Reproduction and ovarian failure

Profesor Aleksandar Ljubić
DIU Libertas
Medigroup Serbia

Reproduction and ovarian failure

- Definition
- Etiology
- Therapy
  - Pretreatment
  - Stimulation protocols
  - Novel therapies

Definitions, incidence

Premature ovarian failure (POF) - 1-3%

A syndrome, characterised by the cessation of ovarian function before the age of 40 years with associated elevated gonadotropin levels (FSH ! 40 mIU/ ml),

It comprises a triad of amenorrhoea, hypergonadotropinism, and hypoestrogenism.

Premature ovarian insufficiency (POI) .

Premature ovarian senescence (POS) - 10%

Premature ovarian aging (POA),

Occult primary ovarian insufficiency (OPOI),

Low ovarian response - 9 to 24%

  - 500 pg/l peak estradiol levels and/or < 4-5 dominant follicles on day of hCG, < 3 number of embryos

- Perimenopausis
- Postmenopausis

Etiology

a. Genetic factors.

b. Autoimmunity.

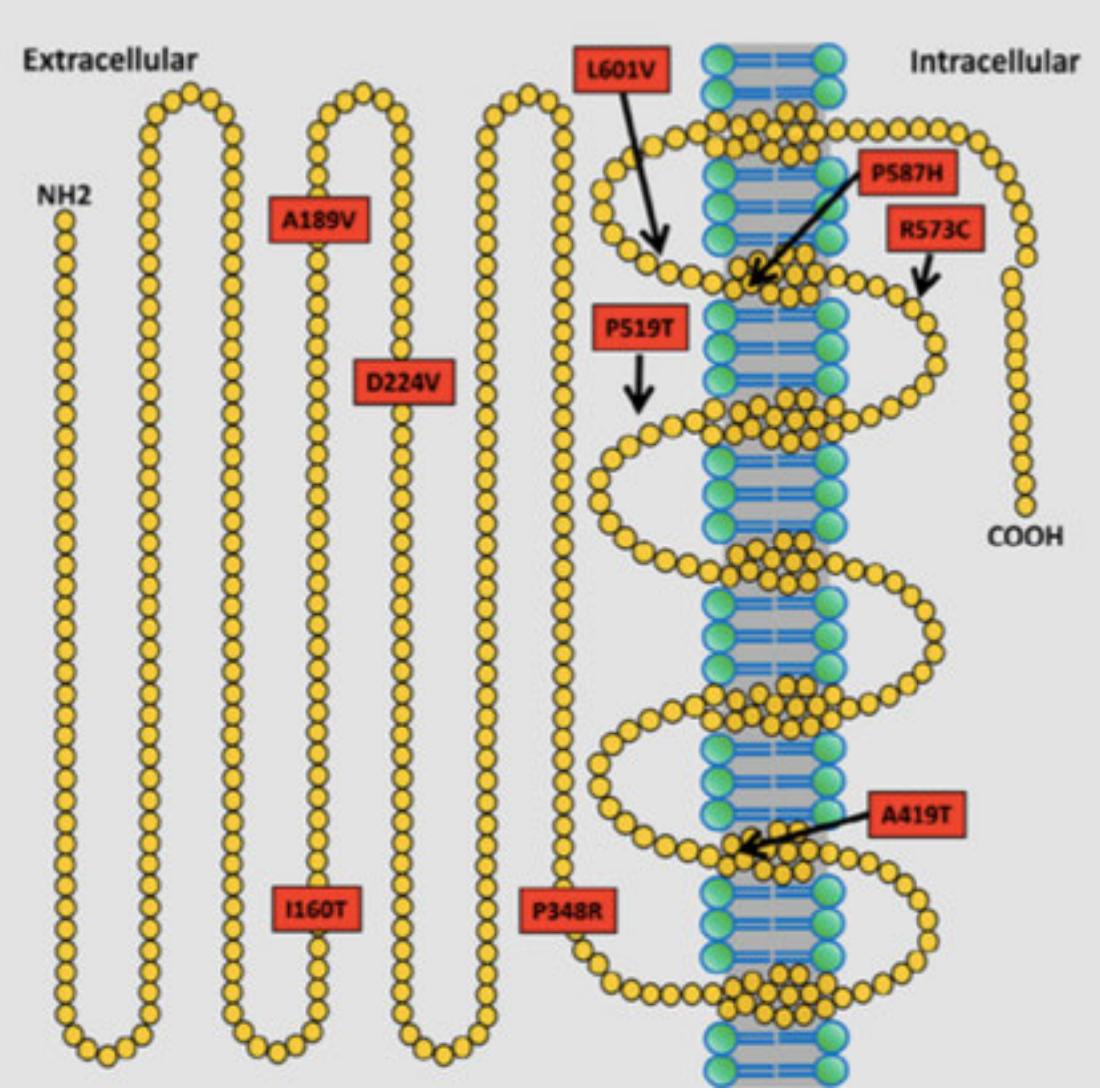
c. Egzogenic factors

d. Jatrogenic procedures.

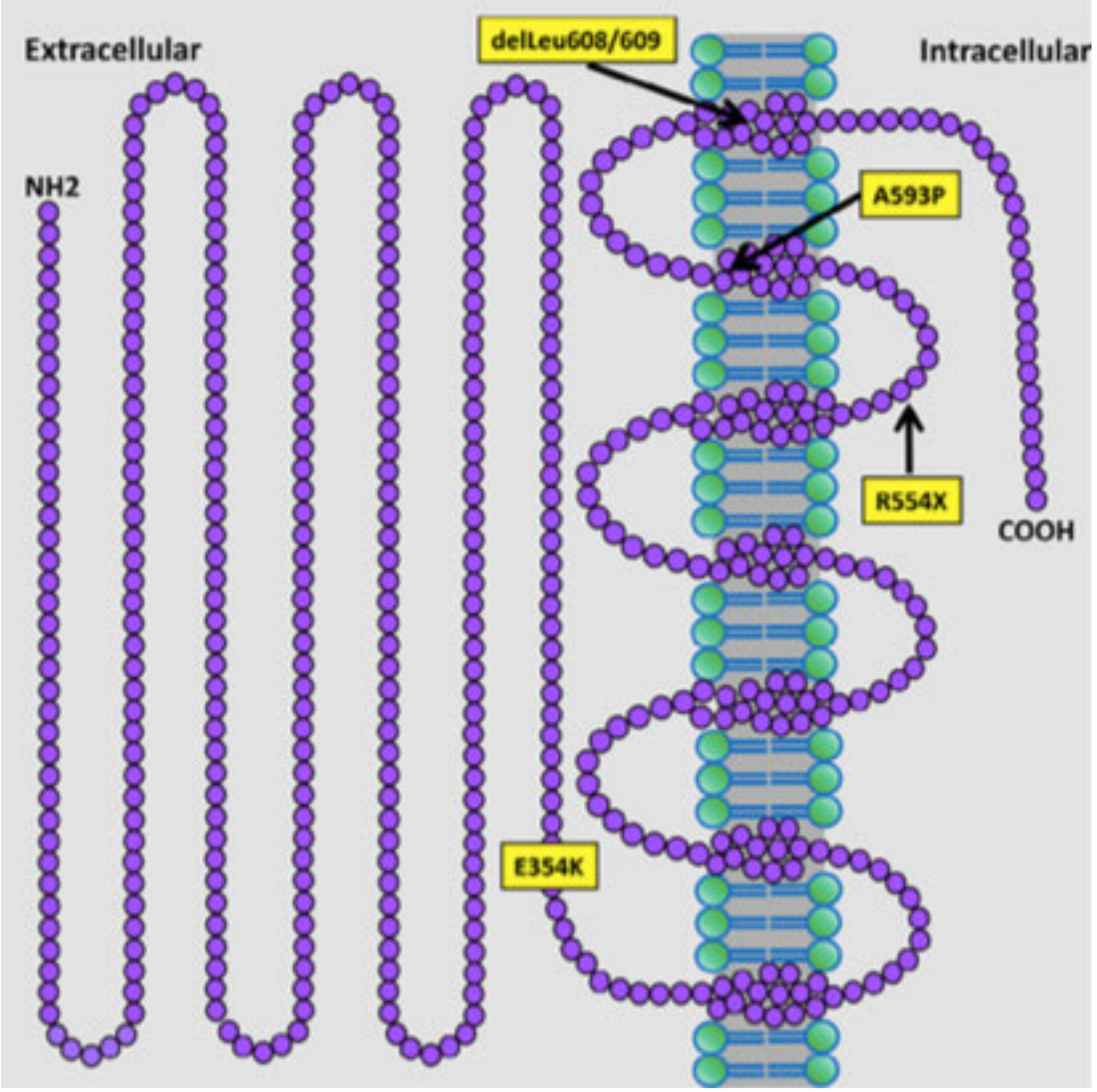
Gleicher et al. Reproductive Biology and Endocrinology (2015) 13:34

Medical history	In association with
Conditions associated with low numbers of follicles at birth/menarche	Turner syndrome – associated with POF/POI
	Idiopathic/genetics – association?
Excessive recruitment	*FMR1* mutations
	Premutation range ($CGG_{n=55-200}$) – associated with POF/POI
	Monoalleleic *low* sub-genotype – associated with POA/OPOI
	Biallelic *low* sub-genotype – associated with POA/OPOI
	AMHR2 gene – associated with POF/POI
	AIRE gene – associated with POF/POI
Other genetic causes	*BRCA1* mutations – associated with POA/OPOI
Space occupying lesions and Iatrogenic factors -mostly associated with POF/POI but also with POA/OPOI	Ovarian surgery
	Chemotherapy
	Radiation therapy
	Bone marrow transplantation
Other medical risk factors	Endometriosis – associated with POA/OPOI
	Polycystic ovarian syndrome (PCOS) – associated with POA/OPOI
	>>> > in association with *low FMR1* mutations and risk further augmented in presence of autoimmunity
Autoimmunity –mostly associated with POA/OPOI but also with POF/POI	Thyroid autoimmunity
	Adrenal autoimmunity
	Any other autoimmunity
	Autoimmune polyglandular syndromes
	Family history of autoimmune disease*
	History of repeated pregnancy loss
Early history of maternal/ sibling menopause	

FSHR and LHCGR mutations causative of non-syndromic POF.



FSHR



LHCGR

P. Laissue/Molecular and Cellular Endocrinology 411 (2015) 243–257

Nuclear receptor subfamily 5 group A member 1 (NRA5A) - Steroidogenic factor 1

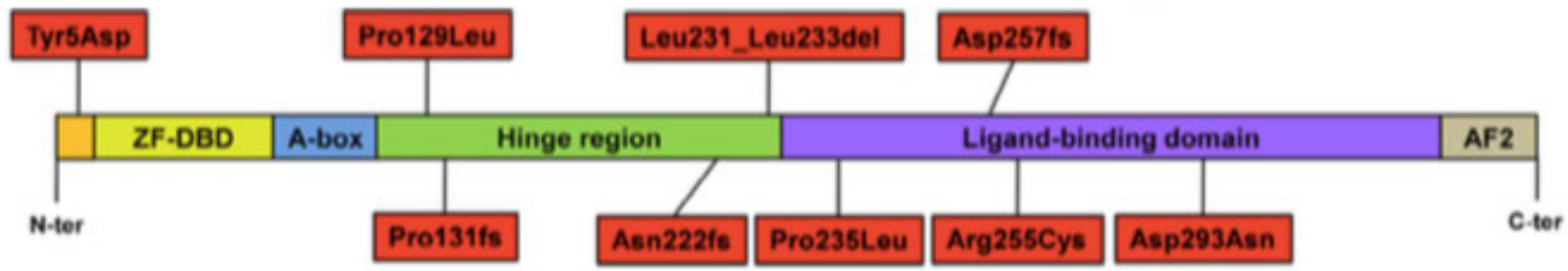


Fig. 3. NRA5A1 mutations causative of non-syndromic POF.

Newborn ovary homeobox (NOBOX) gene

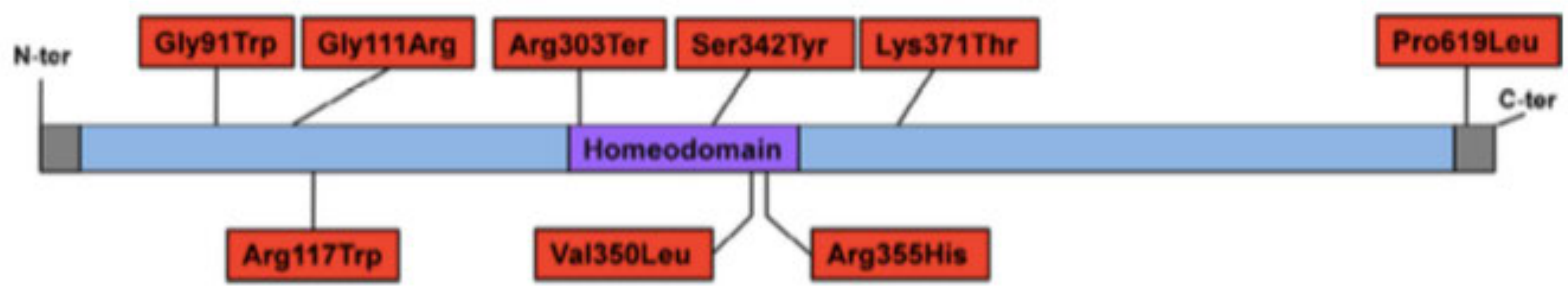


Fig. 4. NOBOX mutations causative of non-syndromic POF.

BMP15 (*GDF9B*), Xp11.2 chromosome, TGF-β superfamily of growth factors - TGF-β molecules, BMP, GDF, inhibins, activins…

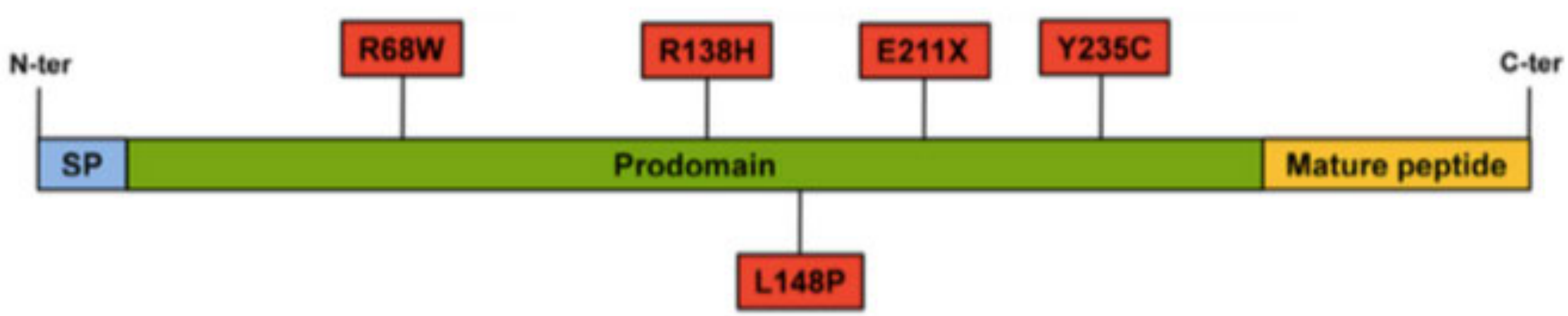
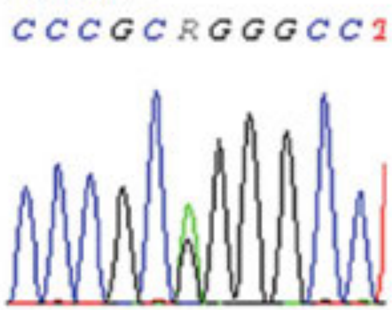
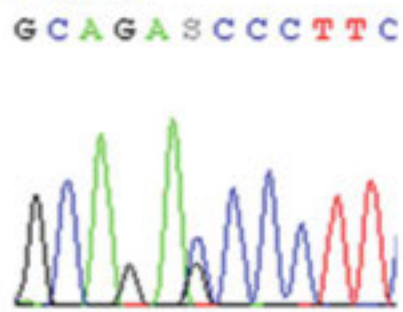
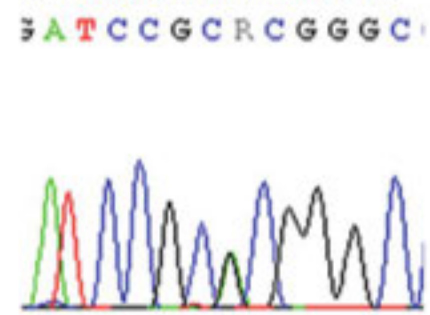


Fig. 5. BMP15 mutations causative of non-syndromic POF.

AMH mutations with reduced *in vitro* bioactivity are related to premature ovarian insufficiency

B. Alvaro Mercadal[1,2,3,*], R. Imbert[3], I. Demeestere[1,3], C. Gervy[4], A. De Leener[5], Y. Englert[1,3], S. Costagliola[2], and A. Delbaere[1,3]

[1]Research Laboratory on Human Reproduction, Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium [2]Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (IRIBHM), Faculté de Médecine, Université Libre de Bruxelles, Brussels, Belgium [3]Fertility Clinic, Department of Gynecology and Obstetrics, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium [4]Biochemistry Department, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium [5]Department of Medical Genetics, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

	G264R (G/C) e4 **TMP_ESP_19_2250973**	**D288E (C/G) e5.1** **Rs 199831511**	**R444H (G/A) e5.2**
Region	Exon 4 N-terminal 	Exon 5 N-terminal 	Exon 5 N-terminal, near cleavage site 
Type of AA change	Glycine: intermediate, non-polar Arginine: hydrophilic, basic	Aspartic acid: hydrophilic, acid Arginine: hydrophilic, basic	Arginine: hydrophilic, basic Histidine: hydrophilic basic
Number of POI patients	1	1	1
Clinical characteristics	Sub-Saharan African Secondary amenorrhea at 30 years old. Family case of 'infertility' after 25 years old (not further investigated)	Caucasian Secondary amenorrhea at 26 years old. Mother with POI at 32 years old, carrier of the AMH variant D288E	Caucasian Secondary amenorrhea at the stop of oral contraceptives at 26 years old Family case of induction of puberty

Human Reproduction, 1196–1202, 2015

Cytoplasmic effects

Increased ooplasmic fraction of vacuoles;

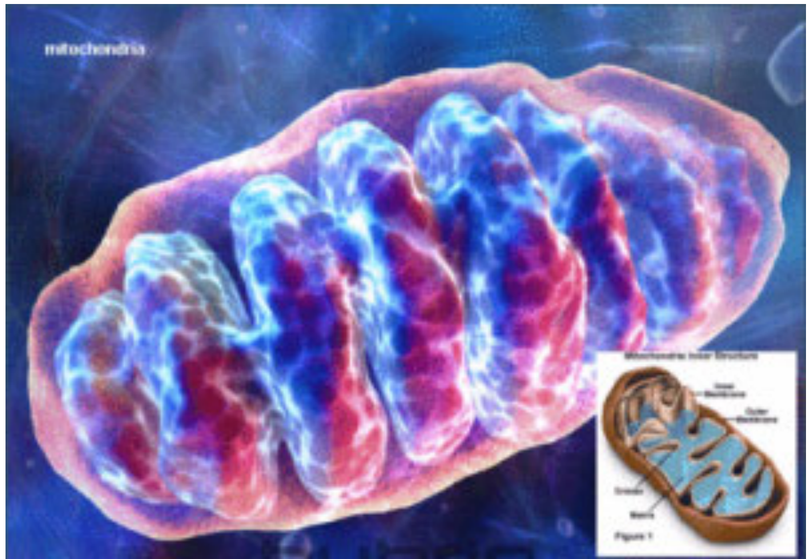
Decrease in the mitochondria fraction;

Increased density of mitochondrial matrix;

Increase of dilated smooth endoplasmic reticulum and Golgi complexes;

Higher frequency of ruptured mitochondrial membranes.

Ann. N.Y. Acad. Sci. 1034: 117–131 (2004).



Therapy

Natural cycle

Different stimulation protocols

- High doses of gonadotrophins (Land et al., 1996),
- ‘Flare-up’ protocol (Karande et al., 1997)
- Agonist-antagonist conversion protocol

Pre/co-treatment

- The use of growth hormone or growth hormone-releasing factor (Howles et al., 1999)
- Aspirin as adjunct therapie
- DHEAs (Lok et al., 2004)

Egg donation

Therapy

Expected poor responders on the basis of an antral follicle count do not benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial*

E.R.Klinkert[1,3], F.J.M.Broekmans[1], C.W.N.Looman[2], J.D.F.Habbema[2] and E.R.te Velde[1]

[1]Department of Reproductive Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht and [2]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 50, 3015 GE Rotterdam, The Netherlands

Human Reproduction Vol.20, No.3 pp. 611–615, 2005

Therapy

Comparisons of GnRH antagonist versus GnRH agonist protocol in poor ovarian responders undergoing IVF

Danhua Pu [1,2], Jie Wu [1,2,*], and Jiayin Liu [1,2]

[1]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Nanjing Medical University, 21
of China [2]State Key Laboratory of Reproductive Medicine, Nanjing Medical University, 210029 Nanjing, P

Human Reproduction Vol.20, No.3 pp.616–621, 2005 doi:10.1093
Advance Access publication December 17, 2004

GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial

Lai-Ping Cheung[1,2], Po-Mui Lam[1], Ingrid Hung Lok[1], Tony Tak-Yu Chiu[1], Sum-Yee Yeung[1], Ching-Ching Tjer[1] and Christopher John Haines[1]

[1]Department of Obstetrics and Gynecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, China

No difference

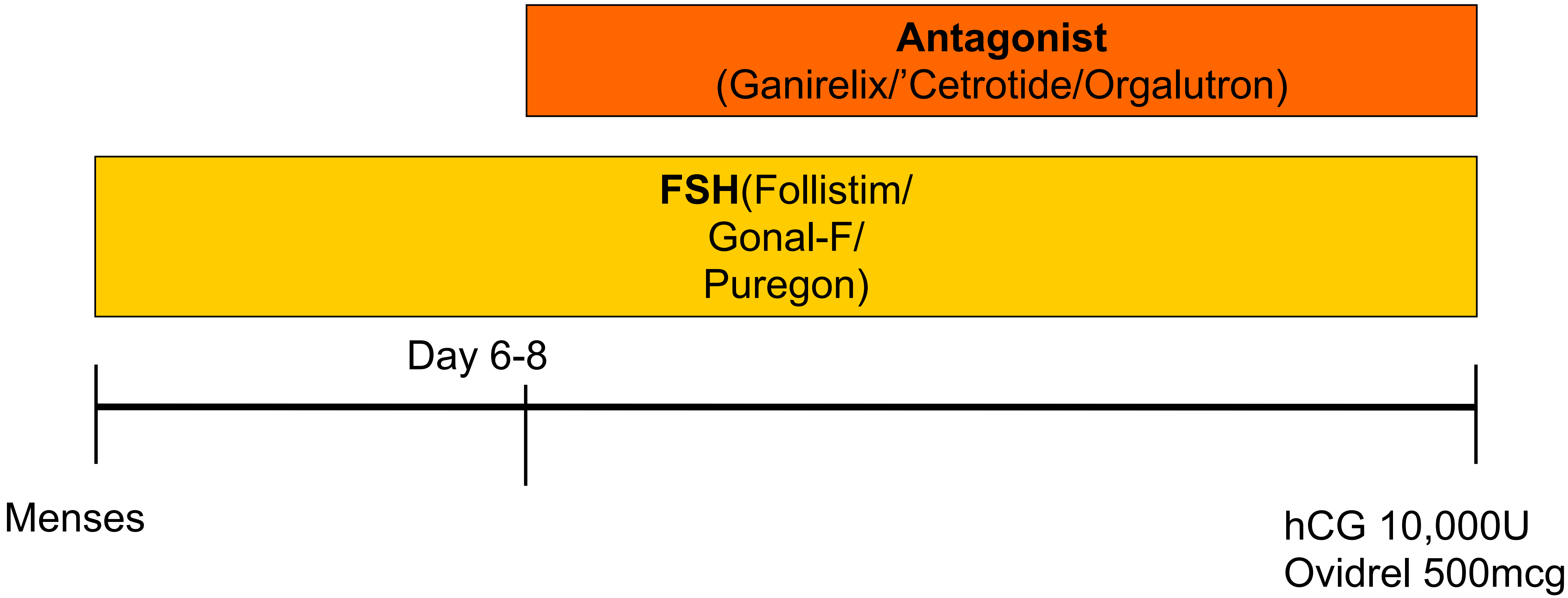
the number of oocytes retrieved,

the number of mature oocytes retrieved, the

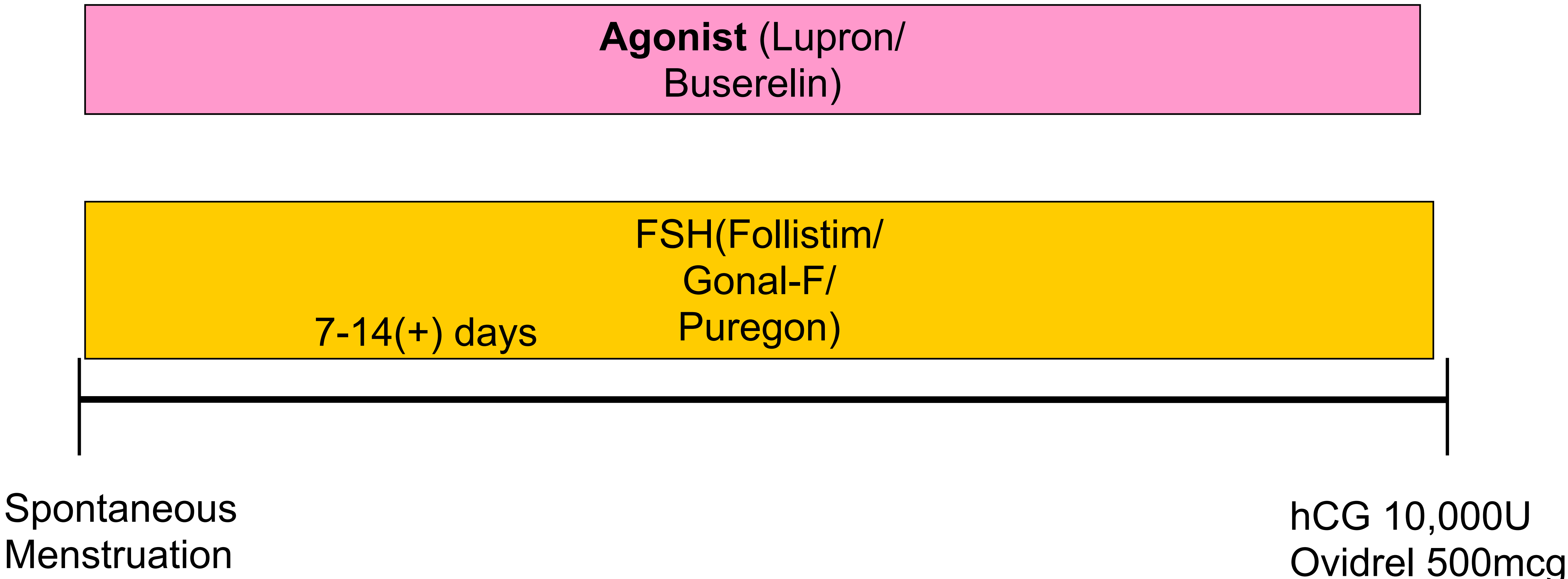
CCR and CPR between GnRH-ant and GnRH-a protocols

Human Reproduction, Vol.26, No.10 pp. 2742–2749, 2011

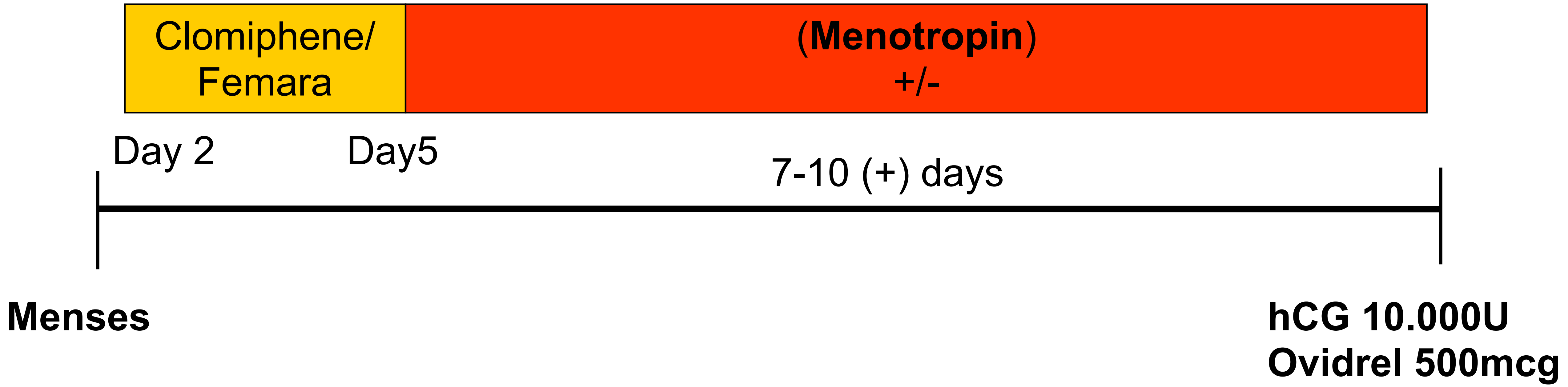
Short Antagonist Protocol



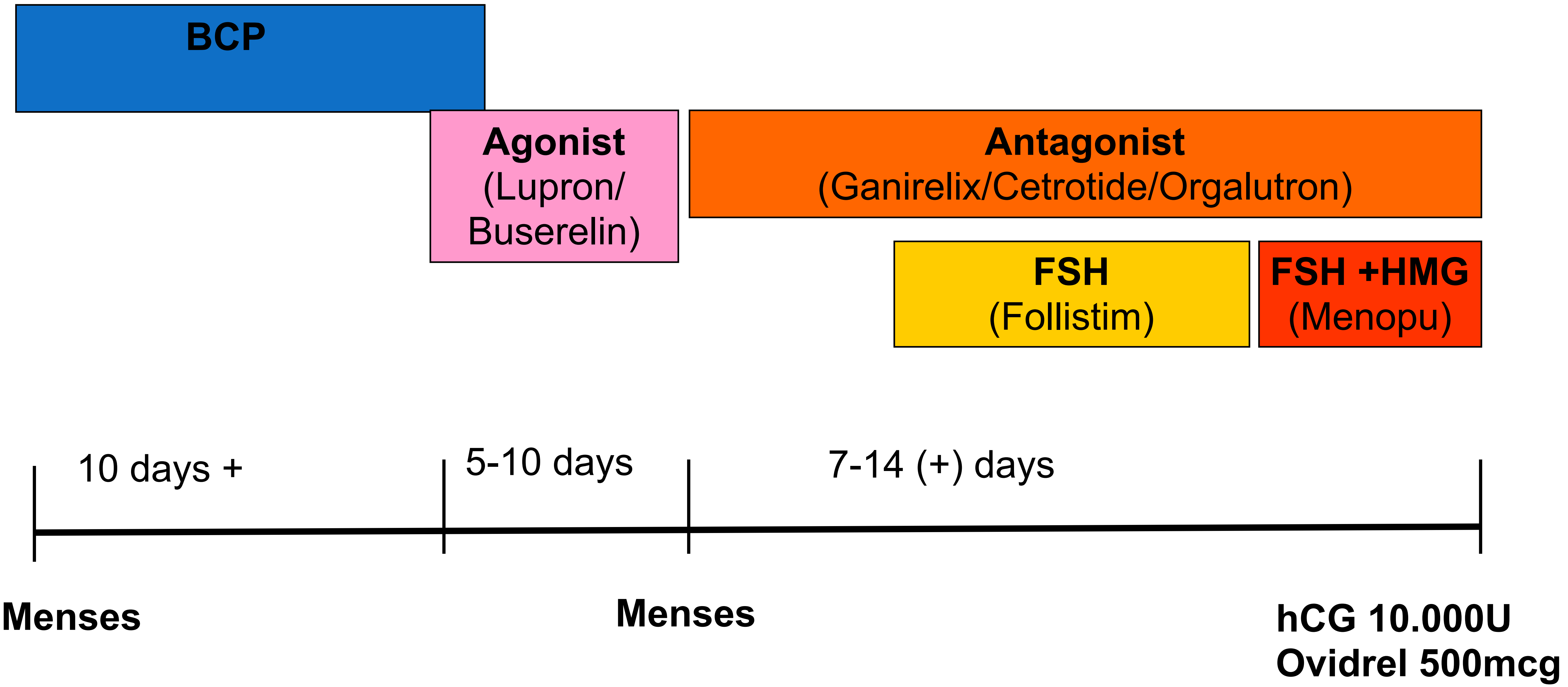
Short Agonist (Micro) “Flare” Protocol



Mini-IVF / EZ-IVF



Agonist/ Antagonist Conversion

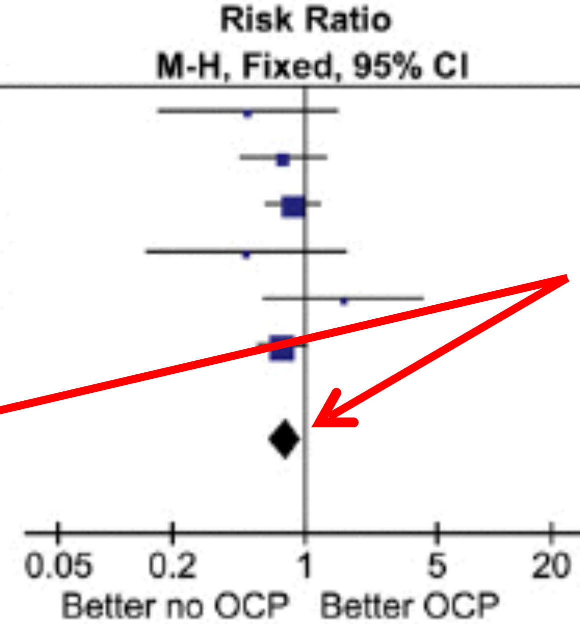


Oral contraceptive pretreatment

A

Study or Subgroup	OCP Events	OCP Total	no OCP Events	no OCP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Huirne	4	32	8	32	4.5%	0.50 [0.17, 1.50]	2006
Rombauts	20	117	26	117	14.7%	0.77 [0.46, 1.30]	2006
Kolibianakis	51	250	60	254	33.7%	0.86 [0.62, 1.20]	2006
Cedrin	3	21	7	24	3.7%	0.49 [0.14, 1.66]	2007
Kim	8	27	5	27	2.8%	1.60 [0.60, 4.27]	2009
Tavmergen	55	223	71	219	40.5%	0.76 [0.56, 1.03]	2009
Total (95% CI)		**670**		**673**	**100.0%**	**0.80 [0.66, 0.97]**	
Total events	141		177				

Heterogeneity: Chi² = 3.58, df = 5 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

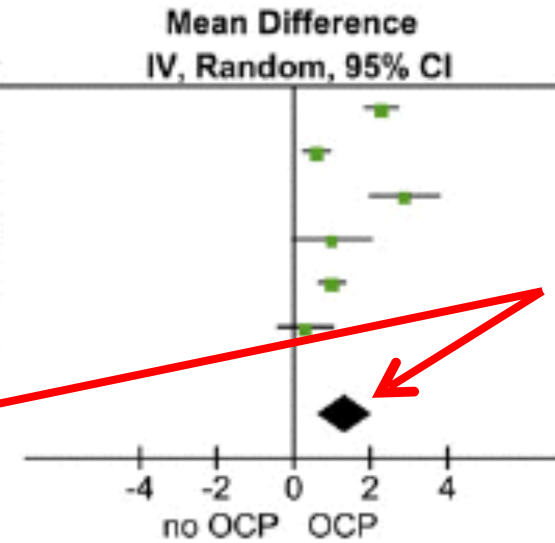


Pregnancy
RR 0.80

B

Study or Subgroup	OCP Mean	OCP SD	OCP Total	no OCP Mean	no OCP SD	no OCP Total	Weight	Mean Difference IV, Random, 95% CI	Year
Rombauts	11.7	1.9	109	9.4	1.6	105	18.1%	2.30 [1.83, 2.77]	2006
Kolibianakis	9.7	2	209	9.1	2	203	18.5%	0.60 [0.21, 0.99]	2006
Huirne	11.6	2.1	31	8.7	1.6	32	14.8%	2.90 [1.98, 3.82]	2006
Cedrin	11.1	1.7	20	10.1	1.9	24	13.7%	1.00 [-0.06, 2.06]	2007
Tavmergen	10	1.75	209	9	2	199	18.6%	1.00 [0.63, 1.37]	2009
Kim	10	1.4	27	9.7	1.4	27	16.2%	0.30 [-0.45, 1.05]	2009
Total (95% CI)			**605**			**590**	**100.0%**	**1.33 [0.61, 2.05]**	

Heterogeneity: Tau² = 0.69; Chi² = 50.16, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.61 (P = 0.0003)

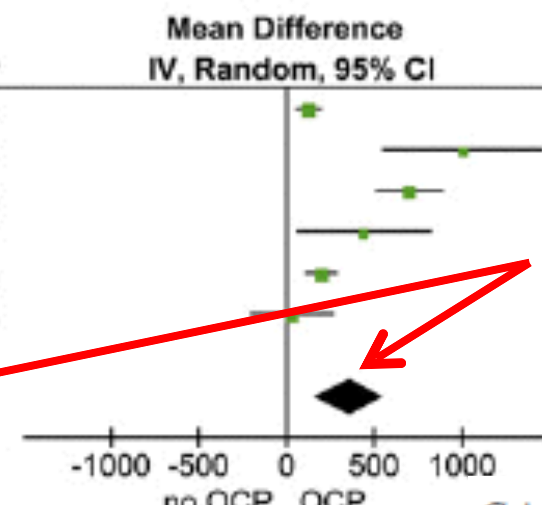


Duration
WMD 1.33 day

C

Study or Subgroup	OCP Mean	OCP SD	OCP Total	no OCP Mean	no OCP SD	no OCP Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kolibianakis	1,943	402	209	1,818	398	203	21.3%	125.00 [47.75, 202.25]	2006
Huirne	2,958	1,162	31	1,950	616	32	10.3%	1008.00 [546.62, 1469.38]	2006
Rombauts	2,667	881	109	1,965	515	105	18.3%	702.00 [509.50, 894.50]	2006
Cedrin	2,174	723	20	1,734	551	24	12.2%	440.00 [54.00, 826.00]	2007
Tavmergen	1,800	500	204	1,600	450	192	21.0%	200.00 [106.41, 293.59]	2009
Kim	2,964	433	27	2,932	464	27	16.8%	32.00 [-207.39, 271.39]	2009
Total (95% CI)			**600**			**583**	**100.0%**	**360.32 [157.51, 563.13]**	

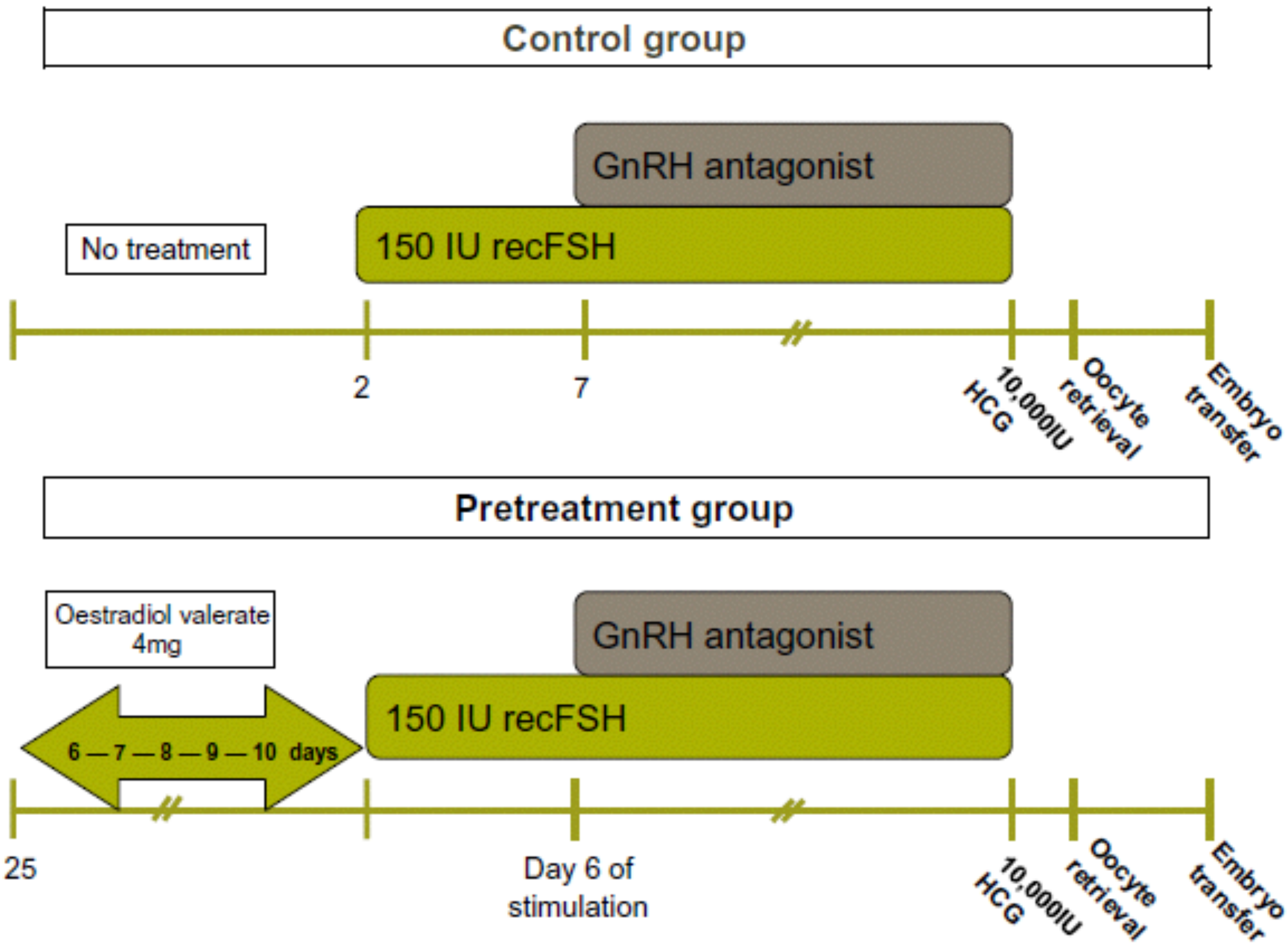
Heterogeneity: Tau² = 48708.30; Chi² = 44.77, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.48 (P = 0.0005)



Stimulation
WMD 360 IU

Griesinger. Correspondence. Fertil Steril 2010.

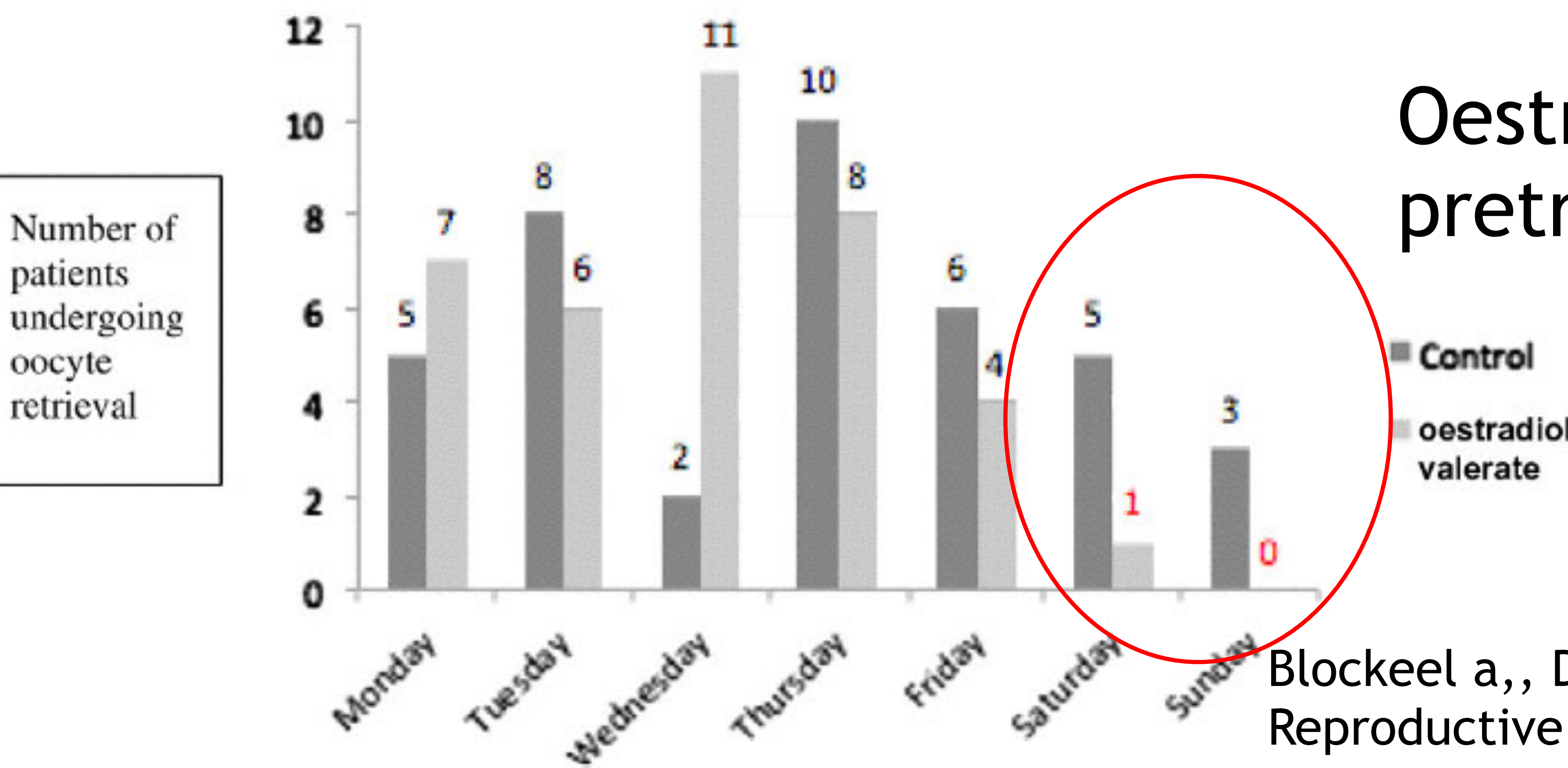
Oestradiol valerate pretreatment in GnRH-antagonist cycles: a randomized controlled trial



Scheduling

Blockeel a,, Devroey
Reproductive BioMedicine Online (2012)

	Control group	Pretreatment group	Between-group difference (%)
Patients undergoing oocyte retrieval during a weekend day (primary end point)	8/39 (20.5)	1/37 (2.7)	−17.8 (−31.5 to −4.1)[a]
Positive HCG			
Per started cycle	20/42 (47.6)	19/44 (43.2)	−4.4 (−25.5 to 16.6)
Per retrieval	20/39 (51.3)	19/37 (51.4)	0.1 (−22.4 to 22.6)
Per embryo transfer	20/37 (54.1)	19/35 (54.3)	0.2 (−22.8 to 23.3)
Outcome for patients with positive HCG test			
Biochemical pregnancy	2/20 (10.0)	1/19 (5.3)	−4.7 (−21.3 to 11.8)
Miscarriage	2/20 (10.0)	1/19 (5.3)	−4.7 (−21.3 to 11.8)
Clinical pregnancy	16/20 (80.0)	17/19 (89.5)	9.5 (12.8 to 31.8)
Clinical pregnancy rate			
Per started cycle	16/42 (38.1)	17/44 (38.6)	0.5 (−20.0 to 21.1)
Per retrieval	16/39 (41.0)	17/37 (45.9)	4.9 (−17.4 to 27.2)
Per embryo transfer	16/37 (43.2)	17/35 (48.6)	5.4 (−17.7 to 28.3)



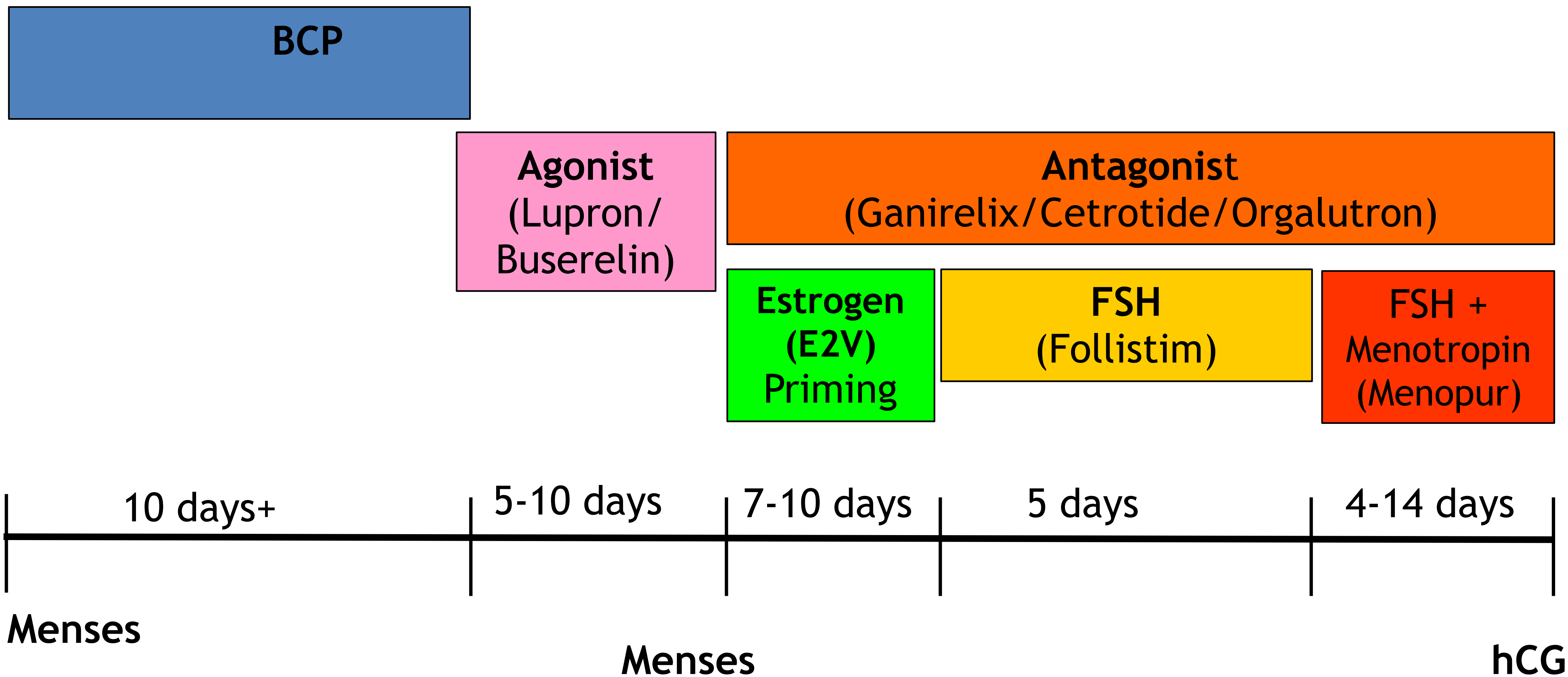
Oestradiol valerate pretreatment

Scheduling

Blockeel a,, Devroey
Reproductive BioMedicine Online (2012

POF; Low responde

Agonist/ Antagonist Conversion with Estrogen Priming (A/ACP+ E2V)



J Assist Reprod Genet (2012) 29:225–230
DOI 10.1007/s10815-011-9685-7

ASSISTED REPRODUCTION TECHNOLOGIES

Effect of estrogen priming through luteal phase and stimulation phase in poor responders in in-vitro fertilization

Eun Mi Chang · Ji Eun Han · Hyung Jae Won · You Shin Kim · Tae Ki Yoon · Woo Sik Lee

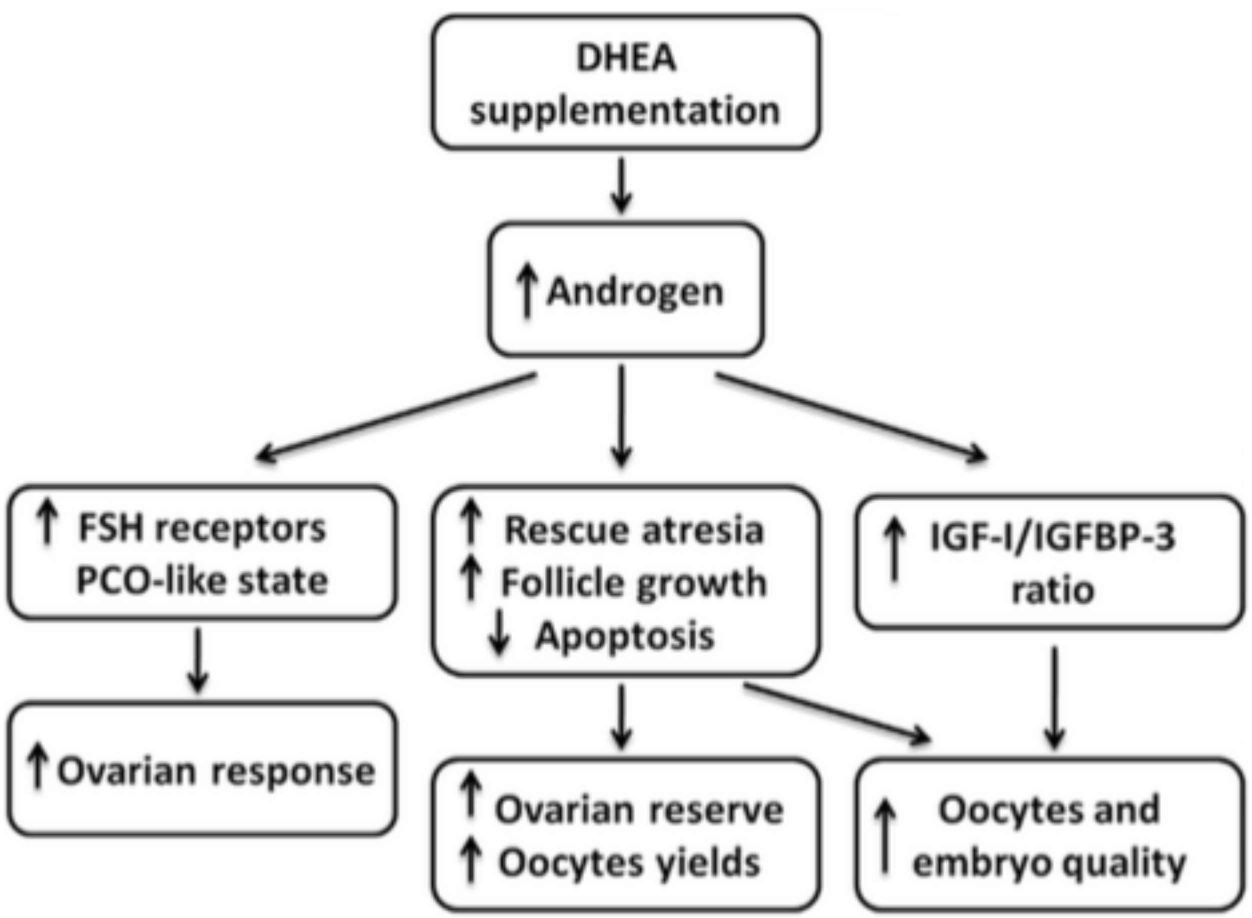
Variable	Luteal E_2 group (*n*=86)	Standard GnRH antagonist group (*n*=69)	P value
Cancellation rate	15.1%	37.7%	.002
Implantation rate	19.3%	8.7%	.020
Pregnancy rate per ET	37.0%	16.3%	.021
Clinical pregnancy rate per ET	30.1%	11.6%	.024
Ongoing pregnancy rate per ET	24.7%	9.3%	.051

Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 131e136

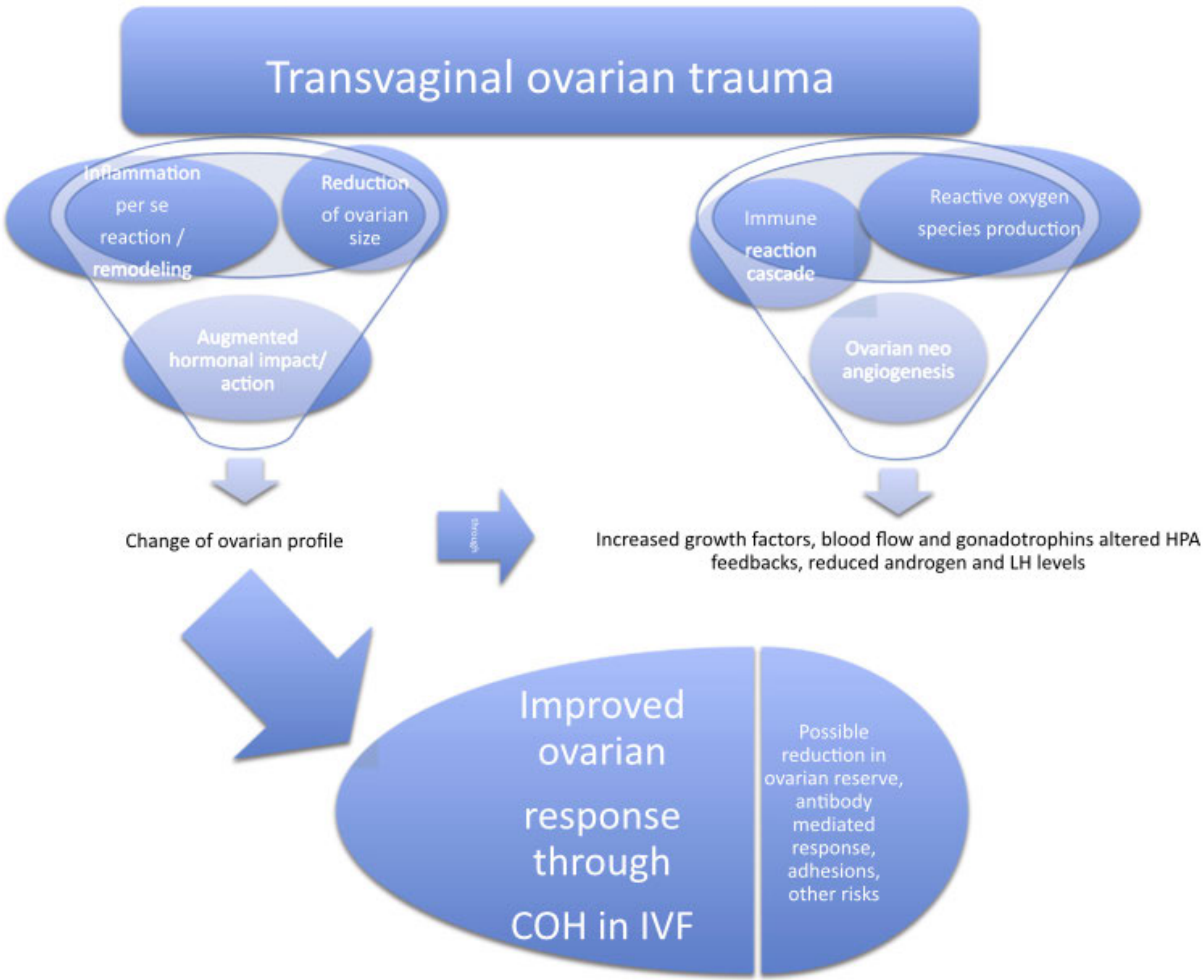
Original Article

Effects of dehydroepiandrosterone supplementation on women with poor ovarian response: A preliminary report and review

Kuan-Hao Tsui [a, b, c, d], Li-Te Lin [b, c, e], Renin Chang [f], Ben-Shian Huang [c, g], Jiin-Tsuey Cheng [a, **], Peng-Hui Wang [c, g, h, i, j, *]



Effects of DHEA
Primary effects
Improvement in ovarian reserve
Improvement in ovarian response
Improvement in oocytes and embryo yields
Improvement in oocytes and embryo quality
Reduction in aneuploid embryos
Secondary effects
Improvement in pregnancy rates of IVF
Improvement in spontaneous pregnancies
Reduction in miscarriage rates
Improvement in live birth rates of IVF
Reduction in cancellation of IVF



Siristatidis et al. / Medical Hypotheses 83 (2014) 227–231

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

RESEARCH Open Access

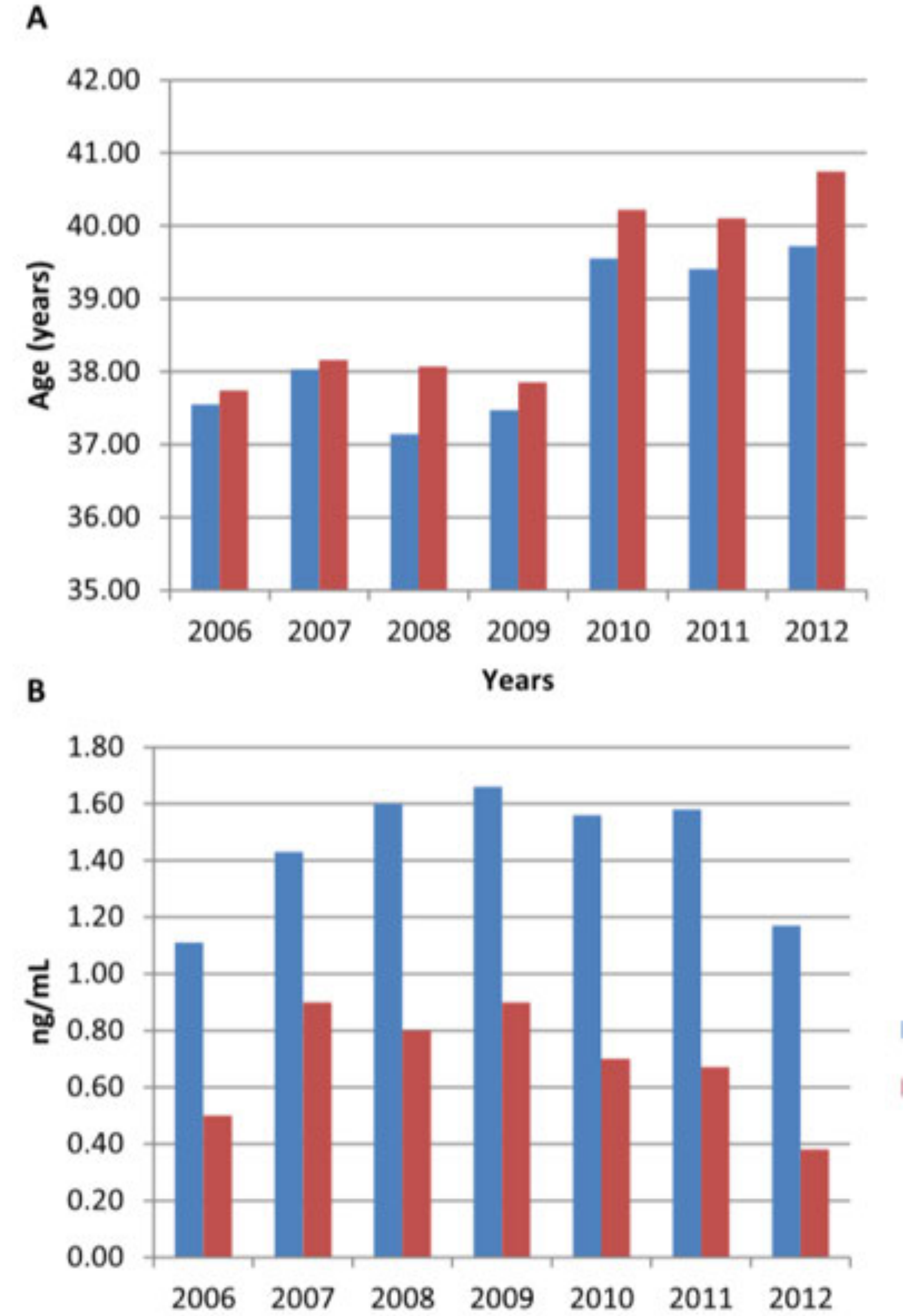
The "graying" of infertility services: an impending revolution nobody is ready for

Norbert Gleicher[1,2*], Vitaly A Kushnir[1], Andrea Weghofer[1,3] and David H Barad[1,2]

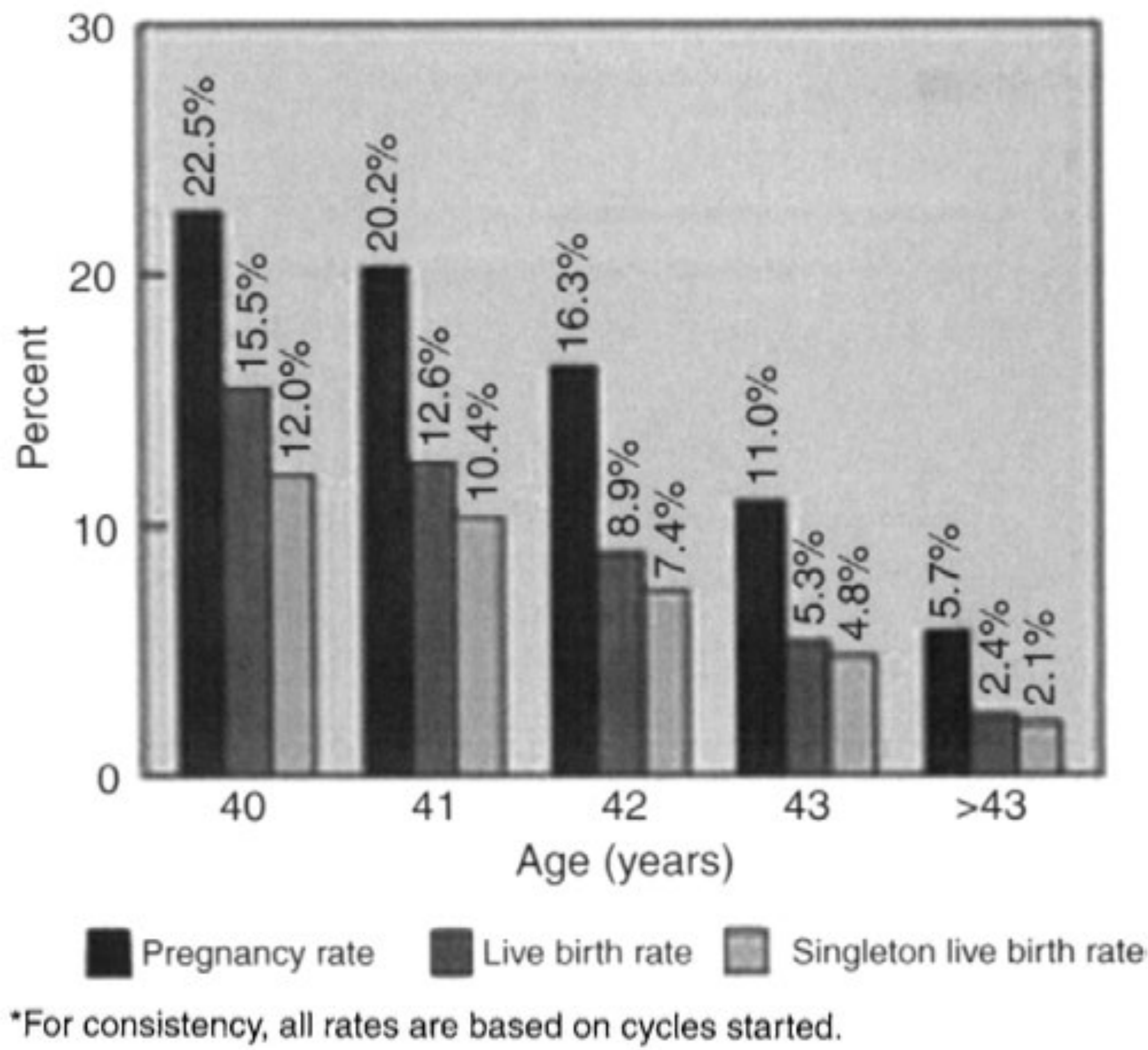
Table 1 Our center's 2010 - 2012 age-specific clinical IVF outcome data by "intent to treat"*/ for women 40 years and older**

Age (years)	47%	Live birth rate (%)	Clinical pregnancy rate (%) if different
40		15.4	
41		42.9	
42		6.3	18.8
43		0.0	16.7
44		1.4	5.4
45		2.7	5.4
46-53		0.0	

*"Intent to treat" reflects denominator of per cycle start for each age group.



ART outcome for 40 and older



www.cdc.gov/ART/ART2003

Mitochondria

Quality-compromised oocytes - mitochondrial dysfunctions

- Infertility,
- Reduced blastocyst cell number
- Embryo loss
- Developmental disorders and diseases:
  - neurological diseases
  - diabetes
  - cancer
  - immune system
  - aging

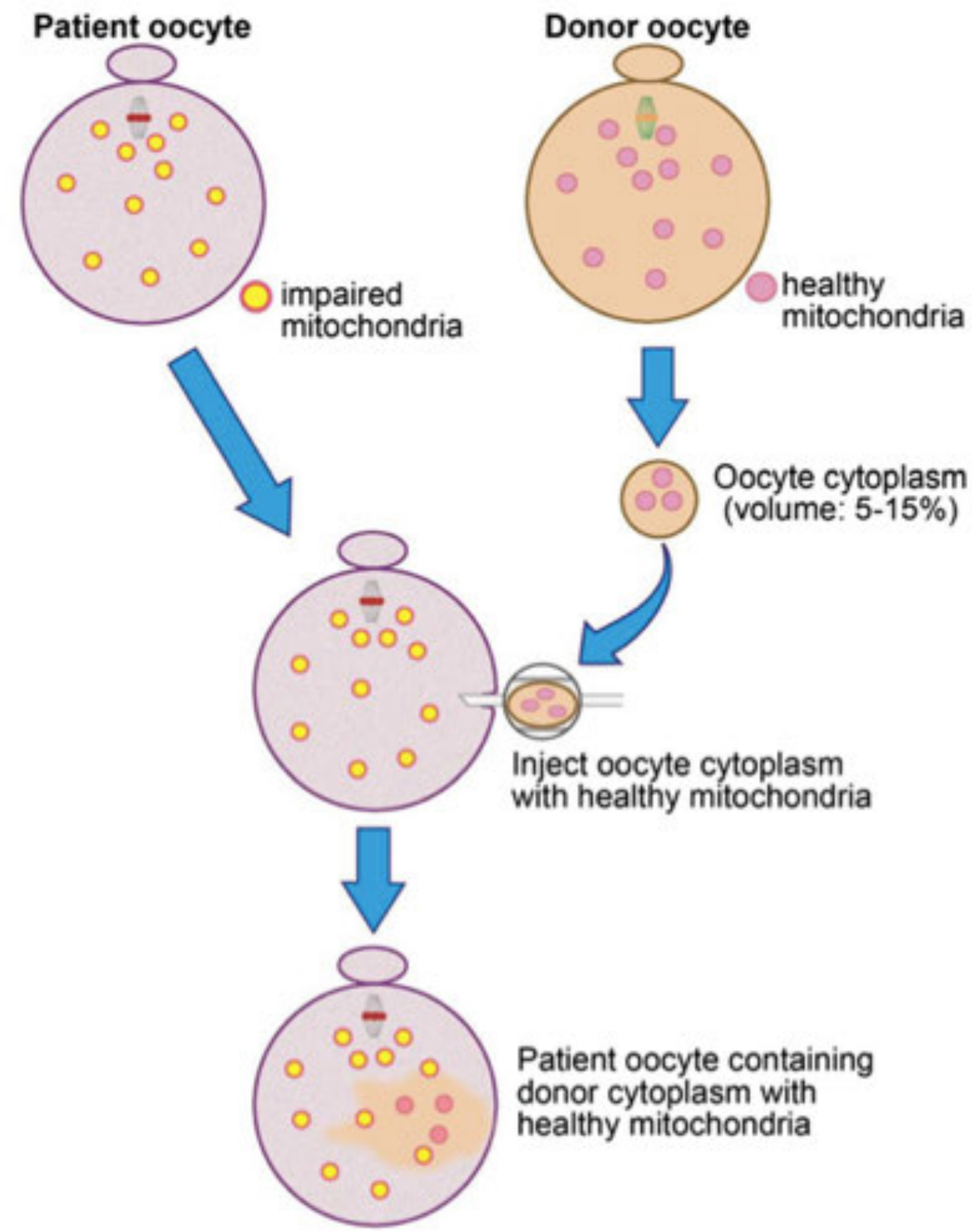
Schatten et al. Reproductive Biology and Endocrinology 2014, 12:111

Mitochondria - Ooplasmic transfer

Clinical protocol using the oocyte cytoplasm extracted from a young donor that was transferred into the eggs of the recipient woman.

Mithocondrial heteroplasmy

13 pregnancies, two fetuses were karyotypically 45, XO



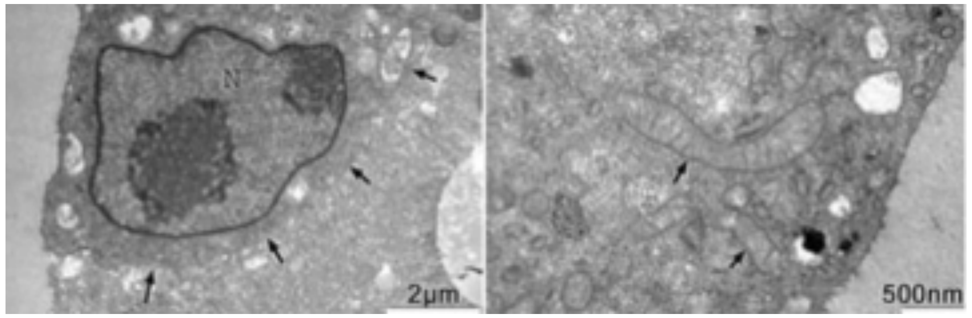
Three parent child - Yabuuchi et al. 2012

16. Smeets HJM: Preventing the transmission of mitochondrial DNA disorders: Selecting the good guys or kicking out the bad guys. Reprod BioMed Online 2013, 27:599–610.

17. Amato P, Tachibana M, Sparman M, Mitalipov: Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases. Fertil Steril 2014, 101(1):31–35.

18. Mitalipov S, Wolf DP: Clinical and ethical implications of mitochondrial gene transfer. Trends Endocrinol Metab 2014, 25(1):5–7.

Three-parent in vitro fertilization

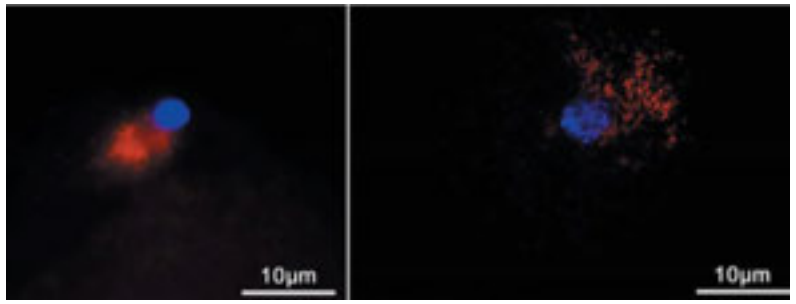


GV or the MII spindle into an enucleated donor egg.

Mitochondria locate near the donor nucleus and disperse into the cytoplasm in developing embryos with heteroplasmy as observed up to the blastocyst stages. From Zhong et al. 2014.

Patient's egg containing abnormal mitochondria is fertilized

At zygote stage - **Pronuclei** transferred to an enucleated donor egg.



The recipient oocyte is enucleated by removing the MII spindle;

Donor oocyte is fertilized and the second **polar body** is removed and then transferred to the recipient oocyte

FDA: Cellular Tissue, and Gene Therapies Advisory Committee. Briefing Document-Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility. 2014. www.fda.gov hom

AUGMENT
autologous germ-line mitochondrial energy transfer

Autologous germline-derived cytoplasmic extract or purified mitochondria bioenergetics reinforcement of oocytes.

Silvestris et al. Journal of Ovarian Research (2015) 8:55

Perspective:
the ovarian stem cells

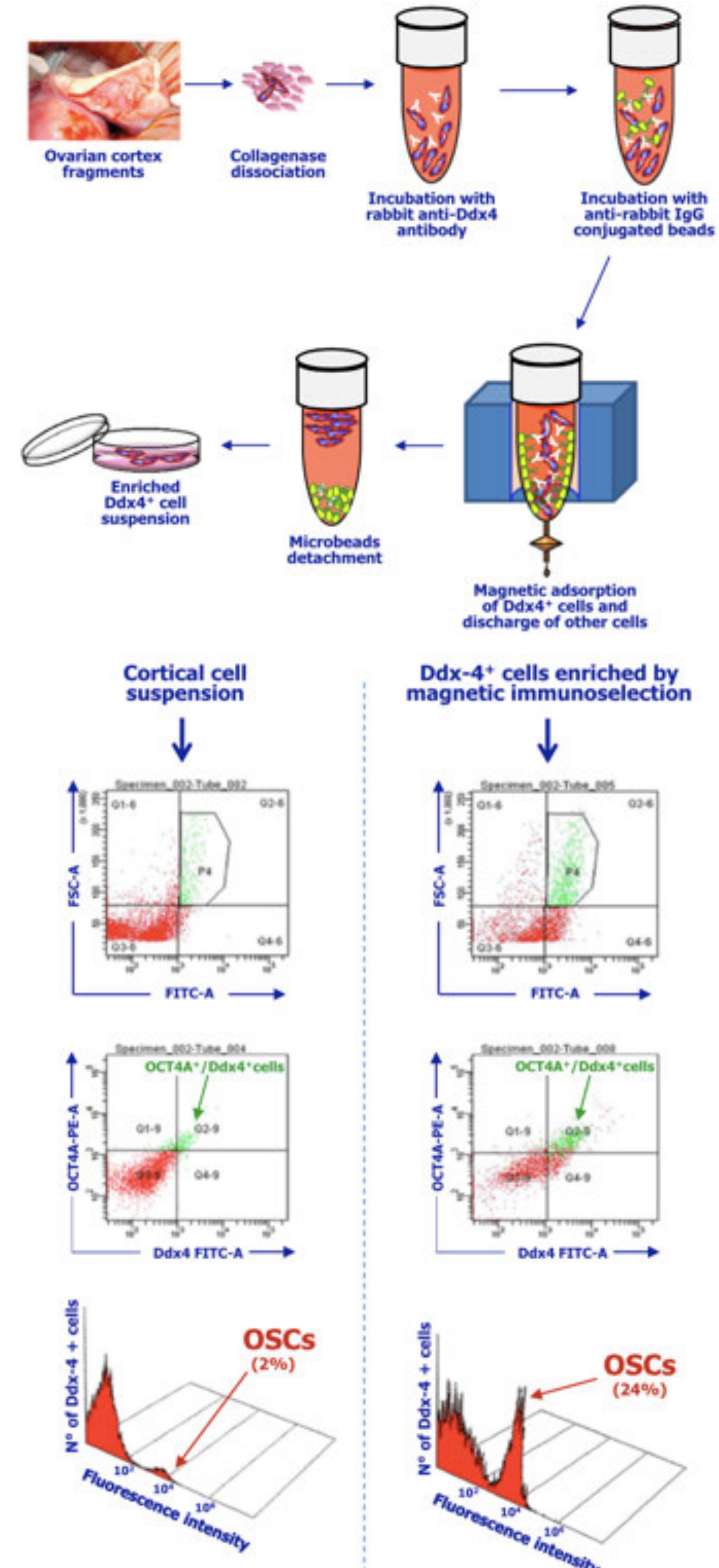
Silvestris et 5

No renewable germinal OSCs - numerically fixed pool of oocytes are committed for the fertility. 1951 Zuckerman.

Mitotically active OSCs in both juvenile and adult murine ovaries capable to warranty both oocyte and follicle availability after birth, Tilly and co-workers.

Isolate and culture germinal OSCs in mammals, Zou

Very small embryonic-like stem cells (VSELs) and germinal OSCs within the ovarian surface epithelium (OSE) of adult mammals



Zuckerman S. Rec Prog Horm Res. 1951;6:63–108.

Zou Nature Cell Biology. 2009;11:631–50.

Molecular markers differentially expressed by OSCs and oocytes.

Ovarian stem cells	Oocytes
Ddx-4 (cell membrane and cytoplasm)	Ddx-4 (cytoplasm)
SSEA-4 (cell membrane and cytoplasm)	SSEA-4 (cytoplasm)
OCT-4 A and B	OCT-4 B
c-kit	c-kit
DAZL (nucleus and cytoplasm)	DAZL (cytoplasm)
Fragilis	ZP (zona pellucida proteins)
CD133	GDF-9 (growth differentiation factor 9)
Stella	NOBOX (newborn ovary hemeobox protein)
Nanog	SCP-3 (synaptonemal complex protein 3)
Sox-2	
Blimp-1	

Silvestris et al. Journal of Ovarian Research (2015) 8:55

Role of mesenchymal stem cell therapy in restoring ovarian function in a rat model of chemotherapy-induced ovarian failure: a histological and immunohistochemical study

Noha M. Afifi[a] and Olfat N. Reyad[b]

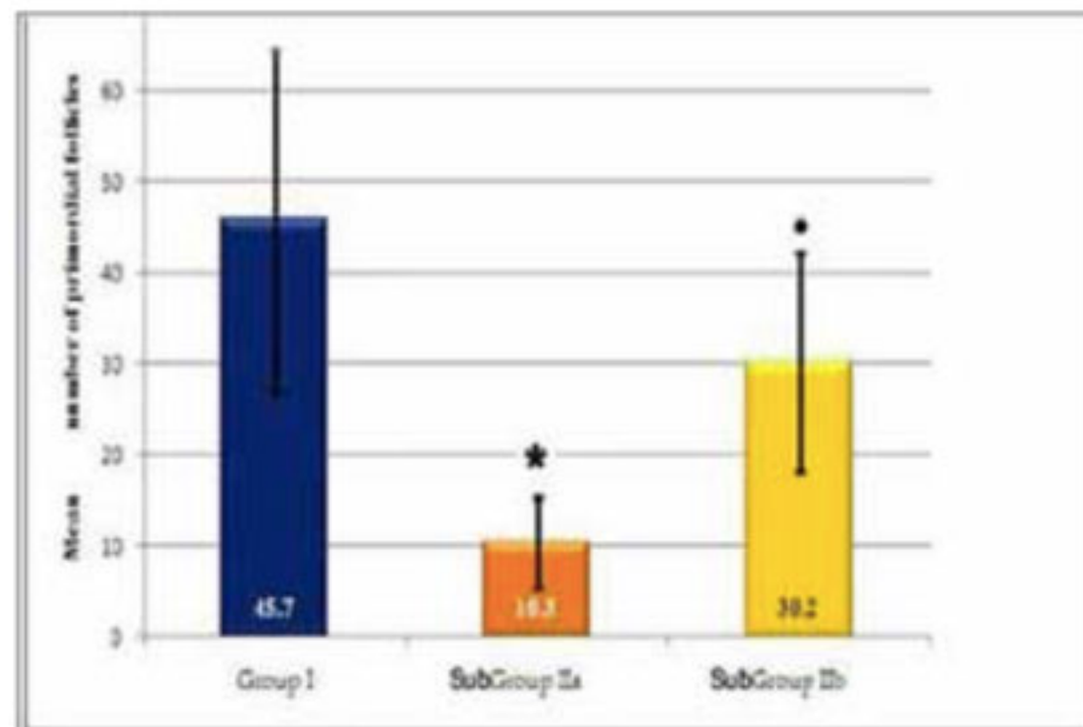
The Egyptian Journal of Histology, 2013, 36:114-126 11 (1350-2013)

Table 1. Mean values ± SD of hormone levels in the groups studied after the 1-month period of cyclophosphamide treatment

Group	Estradiol (pg/ml)	FSH (mIU/ml)	LH (mIU/ml)
Group I (control)	30 ± 0.42	3.9 ± 0.02	18.3 ± 2.24
Subgroup IIa (OF nontreated)	14 ± 2.36*	29.3 ± 4.45*	39.1 ± 4.55*
Subgroup IIb (OF+MSC)	23 ± 3.39•	7.7 ± 0.21•	21.3 ± 2.43•

Table 2. Mean number of primordial follicles ± SD in the ovarian sections

Group	Mean ± SD
Group I	45.7 ± 12.3
Subgroup IIa	10.3 ± 2.6*
Subgroup IIb	30.2 ± 10.4•



Histogram 1. Mean number of primordial follicles in the ovarian sections. *Significant compared with group I ($P<0.05$). •Significant compared with subgroup IIa ($P<0.05$).

Stem cell therapy - in vitro

Induced female embryonic stem cells

Primordial germ cell–like cells (PGCLCs) utilized to reconstitute ovaries.

Transplantation under the ovarian bursa of adult mice

PGCLCs - oocyte formation.

Metaphase II, fertilized, two-cell embryos,

transferred into foster mothers,

pups able to reach adulthood

Hayashi K, et al, Offspring from oocytes derived from in vitro primordial germ cell–like cells in mice. Science. 2012;338:971–5.

Bukovsky *Reproductive Biology and Endocrinology* (2015) 13:10
DOI 10.1186/s12958-015-0001-8

REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

EDITORIAL Open Access

Novel methods of treating ovarian infertility in older and POF women, testicular infertility, and other human functional diseases

Antonin Bukovsky

Transfer of **mononuclear cells** by a small blood volume replacement form young fertile women

Temporary rejuvenation of the immune, ovarian, and endocrine systems.

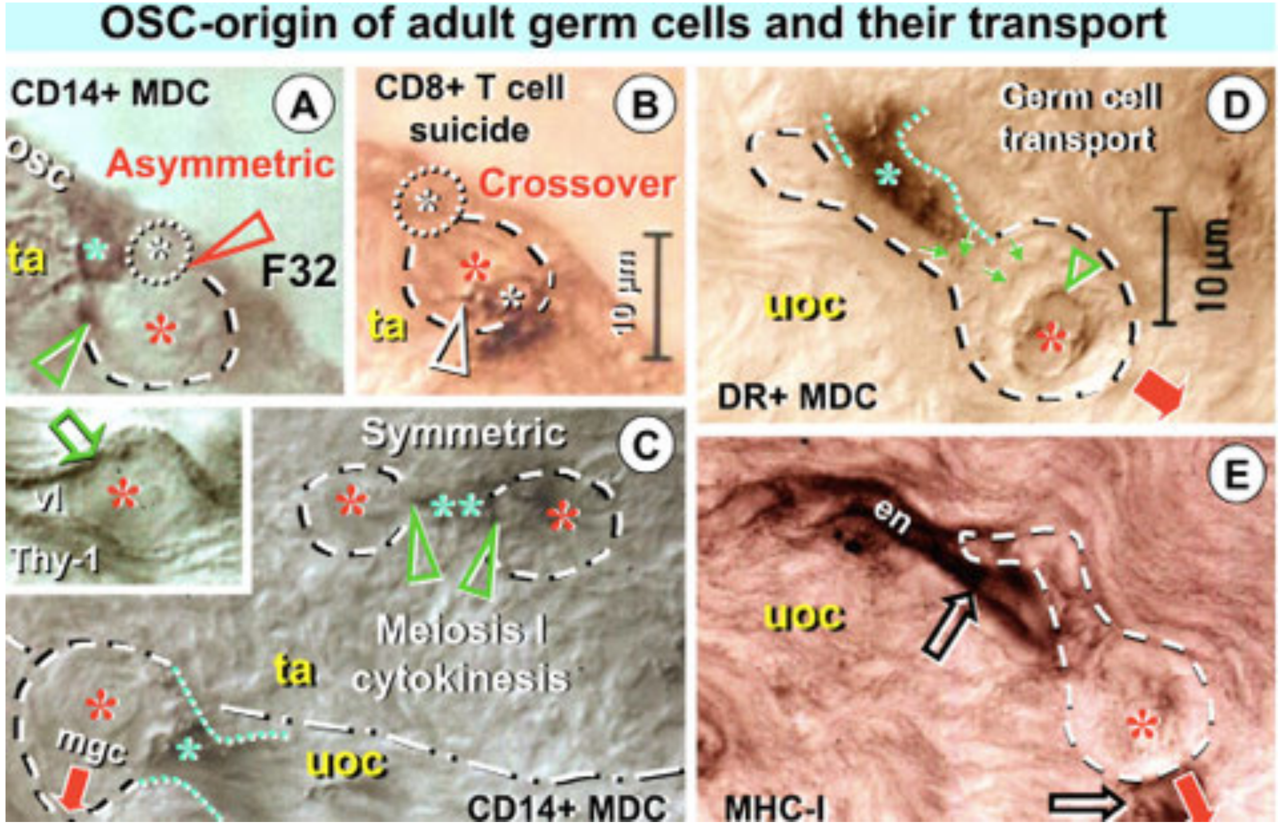
The plasma content of **immune components** in the blood, e.g., antibodies, eliminate persisting follicles with aged oocytes unsuitable for IVF.

Mononuclear cell content cause **follicular renewal** consisting of fresh autologous oocytes and granulosa cells.

Bukovsky Reproductive Biology and Endocrinology (2015) 13:10

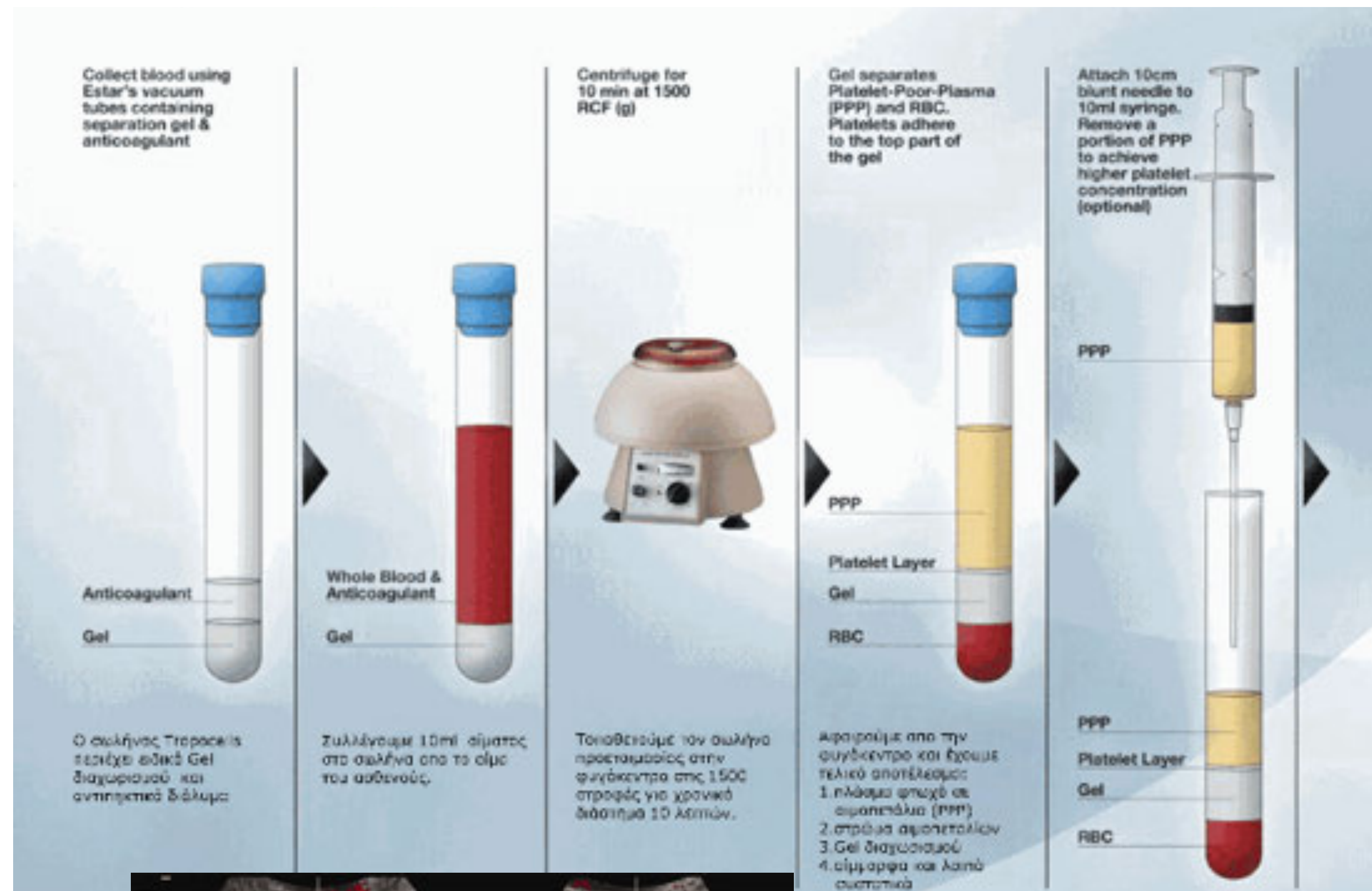
Systemic treatment of ovarian infertility by a small blood volume replacement or separated mononuclear cells from young healthy fertile donor women

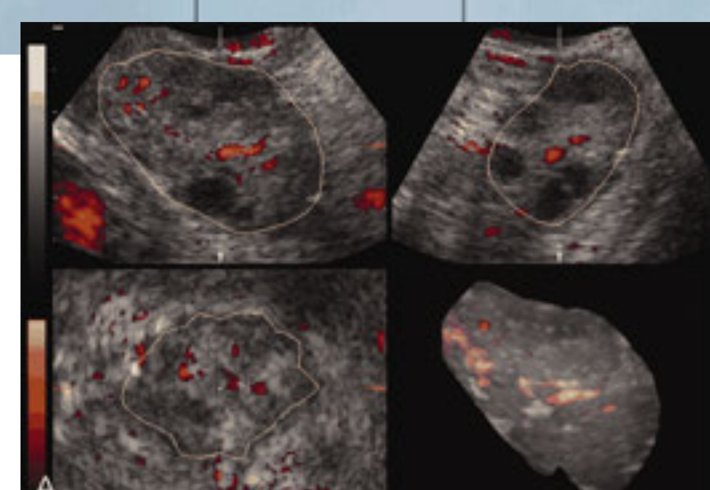
- A) Simple small blood volume replacement
- B) Transfusion of separated mononuclear cells
- C) Transfusion of separated mononuclear cells and blood plasma



Ovarian rejuvenation

- Growth factors
- Immunotherapy



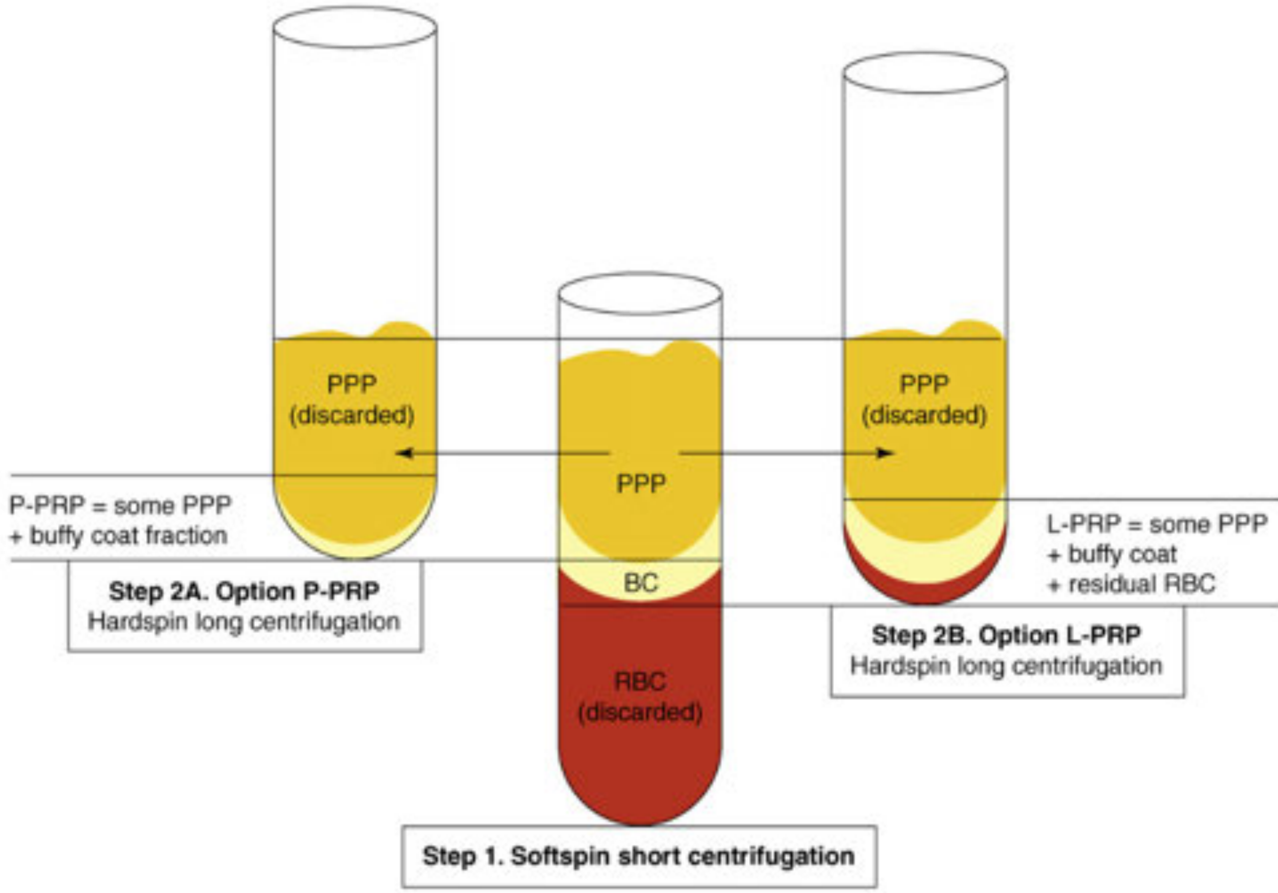


Ovarian rejuvenation techniques

Blood is collected with anticoagulant - processed by centrifugation (1-2h).

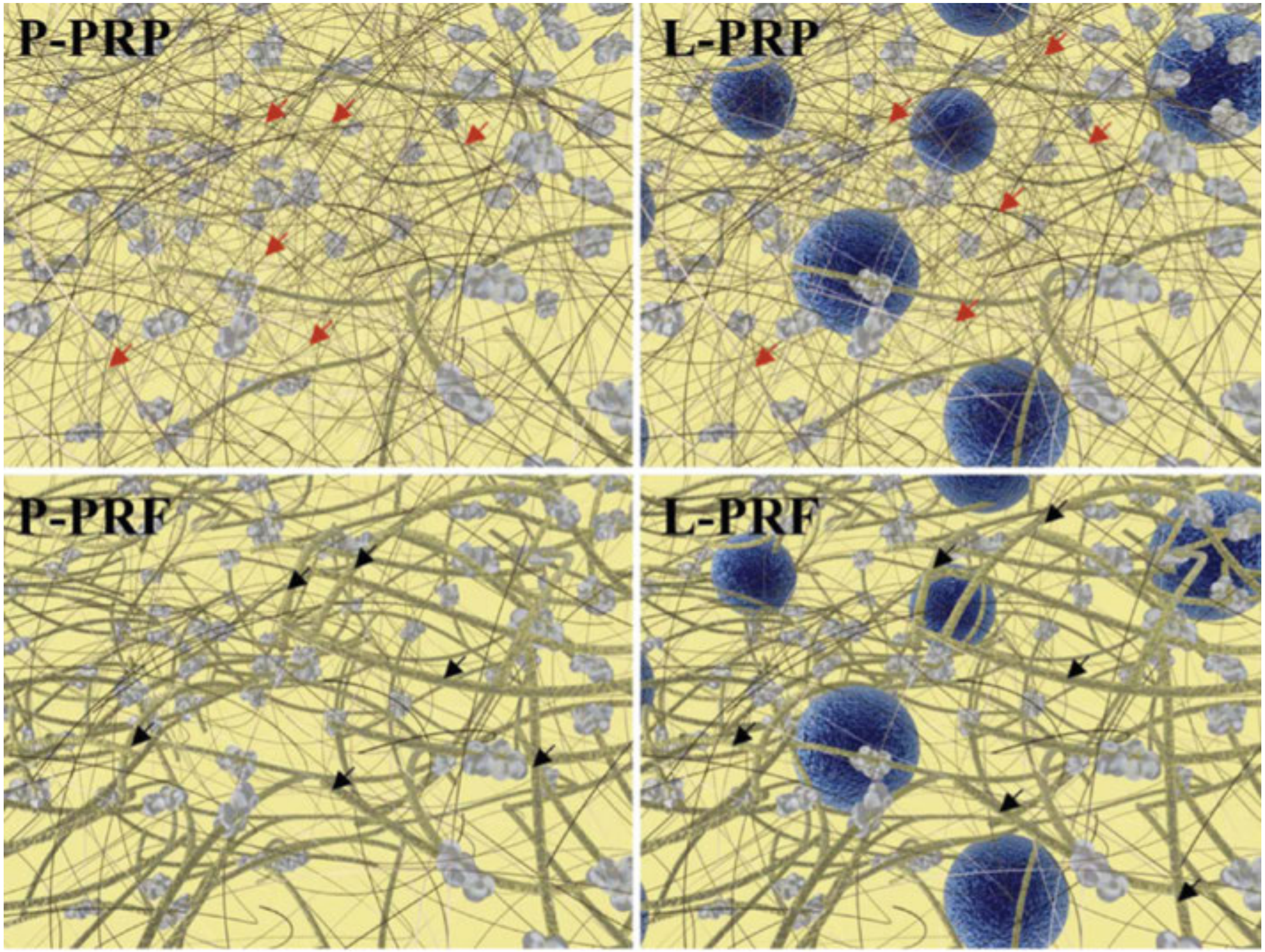
- A first centrifugation - three layers, RBCs,PPP, ‘buffy coat’
- The next steps discard RBC and PPP to collect only the ‘buffy coat’ layer.
- Platelet concentrate activated (thrombin and/or calcium chloride).

US guided subcortical intraovarian application (40 seconds)



Patent procedure **A61K35/16,**

L PRP



Dohan et al, Trends in Biotechnology

Vol.27 No.3 , 2009

Ovarian rejuvenation
Growth factors and cytokines

Mechanisms	Growth factors and cytokines
Proinflammatory cytokines	IL1, IL6, and TNF-alpha [26, 27]
Growth factors	Platelet-derived growth factor (PDGF) [36], transforming growth factor (TGF)-beta, platelet-derived epidermal growth factor (PDEGF), platelet-derived angiogenesis factor (PDAF) [37], insulin-like growth factor (IGF-1), and platelet factor 4 (PF-4) [38, 39], vascular endothelial growth factors (VEGF), and endothelial growth factors (EGF) [40, 41]
Angiogenesis factors	Vascular growth factor (VGF), VEGF, platelet derived membrane microparticles (PMP), and peripheral blood mononuclear cells (PBMNCs) [10]
Factors in other mechanisms of PRP	Serotonin, histamine, dopamine, calcium, and adenosine [18]

1. Albanese et al. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration Immunity & Ageing 2013, 10:23

L-PRP Ovarian rejuvenation

An institutional review board (IRB) approved

Patent procedure **A61K35/16**,

Blood amount	50 - 60 mL
Antikoagulans	ACD-a
HCT	6%
Total PRP	6 mL
Aplicated to ovaries	3.5 mL
Platelet concentration	9,3 X baseline
Leucocyte concentration	2,6 X baseline
Thrombin activation	yes 1:10

red.br.	datum	ime i prezime pacijentkinje	stimulisani	SPC	horm.status pred interv.
1.	07.07.2015.	TINTOR LAJŠIĆ DANIJELA 1976.g.(rejuvenacija ovarijuma)	9 x druga ustanov	4 x kod nas	FSH 14.02,LH 6.12 , E2 28.2 ,AMH 0.15 ,T 0.14 DHEAS 35.2,Kortizol 187.4,Andros
2.	08.08.2015.	BUHA DANKA 1968.g.(rejuvenacija ovarijuma)	nema	6 x SPC	FSH 35.35,LH 12.96,E2 11.23,DHEA-S 457.8,TSH 0.88,
3.	15.08.2015.	BOJOVIĆ MARIJA 1972.g.(rejuvenacija i ubrizgavanje tkiva ovarijuı	nema	2x kod nas	FSH 24.89,LH 6.79,E2 34,3,FT4 16.12,TSH 0.639
4.	26.08.2015.	DUČIĆ OLGA 1980.g. (rejuvenacija ovarijuma)	nema	nema	FSH 33.08,LH 17.1,E248.2,TSH 1.712,DHEA-S 59.2,AMH 0.09
6.	04.09.2015.	MARKOVIĆ MARINA 1978.g. POI	1 x kod nas	7 x kod nas	FSH 17.78,LH 9.21,E2 419.1,Kortizol,784,

Very efficacious treatment

- Social fertility preservation
- Egg donation

On time !?