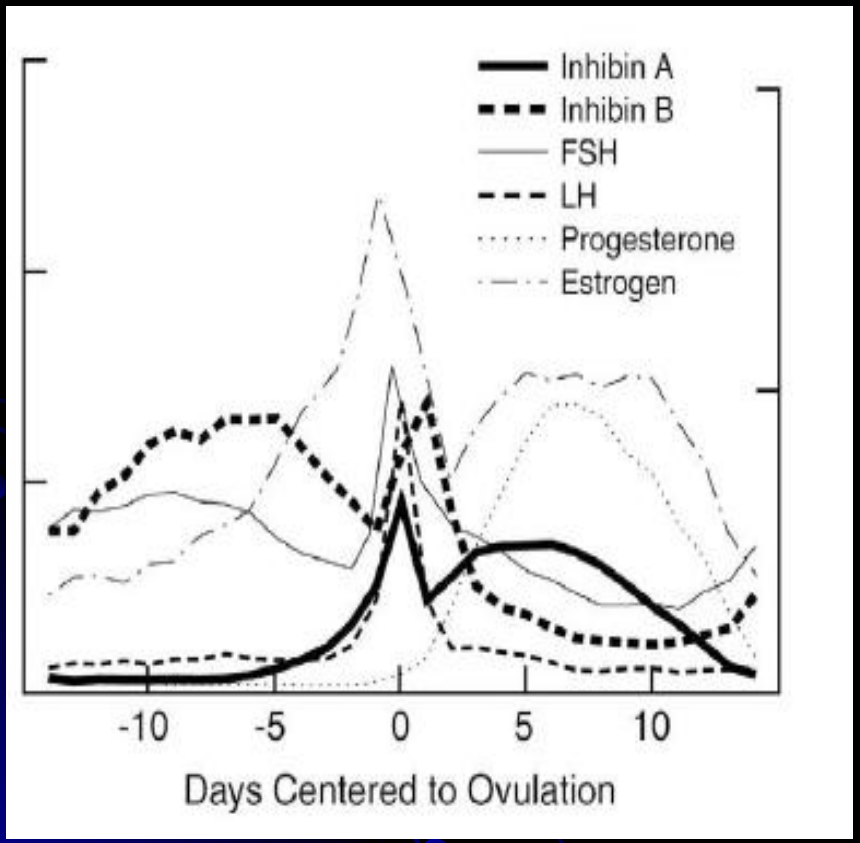
CORPUS LUTEUM

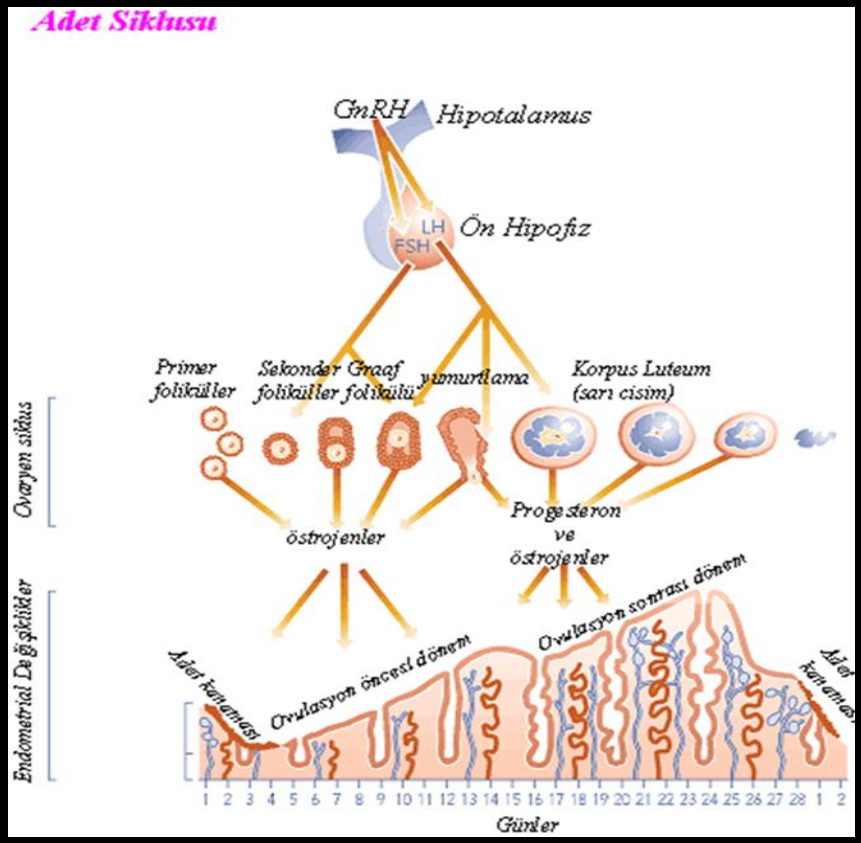
RBM Online - Vol 10. No 6. 2005 786–796 Reproductive BioMedicine Online; www.rbmonline.com/Article/1704 on web 29 March 2005

Review

Significance of inhibin in reproductive pathophysiology and current clinical applications

Kumanov P, Reprod Biomed Online 2005





Reproductive Biology and Endocrinology

BioMed Central

Review

Open Access

Overriding follicle selection in controlled ovarian stimulation protocols: Quality vs quantity

Richard L Stouffer* and Mary B Zelinski-Wooten

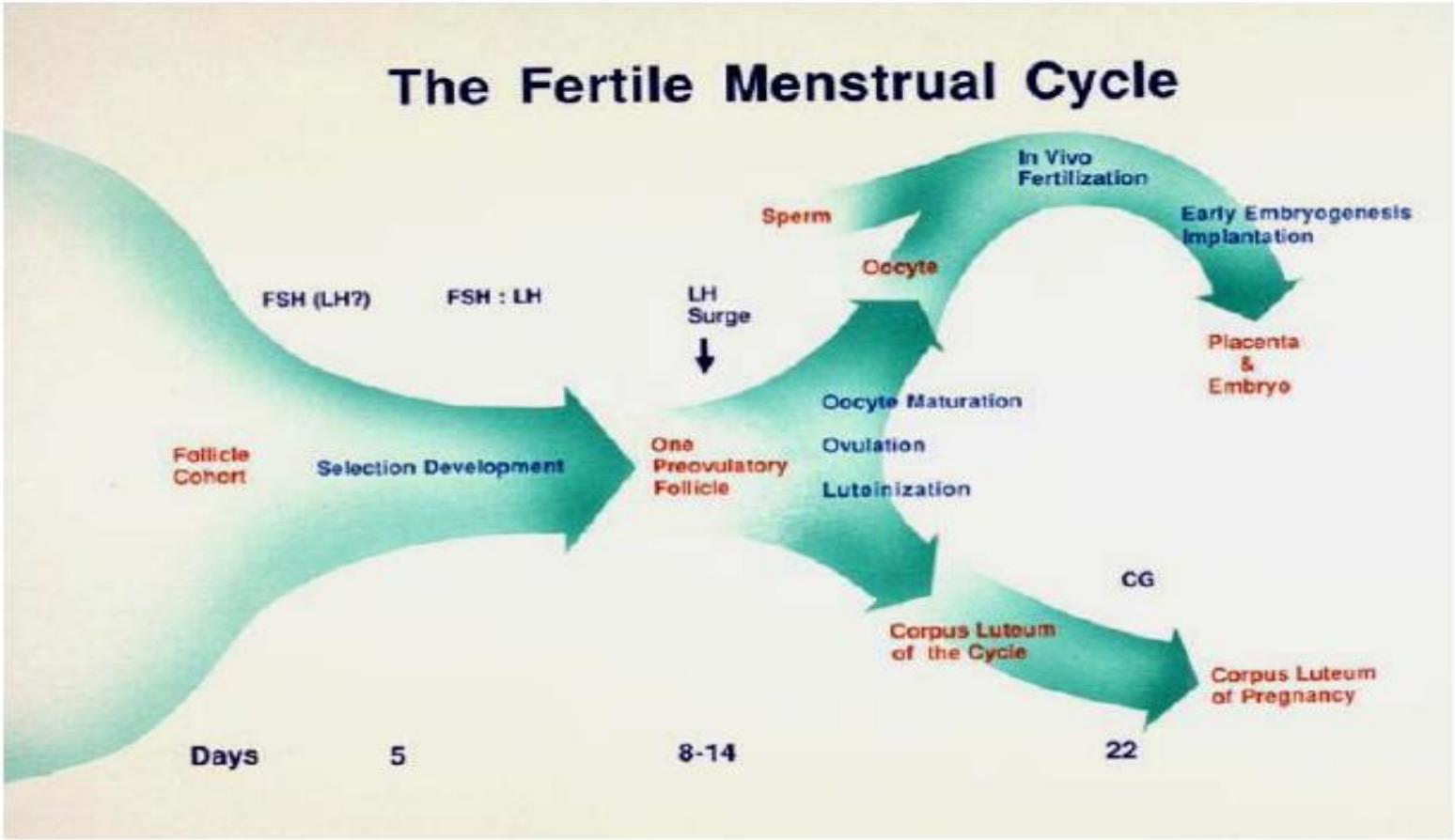


Figure 1
Diagram of the events occurring in the ovary and reproductive tract during the initial three weeks of the fertile menstrual cycle leading to natural reproduction in primates.

Reproductive Biology and Endocrinology

BioMed Central

Review

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Overriding follicle selection in controlled ovarian stimulation protocols: Quality vs quantity

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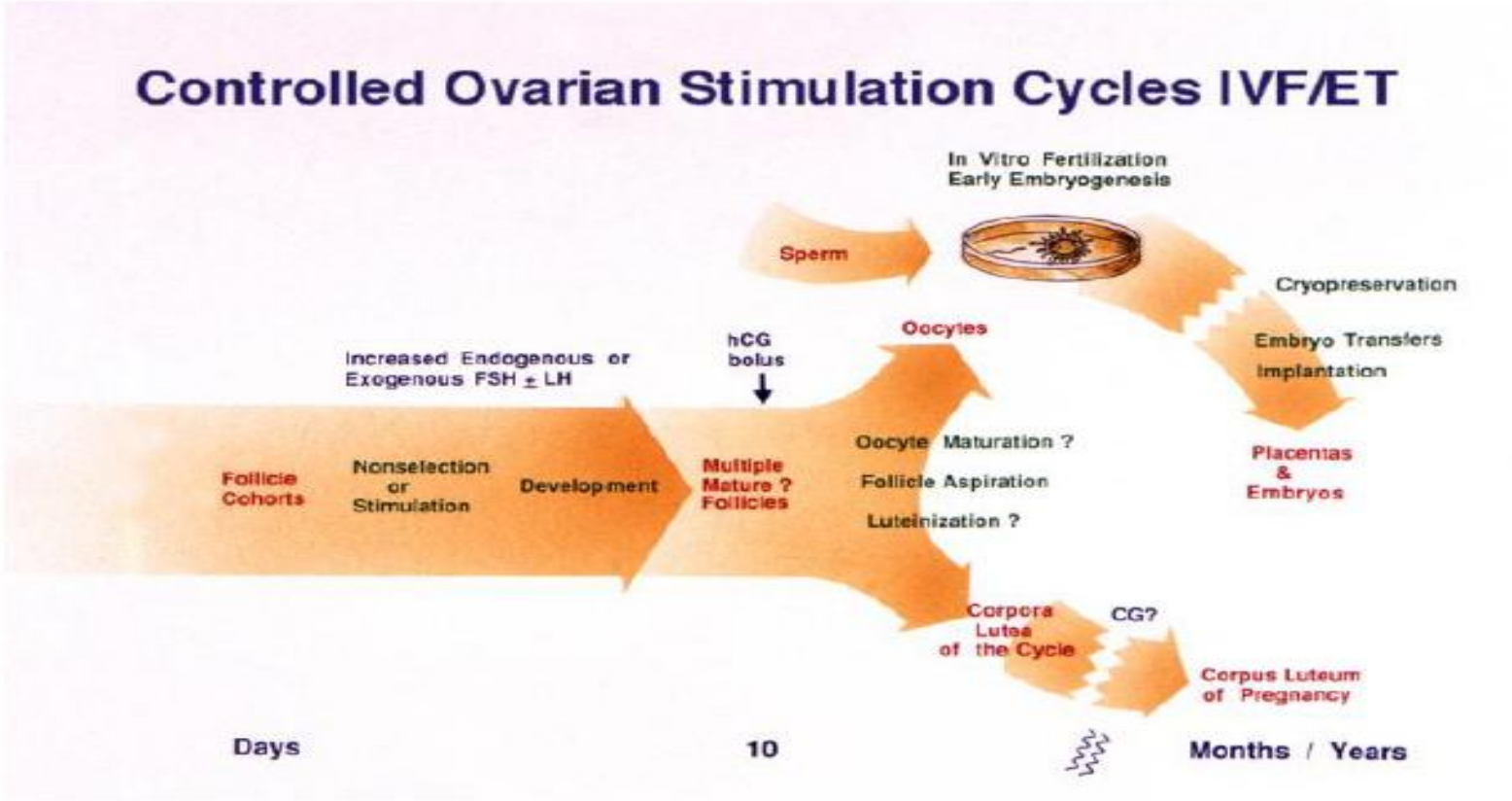


Figure 2

Diagram of events occurring in the ovary and in vitro during controlled ovarian stimulation cycles leading to assisted reproduction in primates. This chapter will discuss the methods and their limitations for increasing circulating levels of gonadotropins (FSH, LH, CG) to override the typical selection and maturation of a single "dominant" follicle in the natural menstrual cycle, thereby stimulating the development and maturation of multiple large follicles whose oocytes can be collected for in vitro manipulation (e.g., in vitro fertilization, IVF) prior to return to the reproductive tract (embryo transfer, ET) for pregnancy initiation.

FOLLICLE STIMULATING HORMONE (FSH)

- FSH -Folliculogenesis, recruitment, selection and dominance phases and follicular differentiation

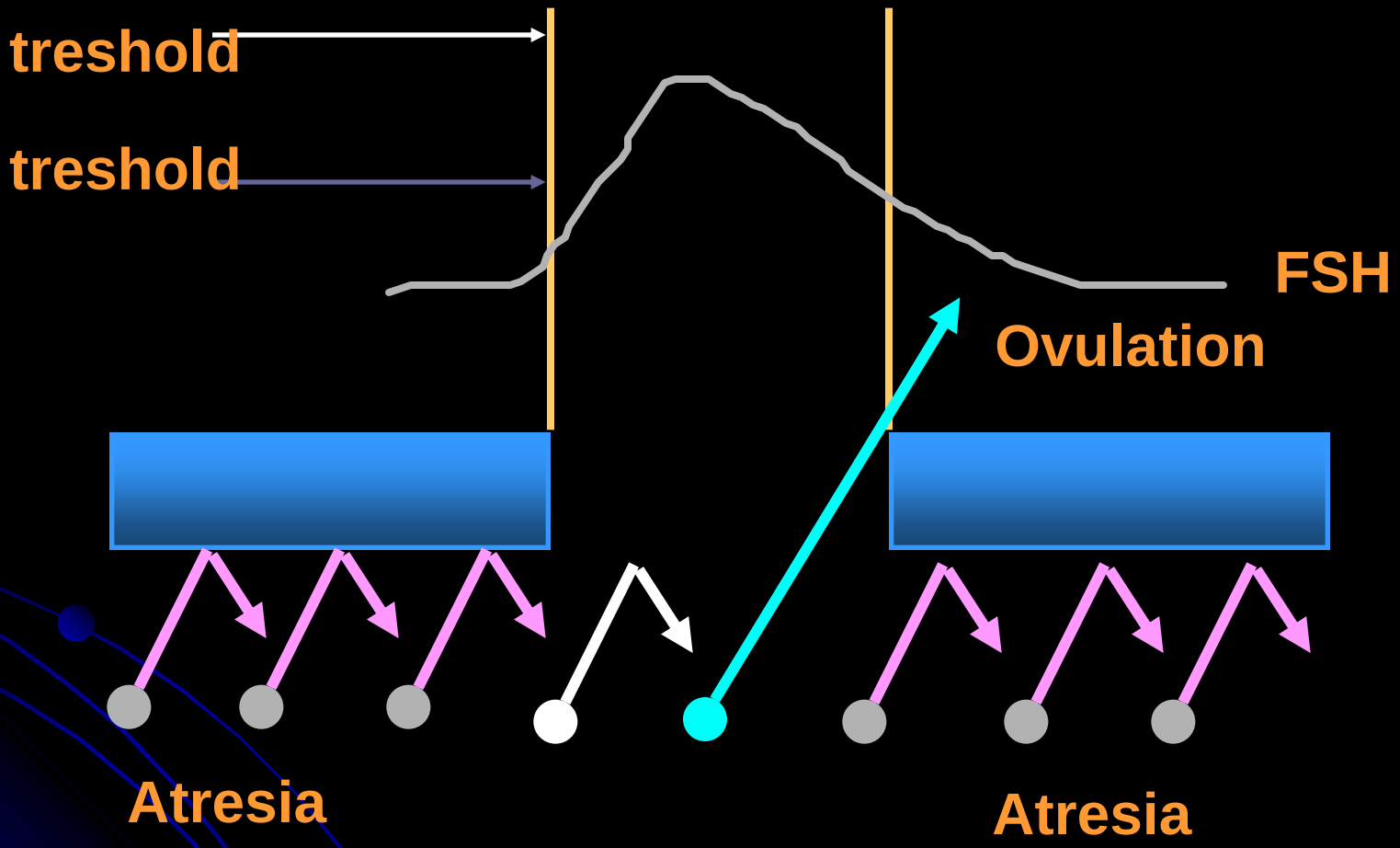
- Trophic effect on granulosa cells, recruitment of the cohort at the early follicular phase

Vegetti et al, Reprod Biomed Online, 2006 Jun;12(6):684-94

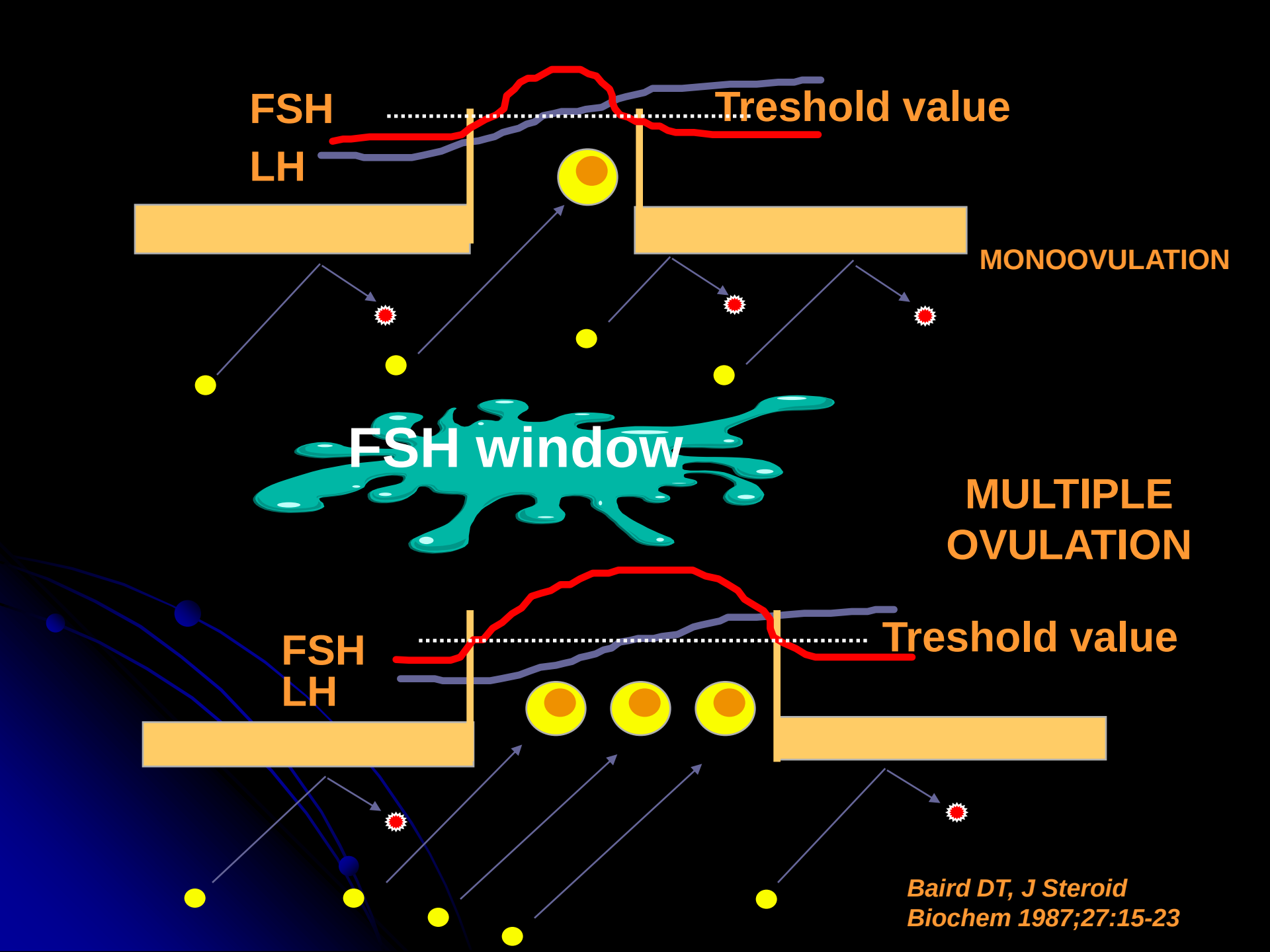
FSH TRESHOLD-FSH WINDOW

- *FSH TRESHOLD- A certain amount of FSH is required to induce the follicular growth*
- *FSH WİNDOW- Follicular growth is maintained as long as FSH is above the follicle's treshold*
- FSH is the crucial therapeutic agent to control the folliculogenesis in ART cycles (except hypohypo)

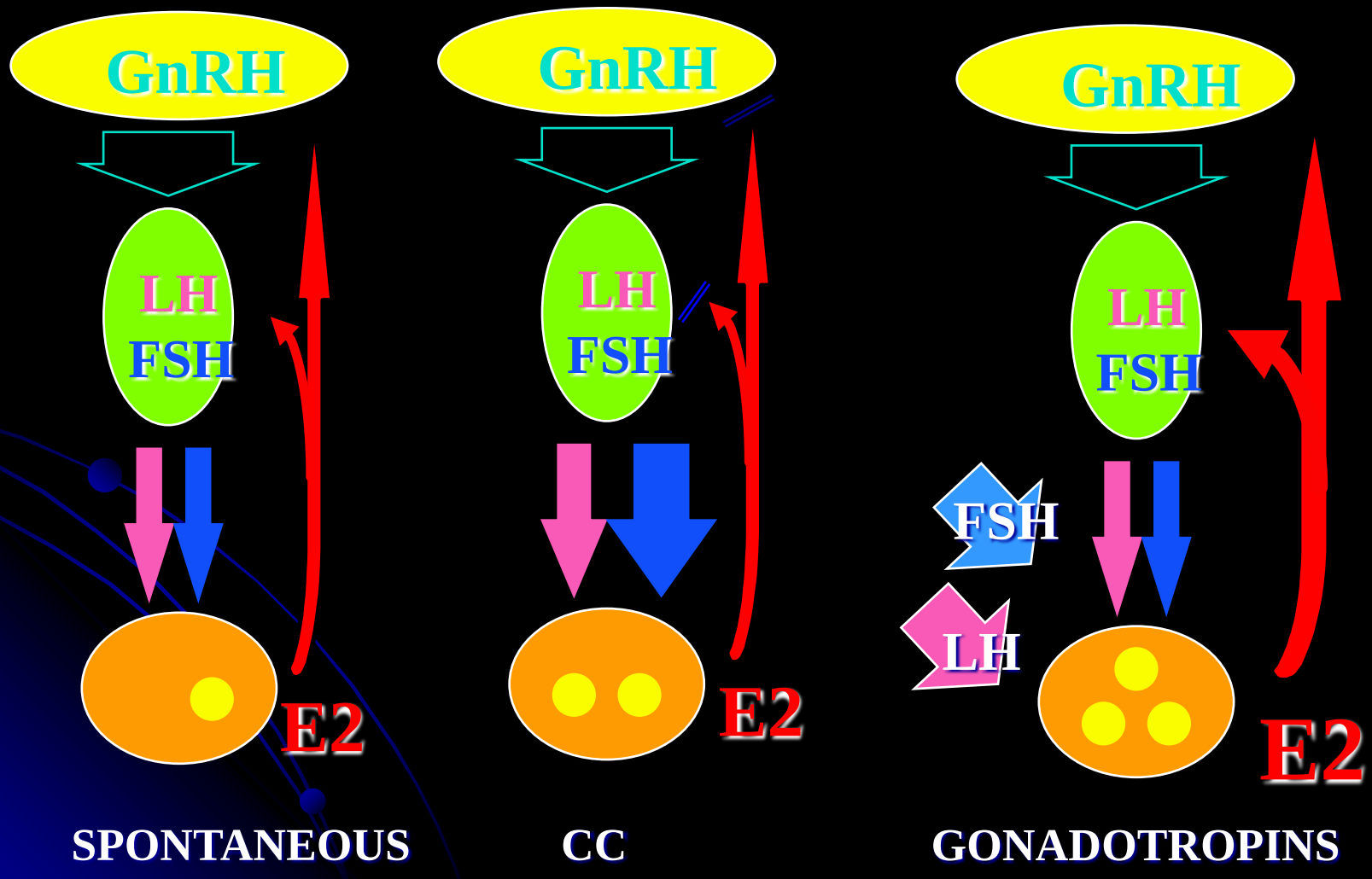
Vegetti et al, Reprod Biomed Online, 2006 Jun;12(6):684-94



Brown J, Aust NZJ Obstet Gynecol 1978;18:47-54



Baird DT, J Steroid Biochem 1987;27:15-23

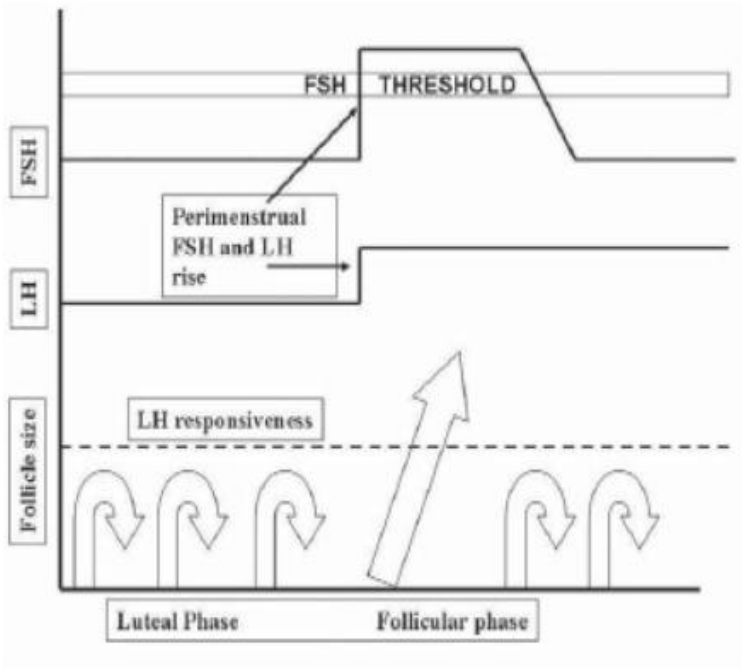

GnRH
LH
FSH
E2
SPONTANEOUS
GnRH
LH
FSH
E2
CC
GnRH
LH
FSH
FSH
LH
E2
GONADOTROPINS

RBM Online - Vol 12. No 6. 2006 684–694 Reproductive BioMedicine Online; www.rbmonline.com/Article/2155 on web 30 March 2006

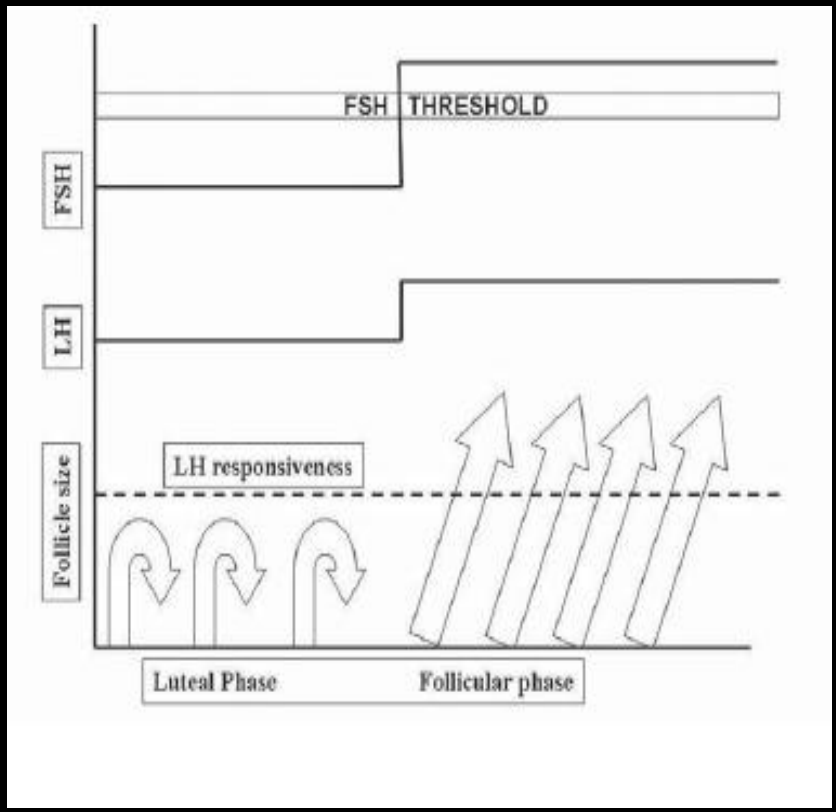
Article

FSH and folliculogenesis: from physiology to ovarian stimulation

SPONTAN SİKLUSLAR



STİMÜLE SİKLUSLAR



Vegetti et al, RBM Online 2006

0163-769X/06/$20.00/0
Printed in U.S.A.

Endocrine Reviews 27(2):170–207
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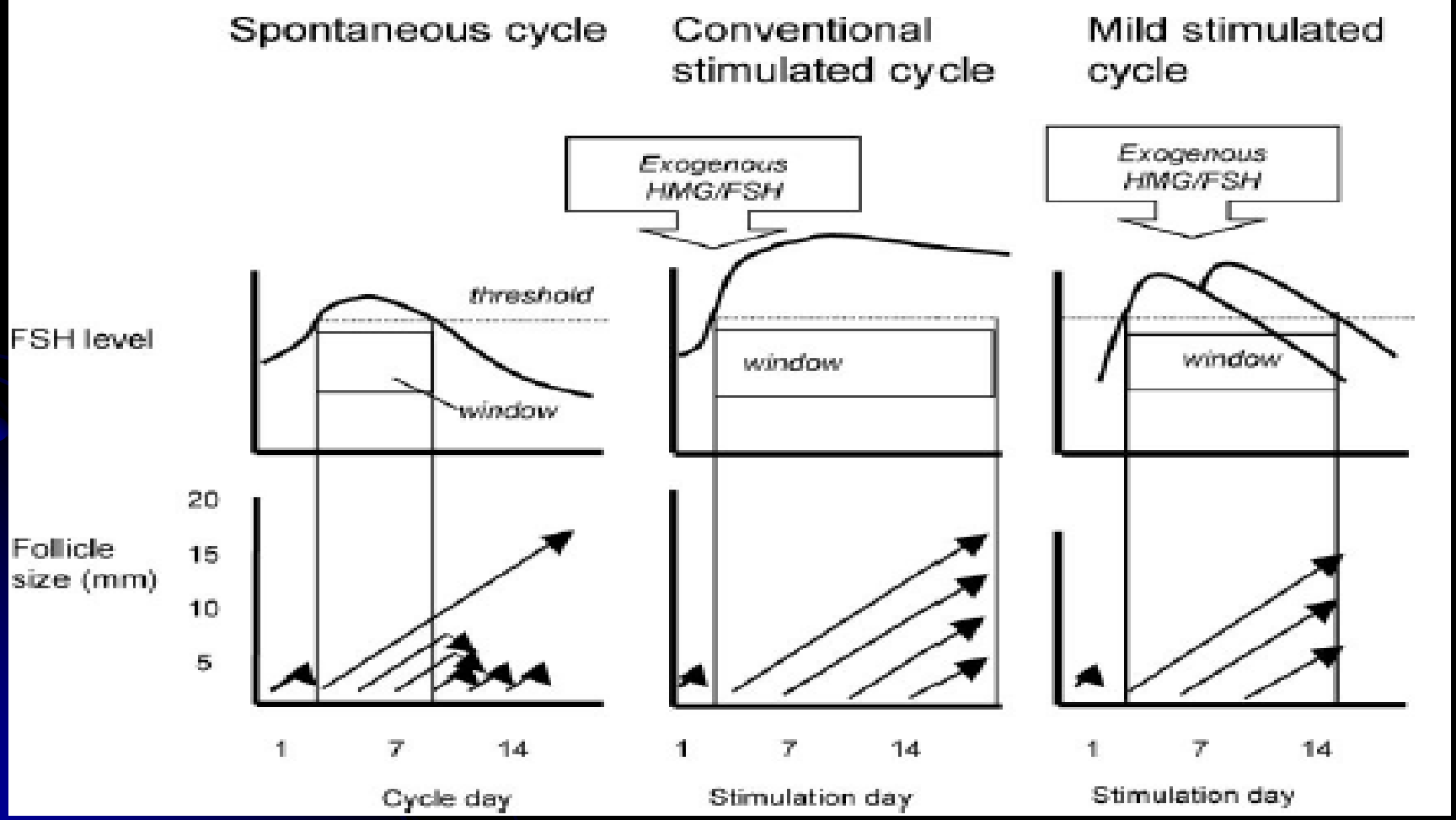
doi: 10.1210/er.2005-0015

The Science behind 25 Years of Ovarian Stimulation for *in Vitro* Fertilization

Nick S. Macklon, Richard L. Stouffer, Linda C. Giudice, and Bart C. J. M. Fauser

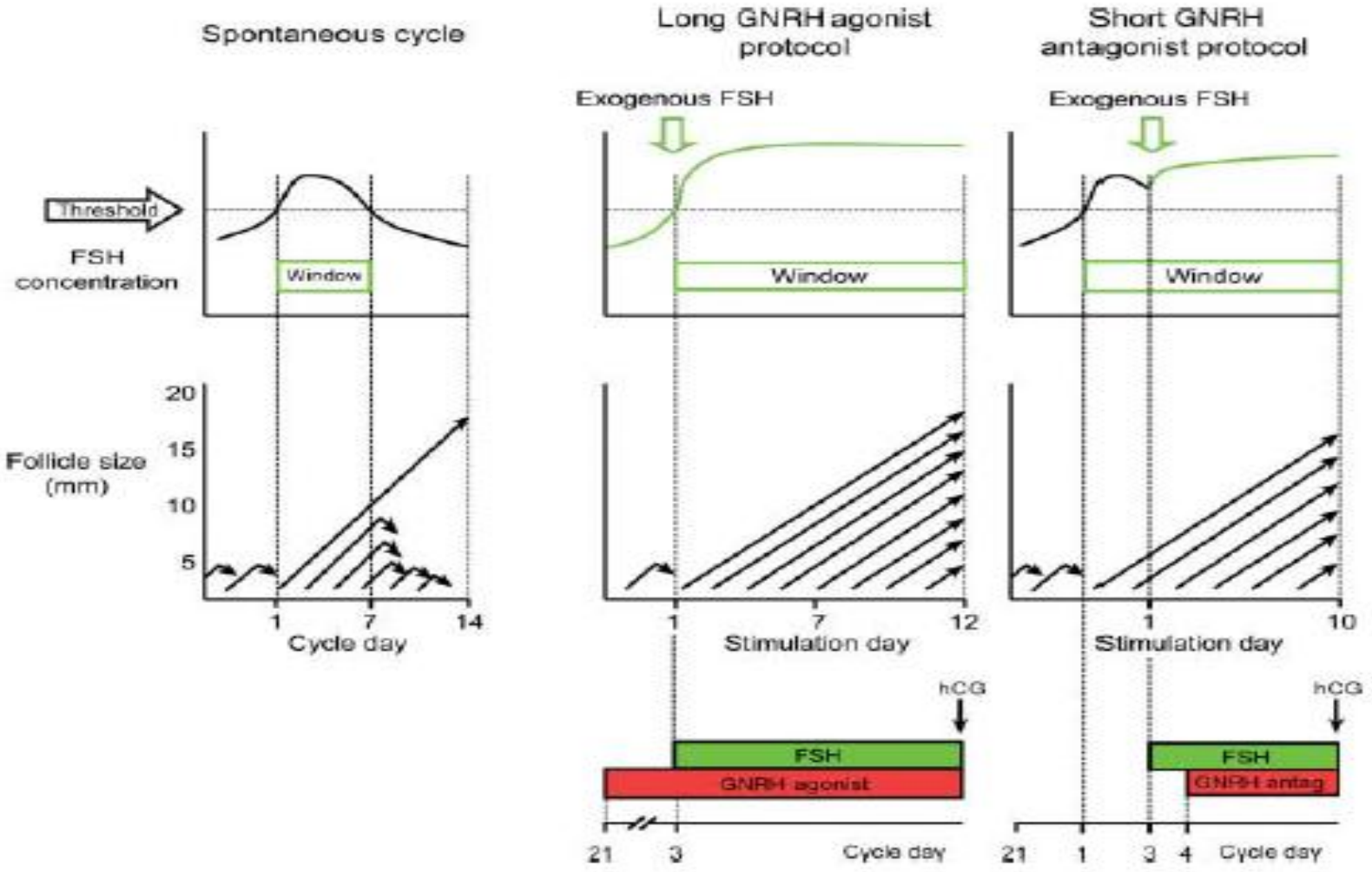
Department of Reproductive Medicine and Gynecology (N.S.M., B.C.J.M.F.), University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands; Division of Reproductive Sciences (R.L.S.), Oregon National Primate Research Center, Oregon Health & Science University, Portland, Oregon 97239-3098; and Department of Obstetrics and Gynecology (L.C.G.), Stanford University School of Medicine, Stanford, California 94305



REPRODUCTION
REVIEW

The impact of ovarian stimulation for IVF on the developing embryo

Margarida Avo Santos, Ewart W Kuijk and Nick S Macklon



Human Reproduction Update, Vol.18, No.1 pp. 73–91, 2012
Advanced Access publication on November 8, 2011 doi:10.1093/humupd/dmr039

human reproduction update

Ovarian antral folliculogenesis during the human menstrual cycle: a review

Angela R. Baerwald[1,*], Gregg P. Adams[2], and Roger A. Pierson[3]

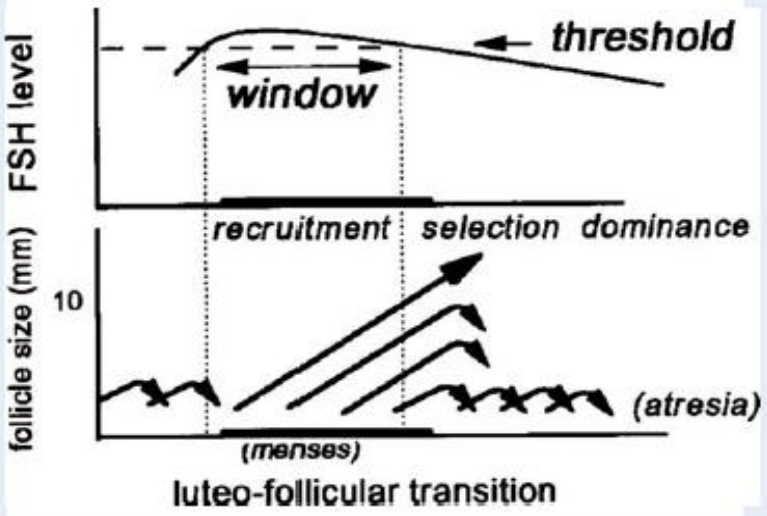


Figure 4 Schematic representation of the FSH threshold (window) concept and follicle growth dynamics (recruitment, selection and dominance) during the follicular phase of the menstrual cycle. [*Reproduced with permission from Elsevier, Fauser and Van Heusden, 1997, Endocrine Reviews, 18(1): 71–105; Originally adapted from Baird et al., 1987, J Steroid Biochem, 71(1): 15–23*].

Reproductive biology and IVF: ovarian stimulation and luteal phase consequences

Bart C.J.M. Fauser[1] and Paul Devroey[2]

[1]Center for Reproductive Medicine, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
[2]Center for Reproductive Medicine, University Hospital, Dutch-speaking Free University of Brussels (Vrije Universiteit), Brussels, Belgium

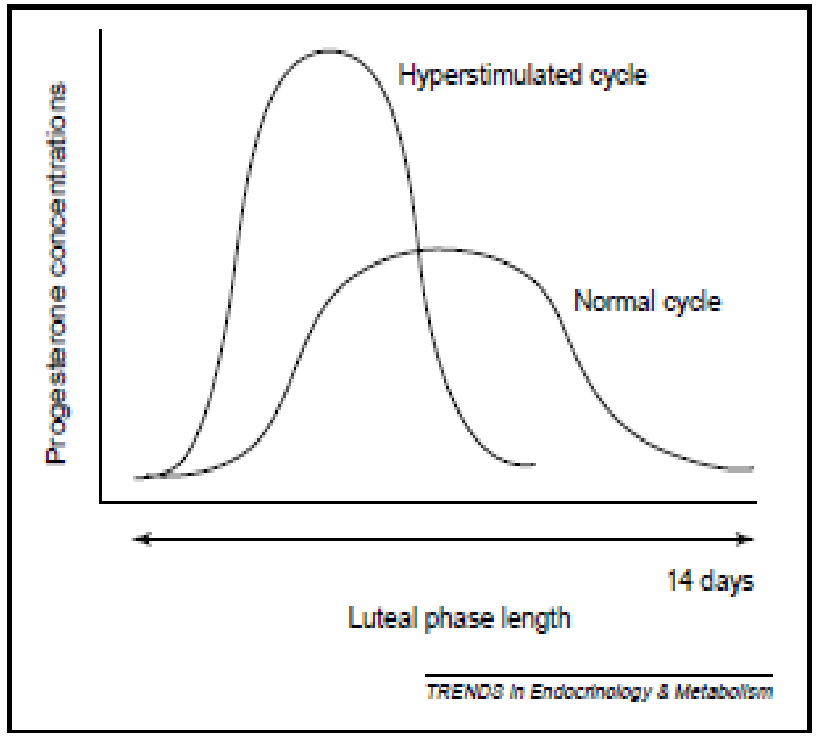


Fig. 2. Abnormal corpus luteum function following ovarian stimulation for *in vitro* fertilization. Abnormally raised progesterone levels during the early luteal phase coincide with premature luteolysis. Adapted, with permission, from [48].

FOLLICLE STIMULATING HORMONE (FSH)

- FSH levels is not suitable to evaluate the adequacy of exogenous FSH supply

- Plasma FSH-not contributive enough to tailor a gonadotropin regimen in a proper manner

Gardner DK, Weissman A, Howles CM, Shoham Z.Textbook of Assisted

Reproductive Technologies. Laboratory and Clinical perpectives. 3. Edition, Volume 2,2009

LUTEINISING HORMONE (LH)

- LH directly acts on granulosa cells as soon as cell differentiation is FSH-induced
- LH ensures the synthesis of androgens through LH receptors located on Theca cells (Two cell-two gonadotropin theory)
- Pivotal role of LH on steroidogenesis in hypo-hypo patients

LUTEINISING HORMONE (LH)

- Addition of LH increases estradiol thus preparing the endometrium for implantation
- CL – luteal phase support
- Minimal amount of LH is required for pregnancy (LH TRESHOLD)

Filicori et al, Trends Endocrinol Metab 2003 Aug;14(6):267-73

Filicori et al, Hum Reprod Update 2002;8(6):543-557

LUTEINISING HORMONE (LH)

- High endogenous LH levels are associated with increased incidence of miscarriages and infertility (Endometrium/oocyte)

- Beyond a certain ceiling level, LH seems to have an inhibitory effect on cell growth and the granulosa proliferation initiating atresia of less mature follicles

Filicori et al, Hum Reprod Update 2002;8(6):543-557

Review TRENDS in Endocrinology and Metabolism Vol. 14 No. 6 August 2003 267

Current concepts and novel applications of LH activity in ovarian stimulation

Marco Filicori, Graciela E. Cognigni, Patrizia Pocognoli, Walter Ciampaglia and Silvia Bernardi

Reproductive Endocrinology Center, University of Bologna, Via Massarenti 13, 40138 Bologna, Italy

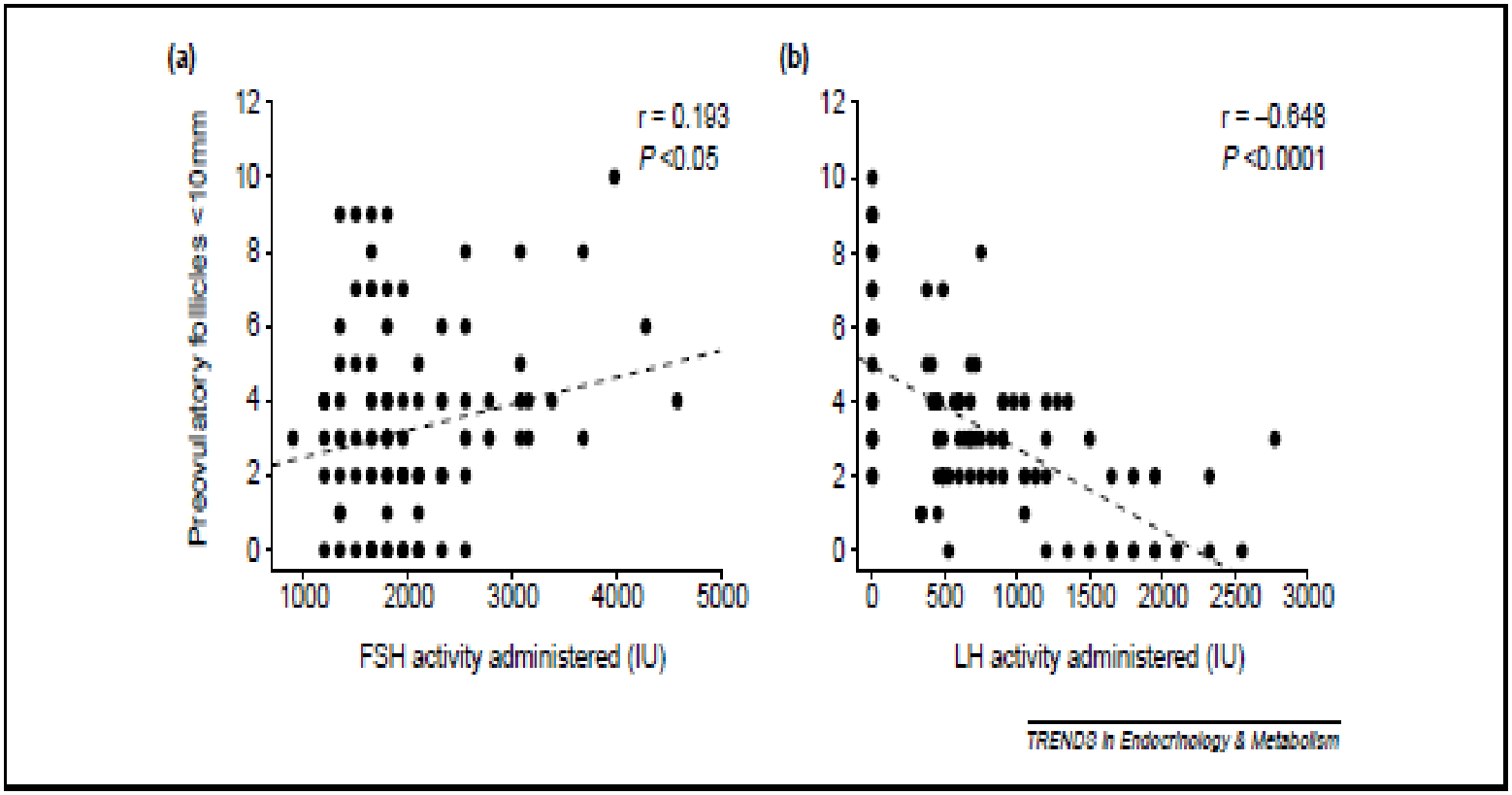


Fig. 2. Correlation between the number of small preovulatory follicles (< 10 mm diameter) and the total amounts of (a) follicle-stimulating hormone (FSH) and (b) luteinizing hormone (LH) activity administered to each patient. Reproduced, with permission, from [89].

LUTEINISING HORMONE (LH)

- Within the interval of LH treshold and ceiling, LH support is adequate for androgen and subsequent estradiol secretion thus participating in folllicular growth

LUTEINISING HORMONE (LH)

- Determining plasma LH levels is not very informative to evaluate the actual consequences of LH preparations

- During stimulated cycles plasma LH level determination is restricted to detection of endogenous LH surge

Filicori et al, Trends Endocrinol Metab 2003 Aug;14(6):267-73

Filicori et al, Hum Reprod Update 2002;8(6):543-557

Human Reproduction Update, Vol.8, No.6 pp. 543–557, 2002

The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction

Marco Filicori[1,3], Graciela E.Cognigni[1], Arafat Samara[1], Silvia Melappioni[1], Tiziana Perri[1], Barbara Cantelli[1], Lodovico Parmegiani[1], Giuseppe Pelusi[2] and Domenico DeAloysio[2]

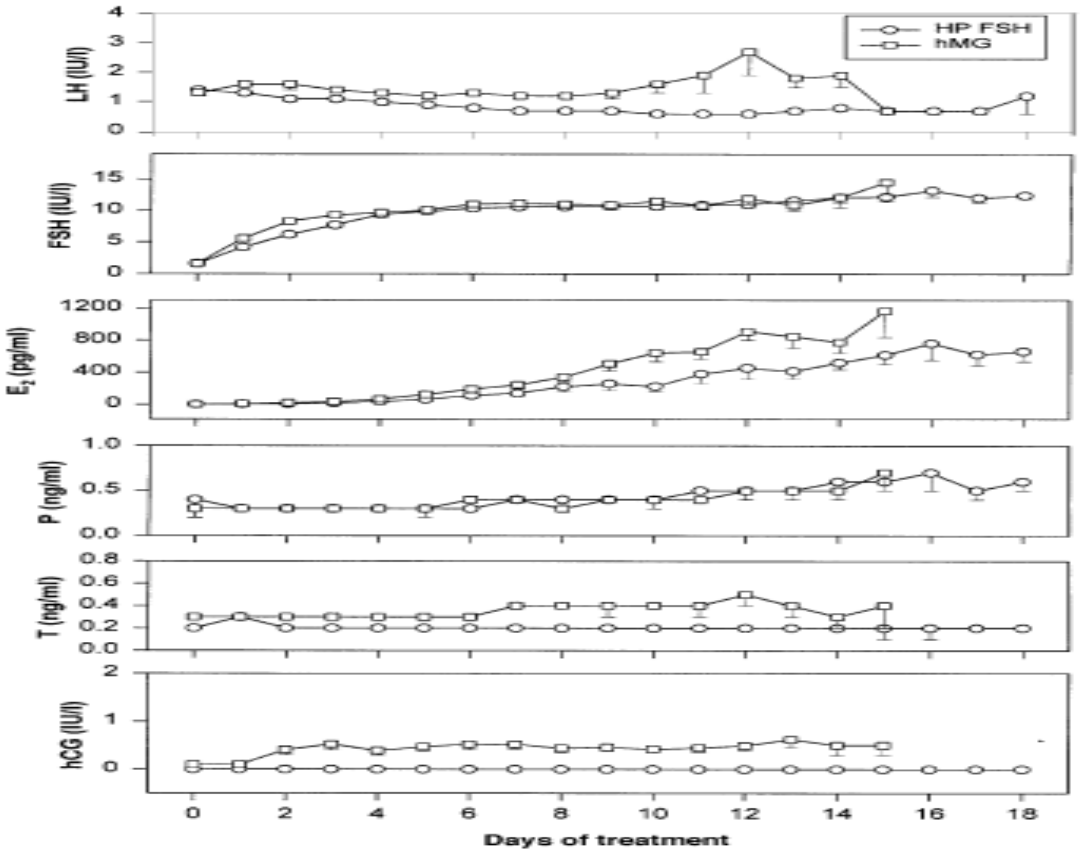


Figure 1. Serum gonadotropin and gonadal steroid levels in two groups of 25 patients, each treated with either HP FSH or hMG for controlled ovarian stimulation. All patients had been suppressed with a long GnRH agonist regimen. E_2 = estradiol; P = progesterone; T = testosterone. Reproduced with permission The Endocrine Society; Filicori, M., Cognigni, G.E., Taraborrelli, S., Spettoli, D., Ciampaglia, W., Tabarelli De Fatis, C., Pocognoli, P., Cantelli, B. and Boschi, S. (2001) Luteinizing hormone activity in menotropins optimizes folliculogenesis and treatment in controlled ovarian stimulation. *J. Clin. Endocrinol. Metab.*, **86**, 337–343. Copyright owner, The Endocrine Society.

RBM Online - Vol 18 Suppl.2 2009 31-36 Reproductive BioMedicine Online; www.rbmonline.com/Article/3784 on web 16 December 2008

Article

Benefits of luteinizing hormone activity in ovarian stimulation for IVF

Coomarasamy et al, 2008

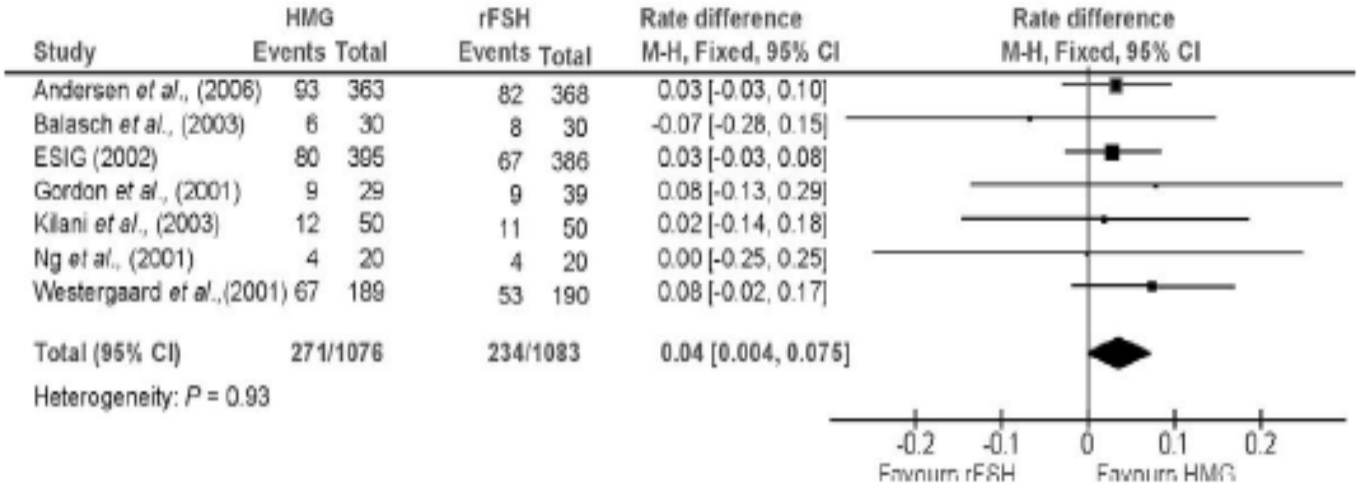


Figure 1. Rate difference in live births between patients stimulated with human menopausal gonadotrophin (HMG) and patients stimulated with recombinant FSH (rFSH) using a long gonadotrophin-releasing hormone agonist protocol (based on data from Coomarasamy *et al.*, 2008, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology). CI = confidence interval; EISG = European and Israeli Study Group on highly purified menotropin versus recombinant follicle-stimulating hormone.

Tarlatzis et al, RBM Online 2009

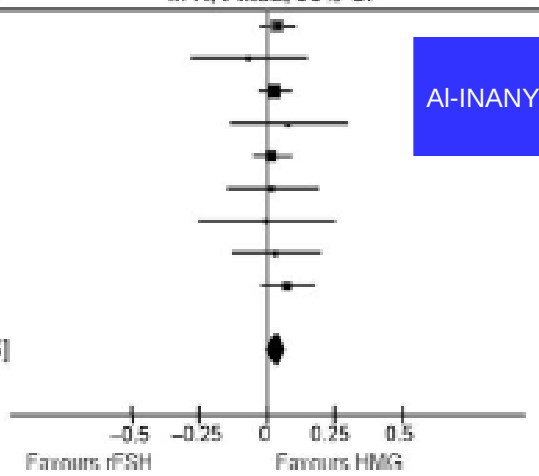
RBM Online - Vol 18 Suppl.2 2009 31-36 Reproductive BioMedicine Online; www.rbmonline.com/Article/3784 on web 16 December 2008

Article

Benefits of luteinizing hormone activity in ovarian stimulation for IVF

Study	HMG Events	HMG Total	rFSH Events	rFSH Total	Rate difference M-H, Fixed, 95% CI
Andersen *et al.* (2006)	96	363	82	368	0.04 [-0.02, 0.10]
Balasch *et al.* (2003)	6	30	8	30	-0.07 [-0.28, 0.15]
EISG (2002)	80	395	67	366	0.03 [-0.03, 0.08]
Gordon *et al.* (2001)	9	29	9	39	0.08 [-0.13, 0.29]
Hompes *et al.* (2006)	79	312	75	317	0.02 [-0.05, 0.08]
Kilani *et al.* (2003)	12	50	11	50	0.02 [-0.14, 0.18]
Ng *et al.* (2001)	4	20	4	20	0.00 [-0.25, 0.25]
Rashidi *et al.* (2005)	4	30	3	30	0.03 [-0.13, 0.20]
Westergaard *et al.* (2001)	67	189	53	190	0.08 [-0.02, 0.17]
Total (95% CI)	357/1418		312/1430		0.034 [0.003, 0.065]

Heterogeneity: $P = 0.97$



Al-INANY et al, 2008

Figure 2. Rate difference in live births between patients stimulated with human menopausal gonadotrophin (HMG) and patients stimulated with recombinant FSH (rFSH) using a long gonadotrophin-releasing hormone agonist protocol (based on data from Al-Inany *et al.*, 2008). CI = confidence interval; EISG = European and Israeli Study Group on highly purified menotropin versus recombinant follicle-stimulating hormone.

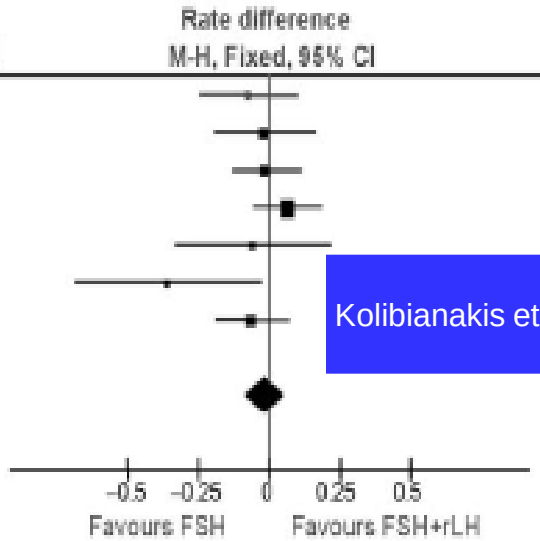
Tarlatzis et al, RBM Online 2009

RBM Online - Vol 18 Suppl.2 2009 31-36 Reproductive BioMedicine Online; www.rbmonline.com/Article/3784 on web 16 December 2008

Article

Benefits of luteinizing hormone activity in ovarian stimulation for IVF

Study	FSH+LH Events	FSH+LH Total	FSH Events	FSH Total	Rate difference M-H, Fixed, 95% CI
Balasch *et al.* (2001)	0	16	1	14	-0.07 [-0.24, 0.10]
Fabregues *et al.* (2006)	24	60	25	60	-0.02 [-0.19, 0.16]
Griesinger *et al.* (2005)	8	62	9	65	-0.01 [-0.13, 0.11]
Humaidan *et al.* (2004)	39	116	31	115	0.07 [-0.05, 0.18]
Sauer *et al.* (2004)	9	25	10	24	-0.06 [-0.33, 0.22]
Sills *et al.* (1999)	3	13	10	17	-0.36 [-0.68, -0.03]
Tarlatzis *et al.* (2006)	6	55	10	59	-0.06 [-0.19, 0.07]
Total (95% CI)	89/347		96/354		-0.01 [-0.08, 0.05]
Heterogeneity: $P = 0.32$					



Kolibianakis et al, 2007

Figure 3. Rate difference in live births between patients stimulated with FSH+LH and patients stimulated with FSH only (based on data from Kolibianakis *et al.*, 2007, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology). CI = confidence interval.

Tarlatzis et al, RBM Online 2009

RBM Online - Vol 18 Suppl.2 2009 37-43 Reproductive BioMedicine Online; www.rbmonline.com/Article/3779 on web 19 November 2008

Article

Role of the endocrine profile for the achievement of pregnancy with IVF

Table 2. Association of endogenous LH concentrations and the probability of ongoing pregnancy above 12 weeks in normo-ovulatory or World Health Organization II patients undergoing IVF using gonadotrophin-releasing hormone analogues for inhibition of premature LH surge.

	Endogenous LH concentrations (IU/l)			
Westergaard *et al.*, 2000	Day 8 of stimulation			
	<0.5	>0.5		
Patients/cycles (mean age in years, range)	98 (32.9, 24–40)	102 (32.2, 24–39)		
Delivery (%)	15 (15.3)	27 (26.5)		
Balasch *et al.*, 2001[a]	Day 7 of stimulation			
Patients/cycles (mean age in years, range)	144 (34.0, 23–42)			
Ongoing pregnancy (20 weeks) (%)	58 (40.3)			
Esposito *et al.*, 2001	Average of 4–5 assessments starting from day 5 of stimulation			
	<3	≥3		
Patients/cycles (mean age in years)	116 (34.4)	50 (34.3)		
Ongoing pregnancy (20 weeks) (%)	40 (34.5)	16 (32.0)		
Humaidan *et al.*, 2002	Day 8 of stimulation			
	<0.5	0.6–1.0	1.1–1.5	≥1.5
Patients/cycles (mean age in years ± SEM)	24 (31.4 ± 0.6)	108 (30.9 ± 0.4)	38 (30.4 ± 0.5)	37 (29.8 ± 0.6)
Ongoing pregnancy (12 weeks) (%)	8 (33.3)	48 (44.4)	17 (44.7)	9 (24.3)
Merviel *et al.*, 2004	Day of HCG			
	<0.5	>0.5		
Patients/cycles (mean age in years ± SD)	119 (33.7 ± 9)	151 (33.6 ± 4.7)		
Delivery (%)	17 (14.3)	19 (12.6)		
Kolibianakis *et al.*, 2004	Day 8 of stimulation			
	<0.5	0.6–1.9	≥1.9	
Patients/cycles (mean age in years ± SEM)	25 (31.8 ± 0.6)	62 (32.1 ± 0.4)	29 (32.7 ± 0.7)	
Ongoing pregnancy (12 weeks) (%)	14 (56.0)	25 (40.3)	7 (24.1)	

Differences between groups are not significant with the exception of Kolibianakis *et al.* 2004b (modified from Kolibianakis *et al.* 2006, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology). HCG = human chorionic gonadotrophin.
[a]Receiver operating characteristic curve analysis found no correlation between LH concentration and conception.

Humaidan and Kolibianakis →↑LH is associated with ↓ ongoing pregnancy rates

Kolibianakis et al, Reprod Biomed Online 2009

STEROID PROFILES THROUGH ART CYCLES ESTRADIOL

- Cervical mucus production, endometrial proliferation and the induction of midcycle LH surge

  Maclon &Fauser, Hum Reprod Update 2000;6(4):307-12

- A good indicator of granulosa cell differentiation and used as an index of follicular maturity

  Stouffer & Zelinski-Wooten, Reprod Biol Endocrinol 2004;16;2:32

- Ovarian response prediction

  Loutradis et al, J Steroid Biochem Mol Biol 2008 Nov;112(1-3):1-4

STEROID PROFILES THROUGH ART CYCLES ESTRADIOL

- To calibrate the gonadotropin doses in conjunction with USG data in stimulated cycles

- Monitorization of the ART cycle in order to detect the risk of OHSS and decide for cycle or transfer cancellation

ESTRADIOL-GnRHa-GNRH ANTAGONISTS

- To assess the effectiveness of the hypophyseal desensitization (<50pg/mL)

- The plasma estradiol pattern of GnRH antagonist treatment is not similar with that of GnRH-a

  (LOWER PREGNANCY RATES)

RBM Online - Vol 18 Suppl.2 2009 37-43 Reproductive BioMedicine Online; www.rbmonline.com/Article/3779 on web 19 November 2008

Article

Role of the endocrine profile for the achievement of pregnancy with IVF

Table 1. Characteristics of the studies that evaluated the association between oestradiol and pregnancy achievement (modified from Kosmas *et al*. 2004, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology).

Study, year	*Sample size (patients/ cycles)*	*Type of down-regulation*	*Gonado-trophin regimen*	*Method of oestradiol assessment*	*Primary outcome*	*Type of association between oestradiol concentrations on the day of HCG administration and pregnancy achievement*
Mettler and Tavmergen, 1989	94/94	Decapeptyl long protocol	HMG	Radioimmunoassays—monoclonal-antibody technique (oestradiol Biermann, Bad Nauheim)	Pregnancy rate[b] per oocyte retrieval	No association
Chenette *et al*., 1990	141/141	Leuprolide acetate long protocol	HMG	Radioimmunoassays (Tandem, Hybritech, San Diego, CA, USA)	Clinical pregnancy per oocyte retrieval	Positive
Dor *et al*., 1992	[a]/216	Decapeptyl long protocol	HMG	Radioimmunoassays (Diagnostic Products Corp., Los Angeles, CA, USA)	Clinical pregnancy rate per oocyte retrieval	No association
Gelety and Buyalos, 1995	50/50	Leuprolide acetate long protocol	HMG	Radioimmunoassays (Pantex, Santa Monica, CA, USA)	Clinical pregnancy rate per embryo transfer	Positive
Simon *et al*., 1995	164/177	Leuprolide acetate long protocol	FSH + HMG	Immuno-enzymatic assay (MEIA; Imx. Abbott Scientific SA)	Pregnancy rate per cycle started	Negative
Sharara and McClamrock, 1999	106/106	Leuprolide acetate long/short protocol	FSH + HMG	Radioimmunoassays (Coat-a-Count Diagnostic Products Corporation, Los Angeles, CA, USA)	Clinical pregnancy per oocyte retrieval	No association
Yu Ng *et al*., 2000	1122/1122	Buserelin long protocol	HMG	Not mentioned (Diagnostic Products Corp., Los Angeles, CA, USA)	Clinical pregnancy rate per embryo transfer	Negative
Papageorgiou *et al*., 2002	762/905	Decapeptyl short protocol	rFSH (follitropin α/β)	Immuno-enzymatic assay (Bayer, Germany)	Pregnancy rate[b]	No association
Chen *et al*., 2003	697/697	Leuprolide acetate long protocol	FSH	Not mentioned	Clinical pregnancy per embryo transfer	No association

Kolibianakis et al, Reprod Biomed Online 2009

STEROID PROFILES THROUGH ART CYCLES PROGESTERONE

- To detect the hypophyseal desensitization to make sure that the corpus luteum is not still active

- Plasma P levels in early and late follicular phases are recently assessed to predict the cycle outcome

STEROID PROFILES THROUGH ART CYCLES PROGESTERONE

- Adverse effect on folliculogenesis, oocyte quality and pregnancy outcome (early follicular phase)
- Despite supression by GnRH-a, a small increment in P has been reported in 20% of the stimulated cycles (late follicular phase, endometrium)
- Premature endogenous LH surges related with subsequent luteinization of granulosa cells

Review TRENDS in Endocrinology and Metabolism Vol. 14 No. 6 August 2003 267

Current concepts and novel applications of LH activity in ovarian stimulation

Marco Filicori, Graciela E. Cognigni, Patrizia Pocognoli, Walter Ciampaglia and Silvia Bernardi

Reproductive Endocrinology Center, University of Bologna, Via Massarenti 13, 40138 Bologna, Italy

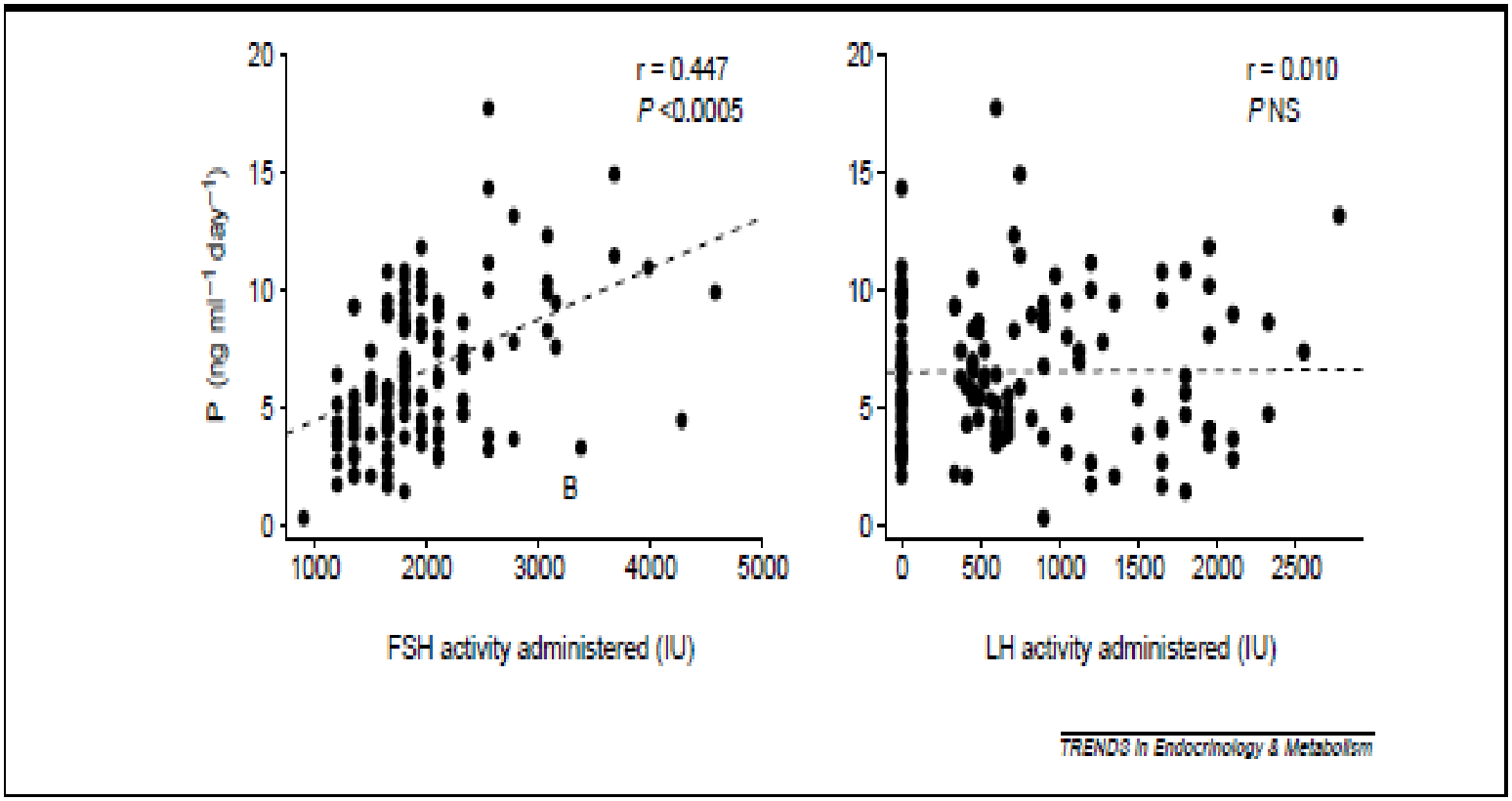


Fig. 1. Correlation between serum progesterone (P) levels during ovulation induction and the total amounts of (a) follicle-stimulating hormone (FSH) activity and (b) luteinizing hormone (LH) activity administered to each patient. P levels were determined daily throughout gonadotropin administration in each patient and expressed as area under the curve. Reproduced, with permission, from [69].

PROGESTERONE RISE IN FOLLICULAR PHASE

- P450 side-chain cleavage enzyme is required for de novo P synthesis

CL, THECA INTERNA CELLS OF THE FOLLICLE, ADRENAL GLAND

Residual activity of CL, developing follicle, adrenal gland activity, indirect sign of ovarian aging, different FSH isoforms

Al-Azemi et al, Reprod Biomed Online 2012 Apr;24(4):381-8

STEROID PROFILES THROUGH ART CYCLES PROGESTERONE

- *EXPOSURE TO LARGE DOSES OF EXOGENOUS FSH*

- Potential adverse effect and plasma P cut off values for a decision making for the cycle outcome

De Ziegler et al, J Assist Reprod Genet 2003 Jan;20(1):29-32
Venetis et al, Hum Reprod Update 2007Jul-Aug;13(4):343-55

Human Reproduction Update, Vol.13, No.4 pp. 343–355, 2007
Advance Access publication April 3, 2007
doi:10.1093/humupd/dmm007

Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in *in vitro* fertilization? A systematic review and meta-analysis

C.A.Venetis[1], E.M.Kolibianakis[1,3], E.Papanikolaou[1], J.Bontis[1], P.Devroey[2] and B.C.Tarlatzis[1]

Table 3: Pregnancy outcomes examined in the studies included in the systematic review

Study number	Authors and year	Pregnancy outcome examined[a]	Definition	OR (CIs)	Association of progesterone elevation with pregnancy outcome examined
1	Edelstein *et al.* (1990)	Clinical pregnancy per hCG	Not reported	1.09 (0.43–2.79)	No association
		Ongoing pregnancy per hCG	Not reported	1.03 (0.38–2.83)	No association
2	Silverberg *et al.* (1991)	Clinical pregnancy per hCG	FH by USS at 7 wks of gestation	0.16 (0.01–2.86)	No association
3	Check *et al.* (1993a)	Live birth per oocyte retrieval	Live birth	0.18 (0.06–0.51)	Negative association
4	Check *et al.* (1994)	Live birth per oocyte retrieval	Viable infant at delivery	0.46 (0.15–1.43)	No association
5	Shechter *et al.* (1994)	Clinical pregnancy per ET	Sac at USS	1.22 (0.47–3.16)	No association
6	Hofmann *et al.* (1996)	Ongoing pregnancy per ET	>20 wks/delivered	1.48 (0.69–3.19)	No association
7	Miller *et al.* (1996) (Group A)[b]	Clinical pregnancy per ET	FH by USS at 7 wks of gestation	0.44 (0.16–1.18)	No association
	Miller *et al.* (1996) (Group B)[b]	Clinical pregnancy per ET	FH by USS at 7 wks of gestation	1.03 (0.53–2.00)	No association
8	Ubaldi *et al.* (1996b)	Clinical pregnancy per hCG	FH by USS at 7 wks of gestation	1.87 (0.24–14.65)	No association
9	Moffitt *et al.* 1997	Clinical pregnancy per ET	Not reported	1.16 (0.59–2.28)	No association
		Ongoing pregnancy per ET	>20 wks	1.65 (0.84–3.25)	No association
10	Urman *et al.* (1999)	Clinical pregnancy per ET	FH by USS at 6 wks of gestation	1.42 (1.07–1.88)	Positive association
		Ongoing pregnancy per ET	>12 wks	1.27 (0.94–1.72)	No association
11	Bosch *et al.* (2003)	Clinical pregnancy per hCG	FH by USS at 6–7 wks of gestation	0.27 (0.10–0.72)	Negative association
		Ongoing pregnancy per hCG	>20 wks	0.29 (0.11–0.79)	Negative association
12	Martinez *et al.* (2004)	Clinical pregnancy per hCG	Sac at USS at 6 wks of gestation	0.89 (0.58–1.35)	No association
		Delivery per hCG	Delivery	0.98 (0.62–1.55)	No association

Human Reproduction Update, Vol.13, No.4 pp. 343–355, 2007
Advance Access publication April 3, 2007
doi:10.1093/humupd/dmm007

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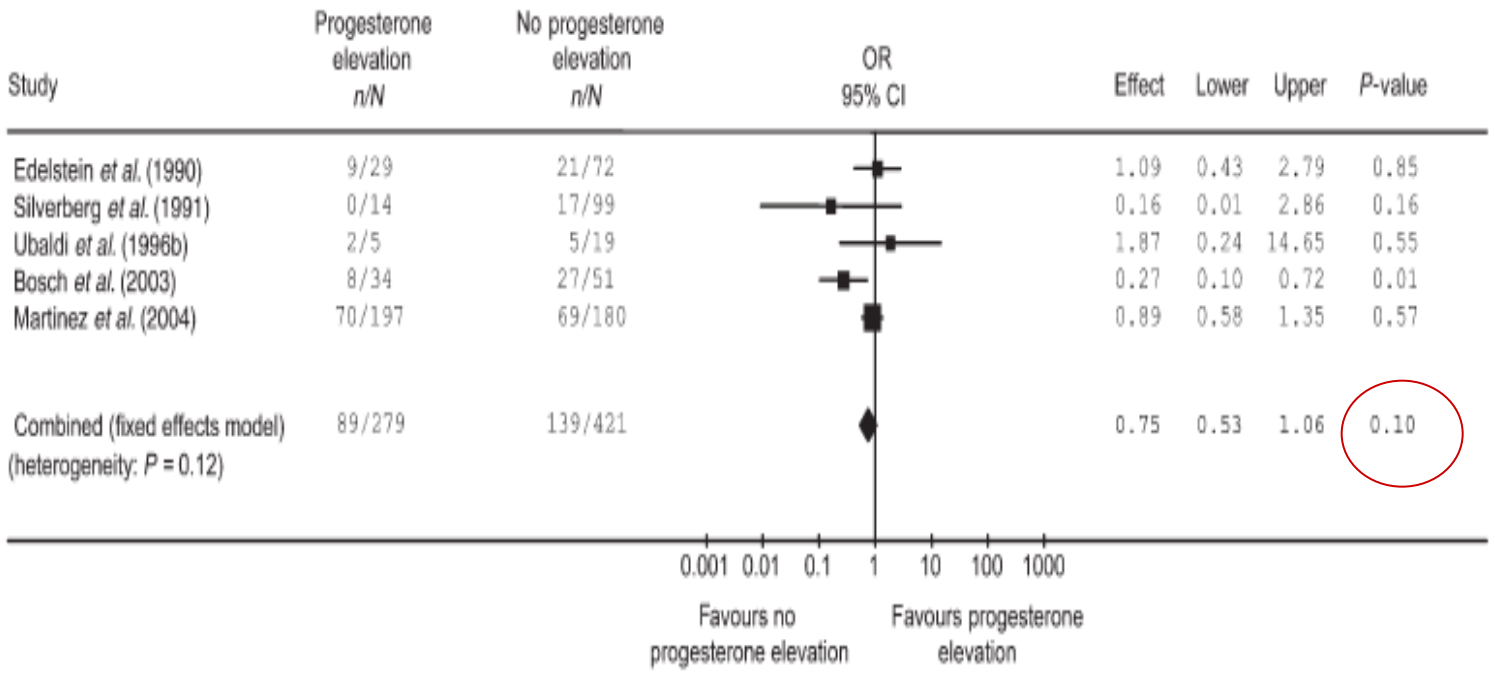


Figure 2: OR of clinical pregnancy rate per patient reaching hCG administration for final oocyte maturation

RBM Online - Vol 18 Suppl.2 2009 37-43 Reproductive BioMedicine Online; www.rbmonline.com/Article/3779 on web 19 November 2008

Article

Role of the endocrine profile for the achievement of pregnancy with IVF

Study or Subgroup	P Elevation Events	Total	No P Elevation Events	Total	Weight	Risk Ratio M–H, Fixed, 95% CI
Bosch 2003	8	34	27	51	19.2%	0.44 [0.23, 0.86]
Edelstein 1990	9	29	21	72	10.7%	1.06 [0.55, 2.04]
Martinez 2004	70	197	69	180	64.1%	0.93 [0.71, 1.21]
Silverberg 1991	0	14	17	99	4.1%	0.19 [0.01, 3.00]
Ubaldi 1996	2	5	5	19	19.%	1.52 [0.41, 5.64]
Total (95% CI)		**279**		**421**	**100.0%**	**0.83 [0.66, 1.04]**
Total events	89		139			

Heterogeneity: $Chi^2 = 6.60$, df = 4 (P = 0.16); $I^2 = 39\%$

Test for overall effect: Z = 1.62 (P = 0.11)

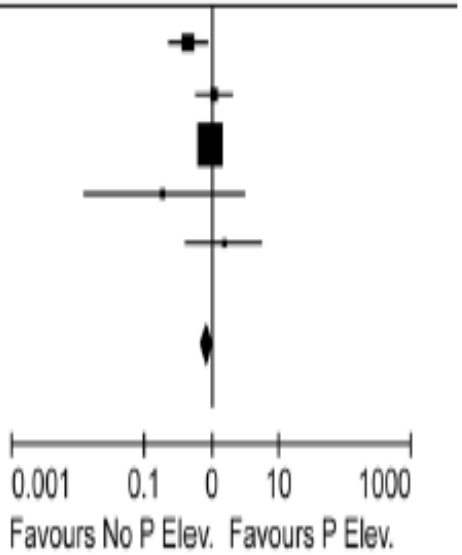


Figure 1. Relative risk for clinical pregnancy per patient reaching human chorionic gonadotrophin administration for final oocyte maturation according to the presence of progesterone (P) elevation. CI = confidence interval.

Kolibianakis et al, Reprod Biomed Online 2009

ANDROGENS

- A stimulatory effect on granulosa cell proliferation, follicular recruitment

  Vendola et al, L Clin Invest 1998;101:2622-9

- Flare-up effect may be related with increased androgen production in ART cycles

- No significant evidence that the oocyte quality is reduced

  San Roman GA et al, Fertil Steril 1992;58:744-9

REVIEW Open Access

The role of androgens in follicle maturation and ovulation induction: friend or foe of infertility treatment?

Norbert Gleicher[1,2,3*], Andrea Weghofer[1,4] and David H Barad[1,2,5]

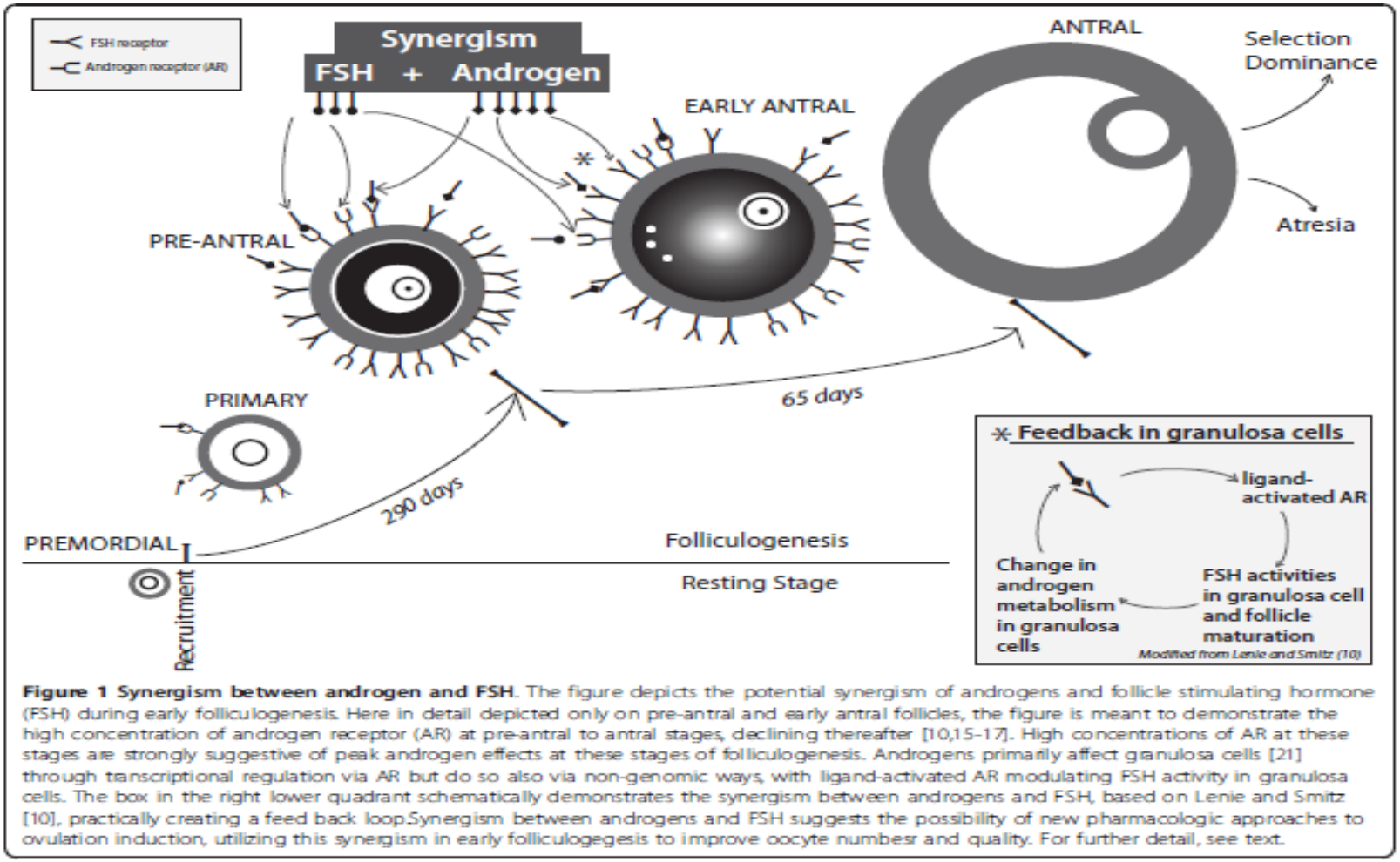


Figure 1 Synergism between androgen and FSH. The figure depicts the potential synergism of androgens and follicle stimulating hormone (FSH) during early folliculogenesis. Here in detail depicted only on pre-antral and early antral follicles, the figure is meant to demonstrate the high concentration of androgen receptor (AR) at pre-antral to antral stages, declining thereafter [10,15-17]. High concentrations of AR at these stages are strongly suggestive of peak androgen effects at these stages of folliculogenesis. Androgens primarily affect granulosa cells [21] through transcriptional regulation via AR but do so also via non-genomic ways, with ligand-activated AR modulating FSH activity in granulosa cells. The box in the right lower quadrant schematically demonstrates the synergism between androgens and FSH, based on Lenie and Smitz [10], practically creating a feed back loop.Synergism between androgens and FSH suggests the possibility of new pharmacologic approaches to ovulation induction, utilizing this synergism in early folliculogegesis to improve oocyte numbesr and quality. For further detail, see text.

ANDROGENS

- Determination of plasma androgens is not required to be routinely included in monitorization of ART cycles, may be worthwhile in clinical research

Gardner DK, Weissman A, Howles CM, Shoham Z. Textbook of Assisted Reproductive Technologies. Laboratory and Clinical perpectives. 3. Edition, Volume 2,2009

INHIBIN A AND B

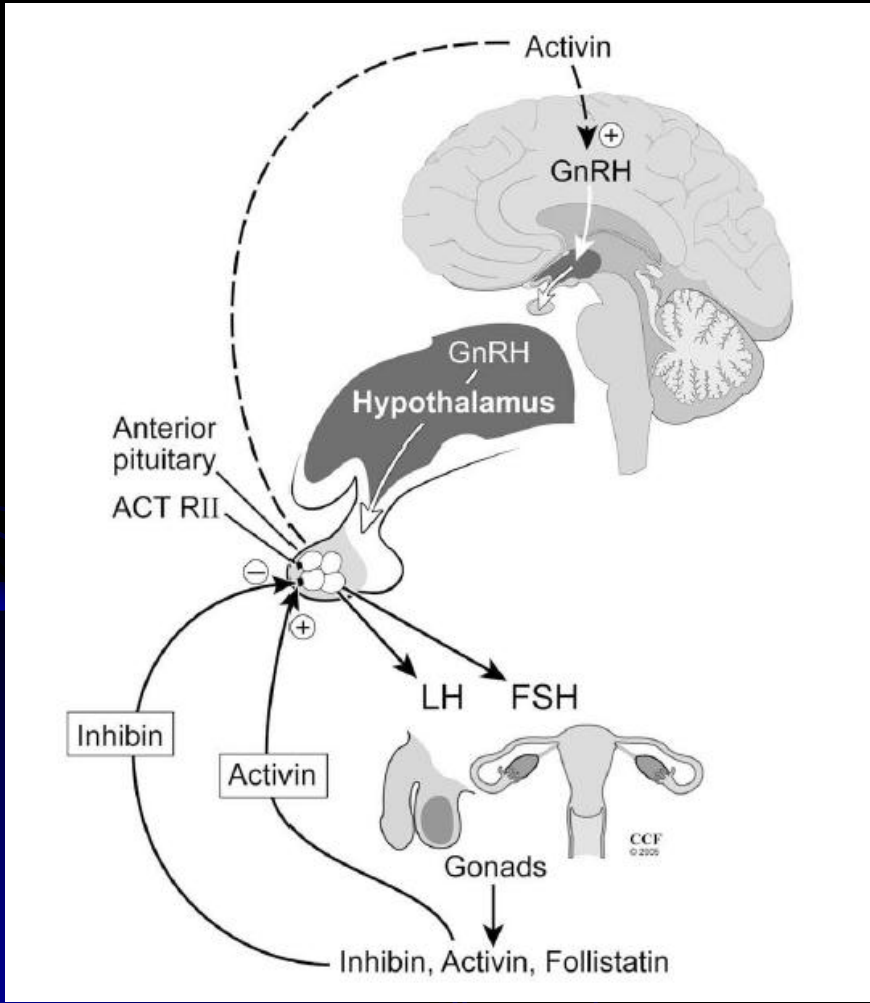
- Heterodimers secreted from granulosa cells following FSH stimulation and regulate FSH secretion by negative feedback
- Small antral follicles potentially secrete Inhibin B whereas preovulatory follicles may secrete Inhibin A
- Serum Inhibin B in the early follicular phase is a valuable tool to evaluate the size of the follicular cohort

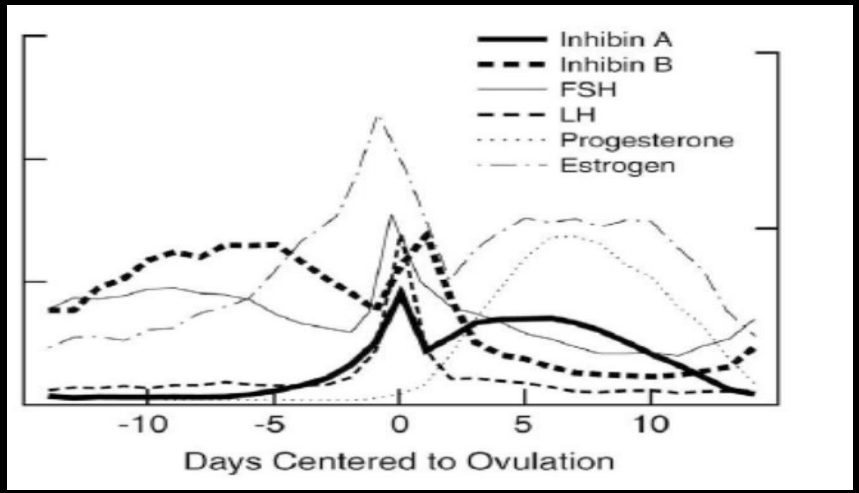
Kumanov et al, Reprod Biomed Online 2005 Jun;10(6):786-812

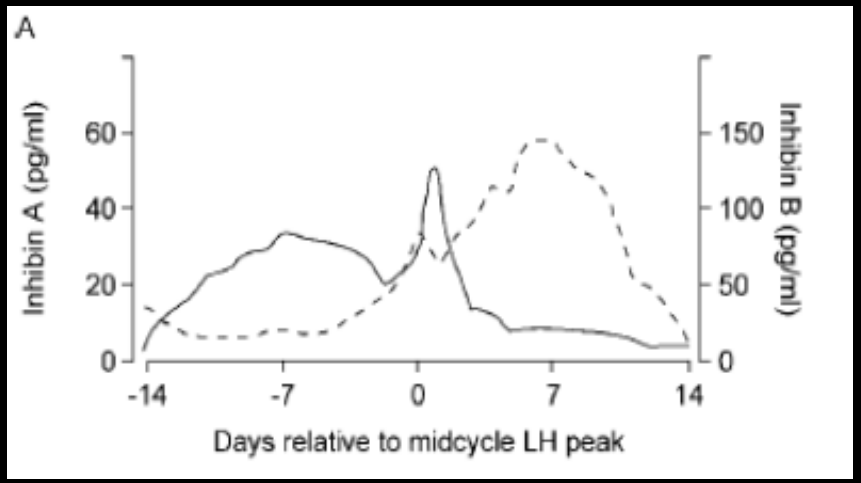
RBM Online - Vol 10. No 6. 2005 786–796 Reproductive BioMedicine Online; www.rbmonline.com/Article/1704 on web 29 March 2005

Review

Significance of inhibin in reproductive pathophysiology and current clinical applications







Kumanov et al, 2005

INHIBIN A AND B

- Inhibin B (4-6. day of FSH stimulation)- Early indicator of the number of recruited follicles destined to form mature oocytes

Pennarubia et al, Hum Reprod 2000;15:1499-1504

- Decision making regarding cycle cancellation or modulating gonadotropin dose

Eldar-Geva et al, Hum Reprod 2002 Sep;17(9):2331-7

Engel et al, Reprod Biomed Online 2001;3:104-108

ANTİMÜLLERIAN HORMONE

- A member of transforming growth factor beta family produced by granulosa cells of secondary, preantral, small antral follicles upto 6 mm

- Serum AMH levels are correlated with antral follicle numbers and cycle day independent

Broer SL et al, Fertil Steril 2008

La Marca et al, Hum Reprod 2006 Dec;21(12):3103-7

- A good predictor of ovarian reserve both for poor and hyperresponders

La Marca et al, Hum Reprod 2007 Mar;22(3):766-71

ANTİMÜLLERIAN HORMONE

- Its performance to predict nonpregnancy is poor since it represents only the size of the FSH-sensitive follicles

Muttukrishina et al, BJOG 2005,112:1384
Ebner et al, Hum Reprod 2006;21:2022-6
Kwee et al, Fertil Steril 2007

- The association with oocyte or embryo quality is much less clear

- *Plasma AMH measurement during stimulated cycles is not actually recommended*

CONCLUSIONS

- The endocrine characteristics of ART cycles are mainly related with the therapeutic agents used for COH
- Although it is clear that FSH is required for every stimulation, plasma FSH levels are not predictive enough for the adequacy of exogenous FSH supply
- Plasma LH levels determination is restricted to hypophyseal desensitization

CONCLUSIONS

- There is no evidence that detection of LH levels could be useful for patients who require some addition of LH during ART cycles
- Plasma estradiol level determination is used in conjunction to USG to assess the follicular growth
- Determination of P levels may be restricted to hypophyseal desensitization

CONCLUSIONS

- Plasma androgens are not routinely determined except research purposes
- Serum Inhibin B in the early follicular phase is a valuable tool to evaluate the size of the follicular cohort
- AMH is a good predictor of ovarian reserve both for poor and hyperresponders