



LABORATORIO DI SEMINOLOGIA
BANCA DEL SEME
"LOREDANA GANDINI"



SAPIENZA
UNIVERSITÀ DI ROMA

**Quello che l'endocrinologo deve
sapere della stimolazione
ovarica per la PMA**

Francesco Lombardo



Fo.Ri.SIE 

Onlus

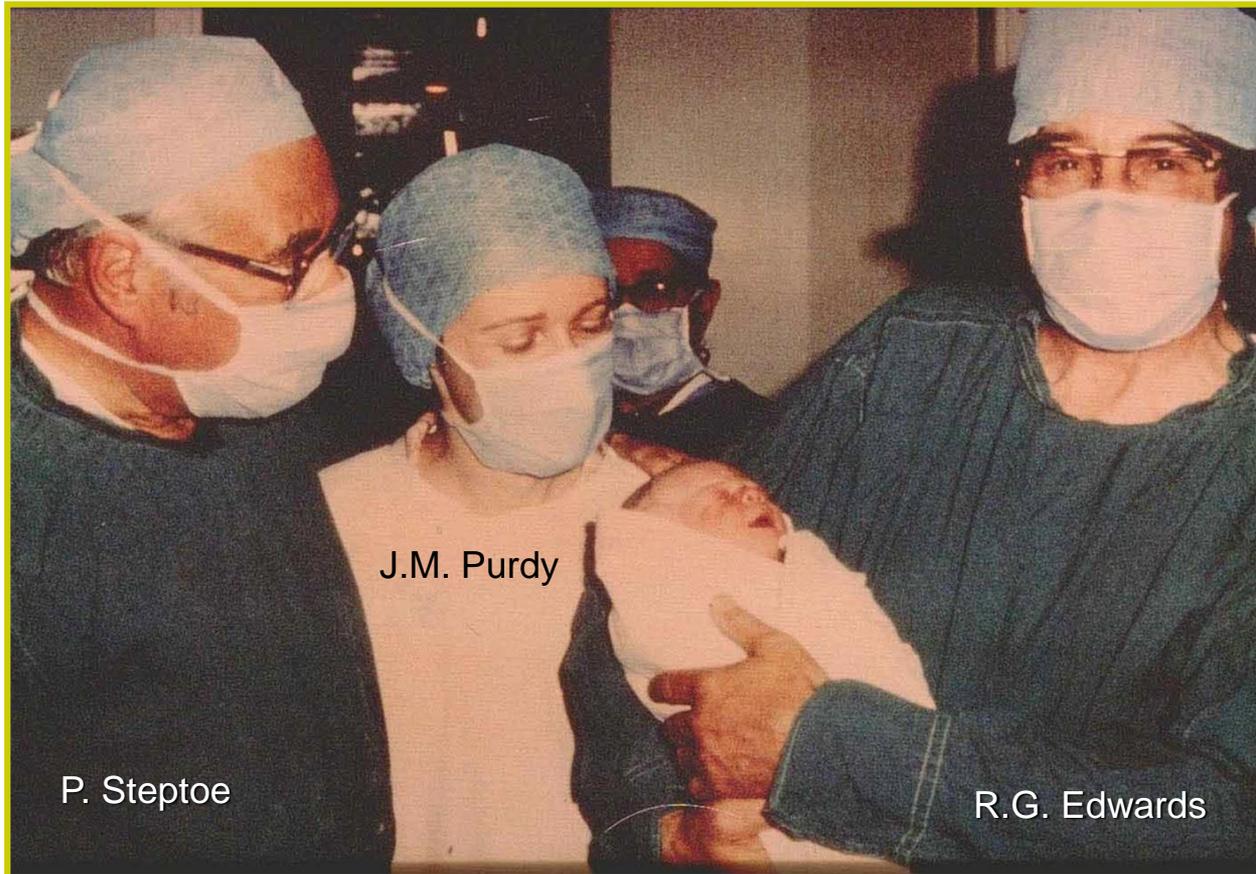
**FoRiSIE Winter School
in Clinical Endocrinology**

7-11 gennaio 2019



Villa Tuscolana
Frascati - Roma

LA FECONDAZIONE IN VITRO



25 Luglio 1978, Oldham and District Hospital, nasce Louise Brown (39 settimane di gestazione)

Stephoe PC, Edwards RG. Birth after reimplantation of a human embryo. Lancet 1978;2:366.

Louise Brown, the first baby born from IVF in the world in 1978, was conceived as a result of fertilization of a **single preovulatory oocyte collected in the course of a natural cycle**.



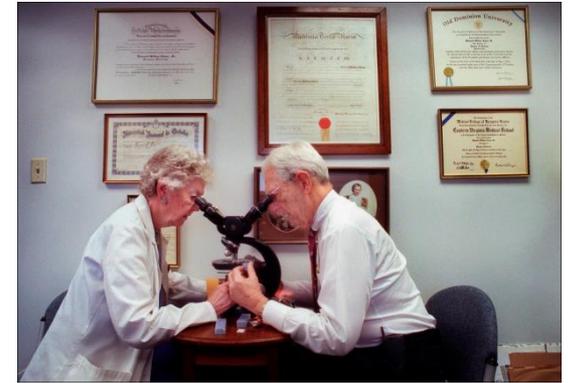
Jones HW Jr, Jones GS, Andrews MC, Acosta A, Bundren C, Garcia J, et al. The program for IVF Norfolk. Fertil Steril 1982;38:14–21. Vital Inization of Pregnancy (VIP)

They employed a **stimulation protocol** consisting of 150 IU of hMG daily starting on the third day of the cycle. The average number of eggs retrieved was 3.7 (only 1.5 mature oocytes) and the pregnancy rate per transfer was 25%.



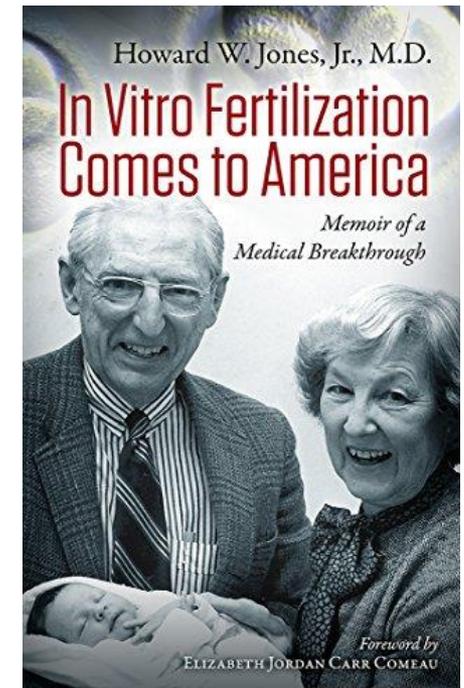
In the early days of IVF the use of “minimal” GT daily doses, as compared with the current dosages used, resulted in very reasonable pregnancy rates despite a low number of preovulatory oocytes retrieved. In addition, multiple pregnancies were rather uncommon, and OHSS was somewhat rare.





She was born December 28, 1981 at 7:46 am, after her mother received a total of 7 ampules of hMG over 4 days. No more than 150 IU of hMG, or two ampules, were given per day.

With this formula, Georgeanna and Howard Jones performed 55 laparoscopic oocyte retrievals resulting in 31 embryo transfers and 7 pregnancies over the course of one year.



A MATTER OF LIFE



ROBERT EDWARDS
& PATRICK STEPTOE

THE SENSATIONAL
STORY OF
THE WORLD'S FIRST
TEST-TUBE BABY



THE MIRACLE OF THE CENTURY

On July 25th 1978, Louise Brown, the world's first test-tube baby, was born. This dramatic medical breakthrough, which was hailed in every country throughout the world, was the climax of ten years of painstaking research and often heartbreaking trial and error by two doctors – gynaecologist Patrick Steptoe and scientist Robert Edwards.

In this book they reveal the secrets of their long collaboration, a unique example of co-operation between consultant and scientist, the hospital ward and the laboratory. They describe their lengthy struggles and the opposition which they encountered from religious groups, official sources, even their own profession. Above all, they tell the story of Louise Brown from the moment that Patrick Steptoe secured a mature egg from the ovary of Mrs Lesley Brown, who was infertile, to the fertilisation of the egg under laboratory conditions. And finally, nine months later, came the triumphant delivery by Caesarean section and the Browns held the normal, healthy daughter they had longed for.

Extraordinary, fascinating and compelling, A MATTER OF LIFE is a testimony to the sheer determination of two doctors to bring hope and joy to thousands of childless couples throughout the world – it is, without doubt, a miracle in the history of medicine.

0 7221 8173 6 AUTOBIOGRAPHY

UNITED KINGDOM £1.50 · AUSTRALIA \$5.50 · MALTA £1.50
Australia recommended price only



Nobel Prize in Physiology or Medicine 2010

Robert G. Edwards

- The development of in vitro fertilization



Born 1925, Manchester, UK.
PhD, Edinburgh University, worked in London and Cambridge
Professor Emeritus, Cambridge University, UK

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Jill Langlois | April 10, 2013 10:39

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Robert Edwards: Nobel Prize-winning test-tube baby pioneer dies at 87

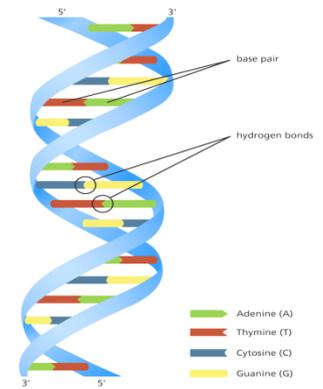
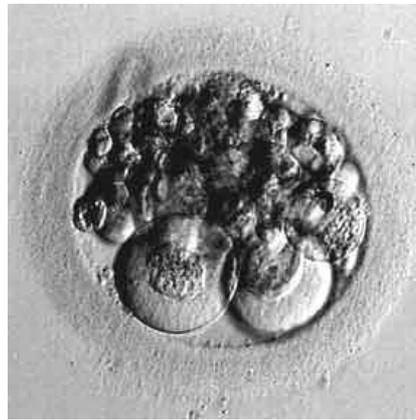
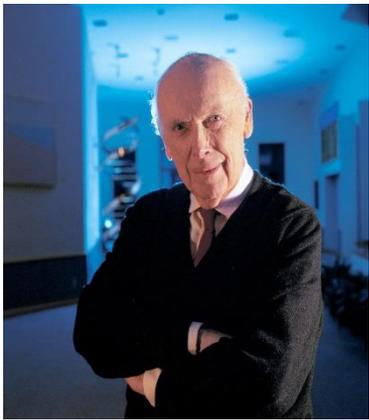
British scientist and Nobel Prize-winner Robert Edwards, known for his pioneering work developing in vitro fertilization (IVF), has died.



**Louse Brown è nata
il 25 luglio del 1978**



**Edwards ha ricevuto il
premio Nobel per la
Fisiologia e Medicina
nel dicembre del 2010**

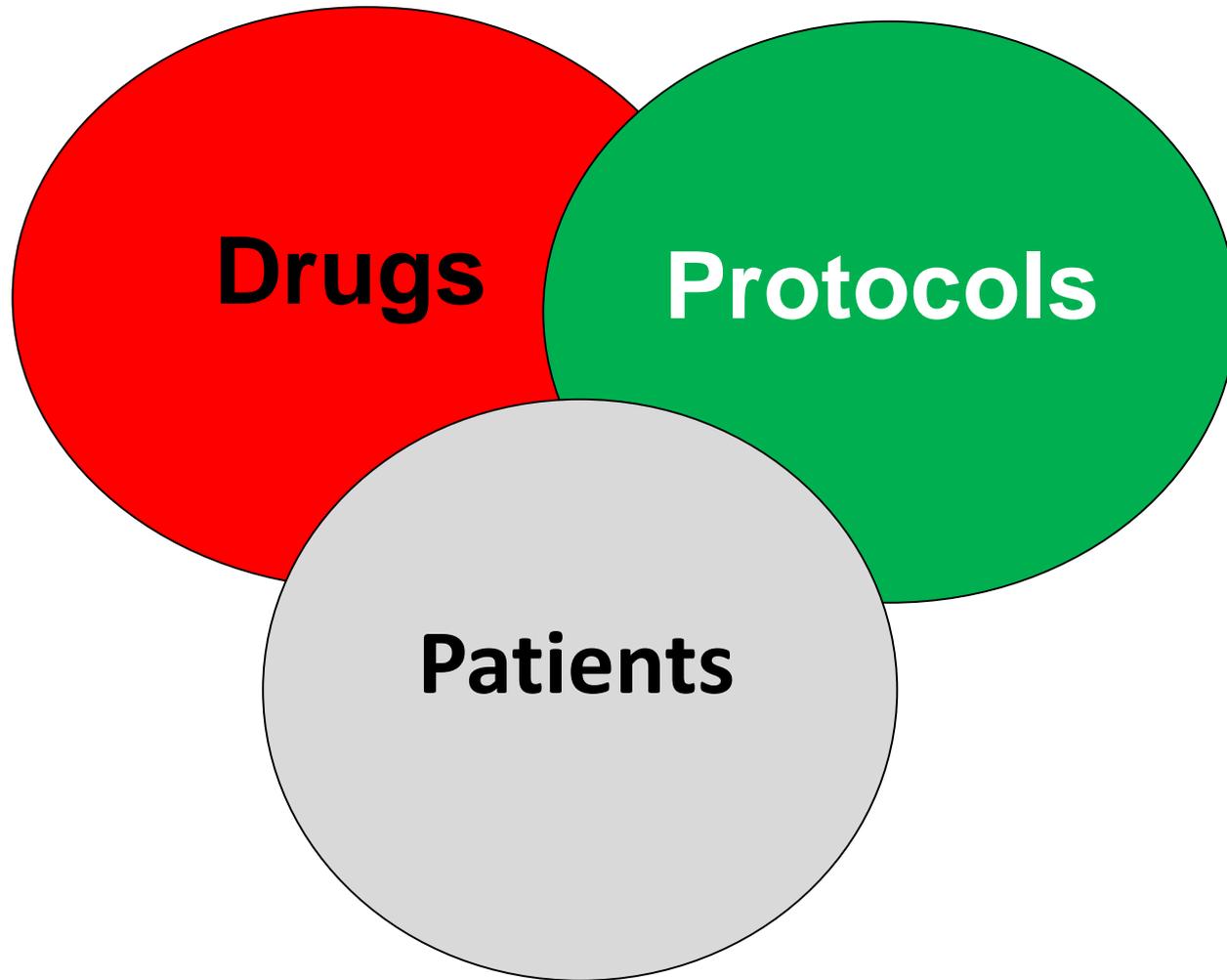


James Watson, premio Nobel nel 1962, sfidò anche lui Edwards:

«Lei può continuare I suoi studi solo se accetterà la necessità di praticare infanticidi. Ci saranno molti errori. Cosa faremo di questi errori? Dobbiamo obbligarci a pensare anche alle cose che rifiutiamo di considerare».

Potete immaginare come la stampa Inglese riportò queste parole.

COH for ART



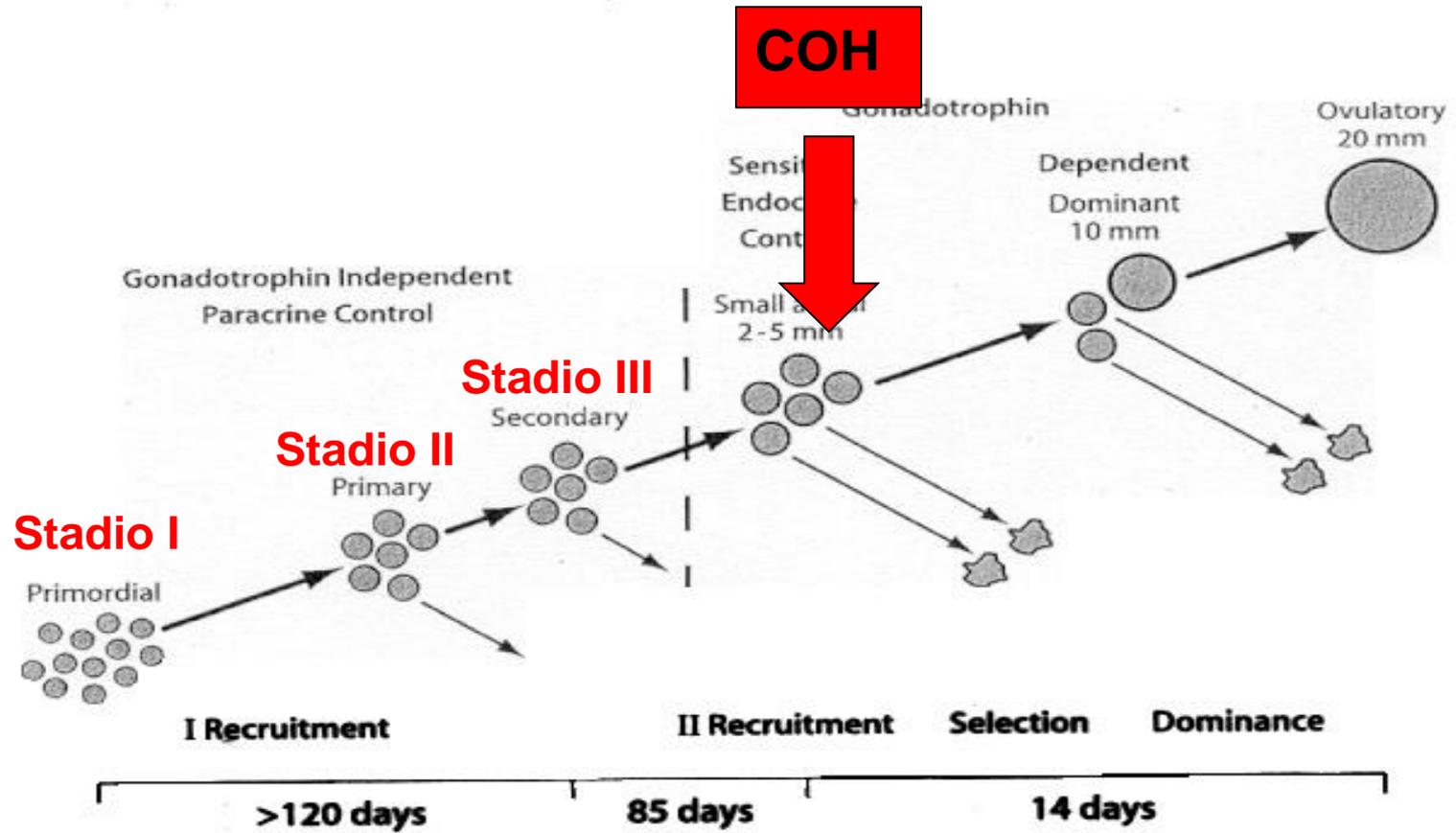
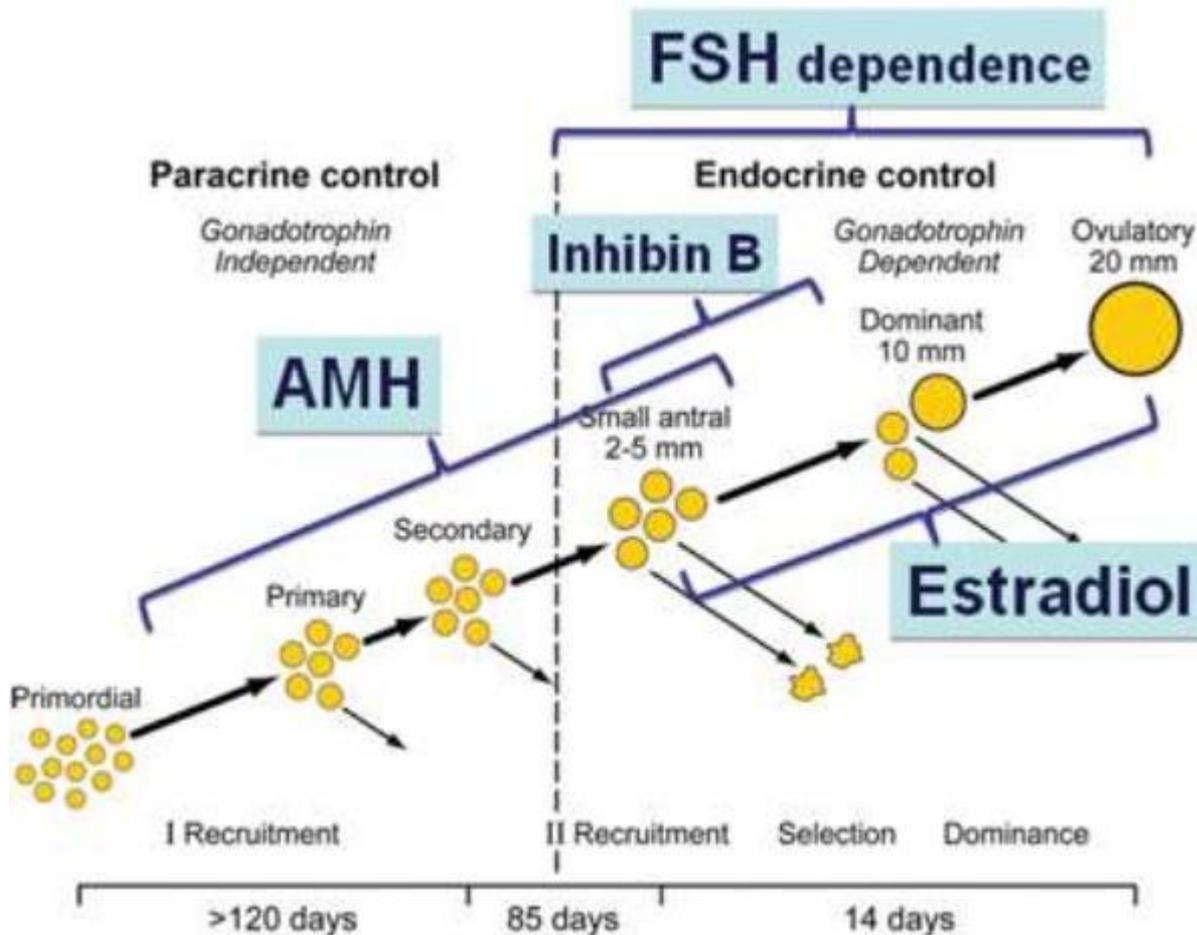
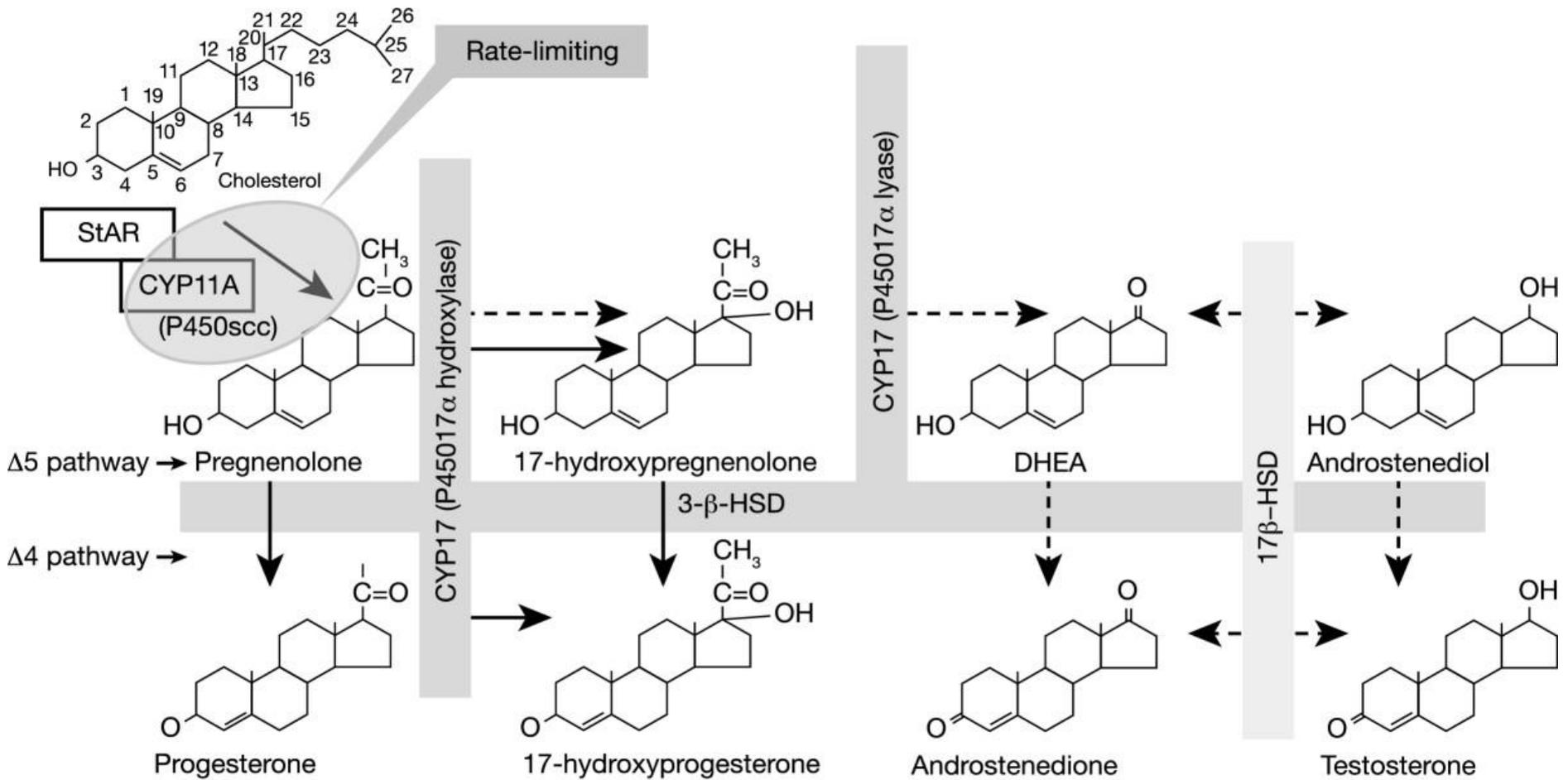


Fig. 1. Folliculogenesis in women. The *dashed line* indicates the time of antrum formation (0.1–0.2 mm diameter)

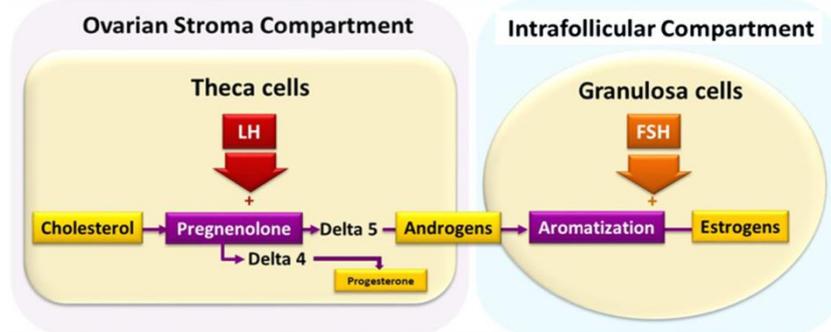
Markers of ovarian reserve



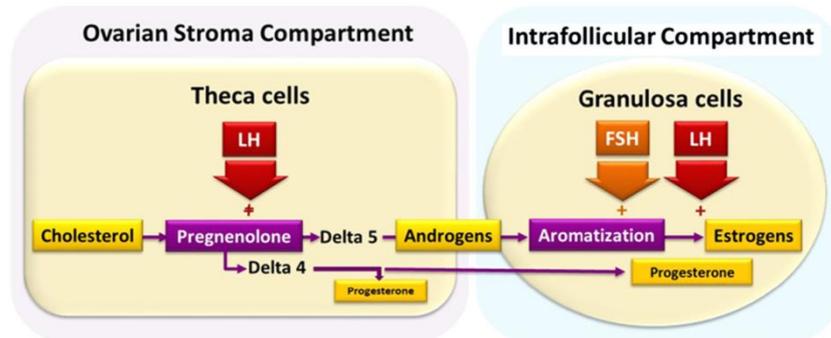


StAR = steroidogenic acute regulatory protein
 3 β -HSD = 3 β -hydroxysteroid dehydrogenase

Follicular Phase



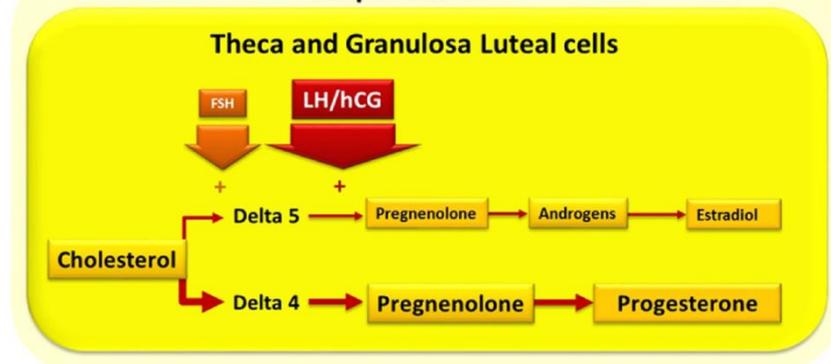
Early follicular phase (follicles <10-12 mm diameter)



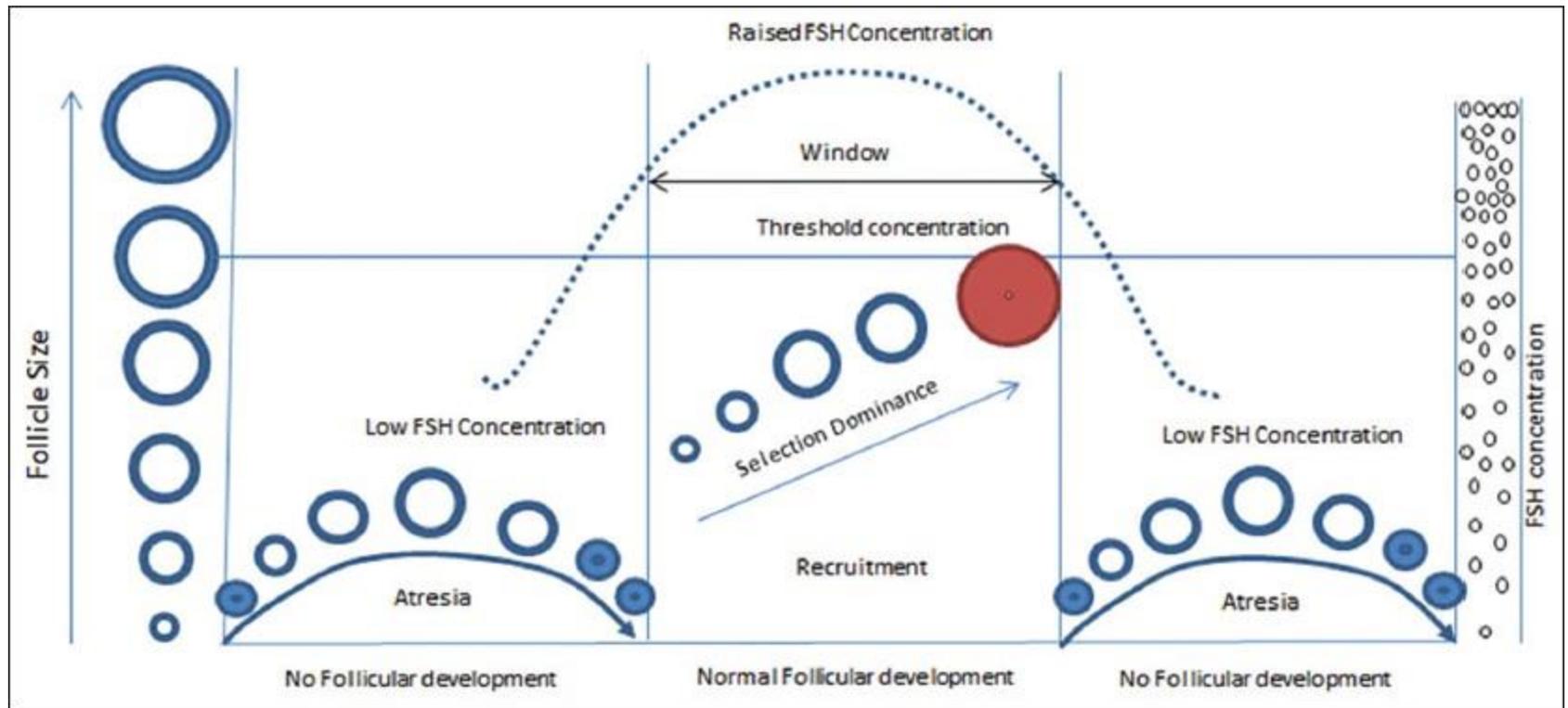
Late follicular phase (follicles > 10-12 mm diameter)

Luteal Phase

Corpus Luteum



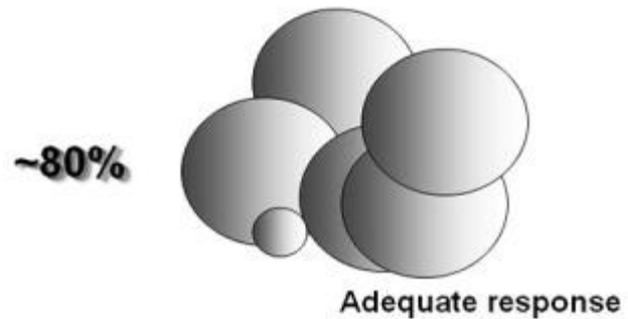
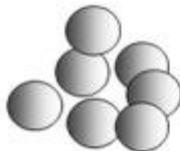
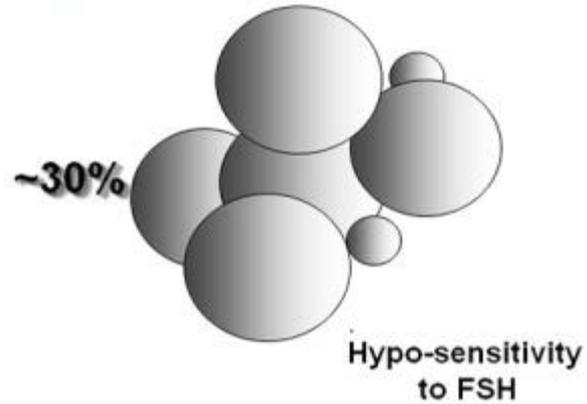
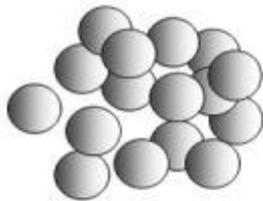
FSH threshold window



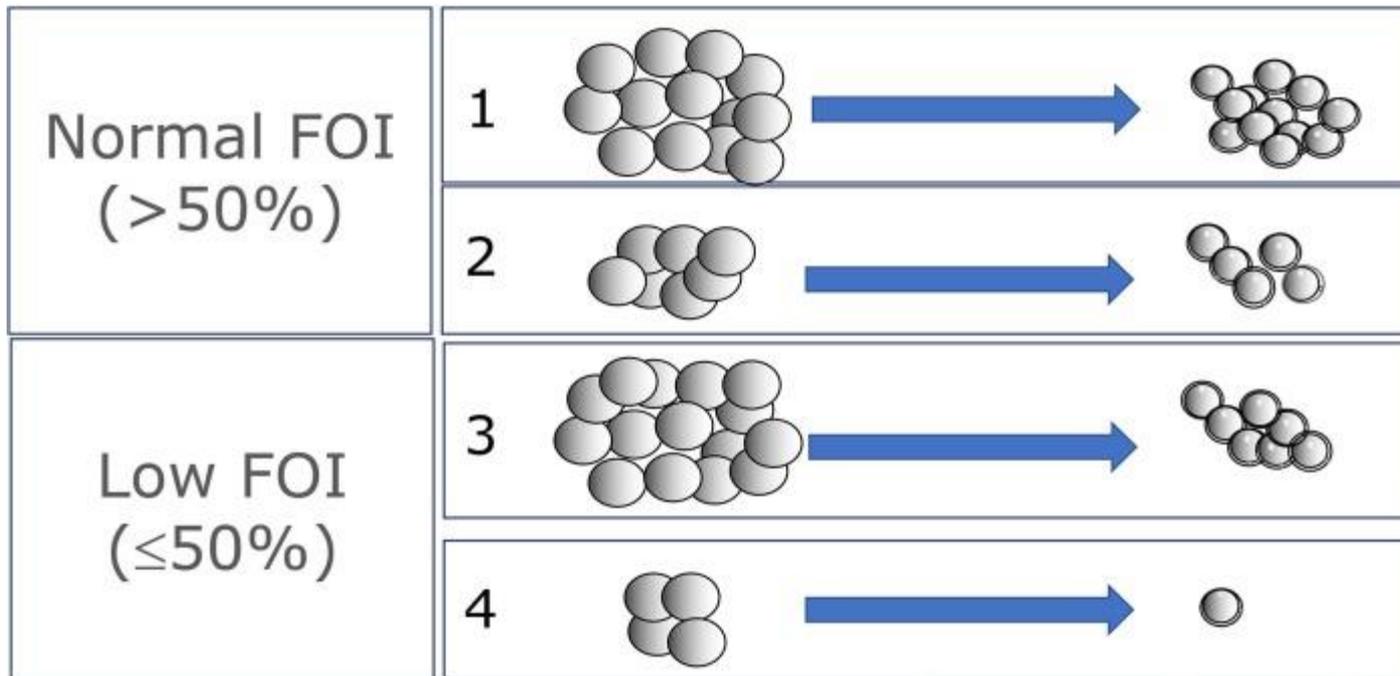
FSH concentrations need to surpass a distinct level to stimulate ovarian follicle growth. The window concept stresses the significance of a limited duration of elevated FSH levels above the threshold for single dominant follicle selection.

The meaning of ovarian "sensitivity" to FSH

Follicle Output Rate (FORT)



Follicle-to-Oocyte Index (FOI)* = Oocyte Number/Antral Follicle Countx100



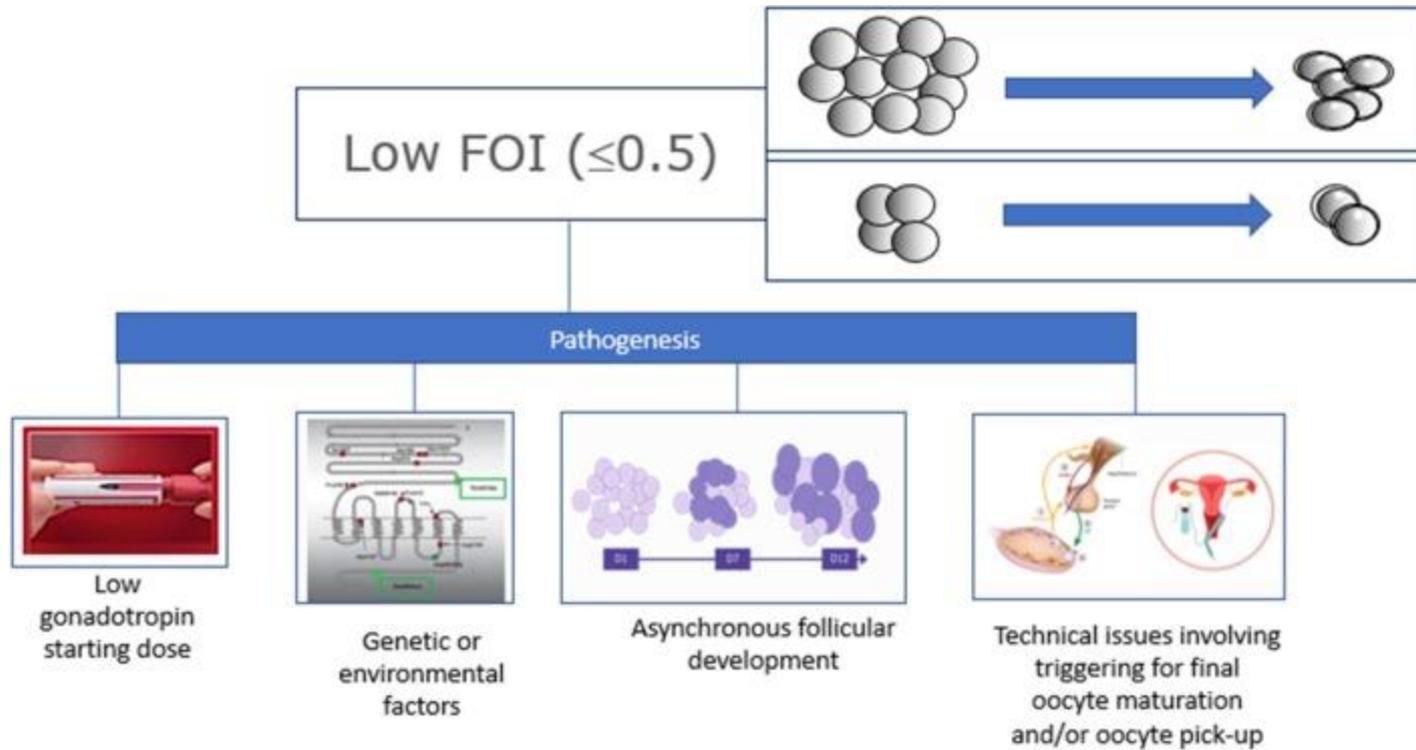
*Ratio between the number of oocytes retrieved at oocyte pick-up and the number of antral follicles at start of stimulation (FOI ranges from 0 to 100)

POSEIDON
Patient Oriented Strategies Encompassing Individualized Oocyte Number

 GROUP
POSEIDON

More information on
<http://www.groupposeidon.com/>
Developed by Calvosa, S.C., Corbelli, A., Alaggio, C. (2018)

Possible causes of low Follicle-to-Oocyte Indexes



Drugs for COH

Anni 80

Clomiphene
HMG
FSH

Anni 90

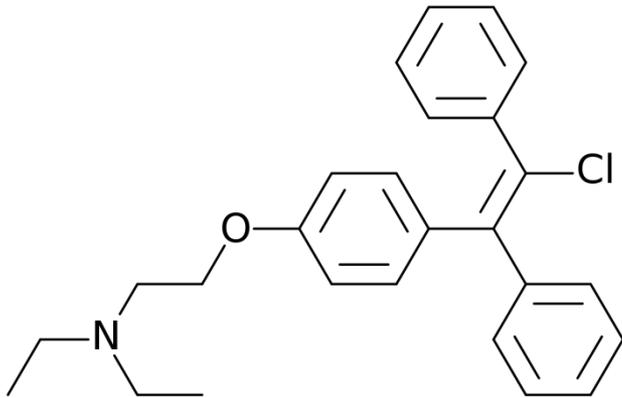
HP FSH
Rec FSH
Agonist

Anni 2000

Rec LH
Rec FSH/LH
HP HMG
Antagonist

Anni 2010: FSH long-acting

Citrato di Clomifene



1- [p (b-dietilaminoetossi) fenil] -1,2-difenilcloroetilene

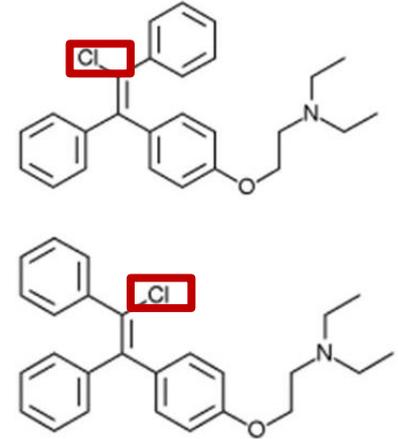
Enclomifene

(E-Clomifene)

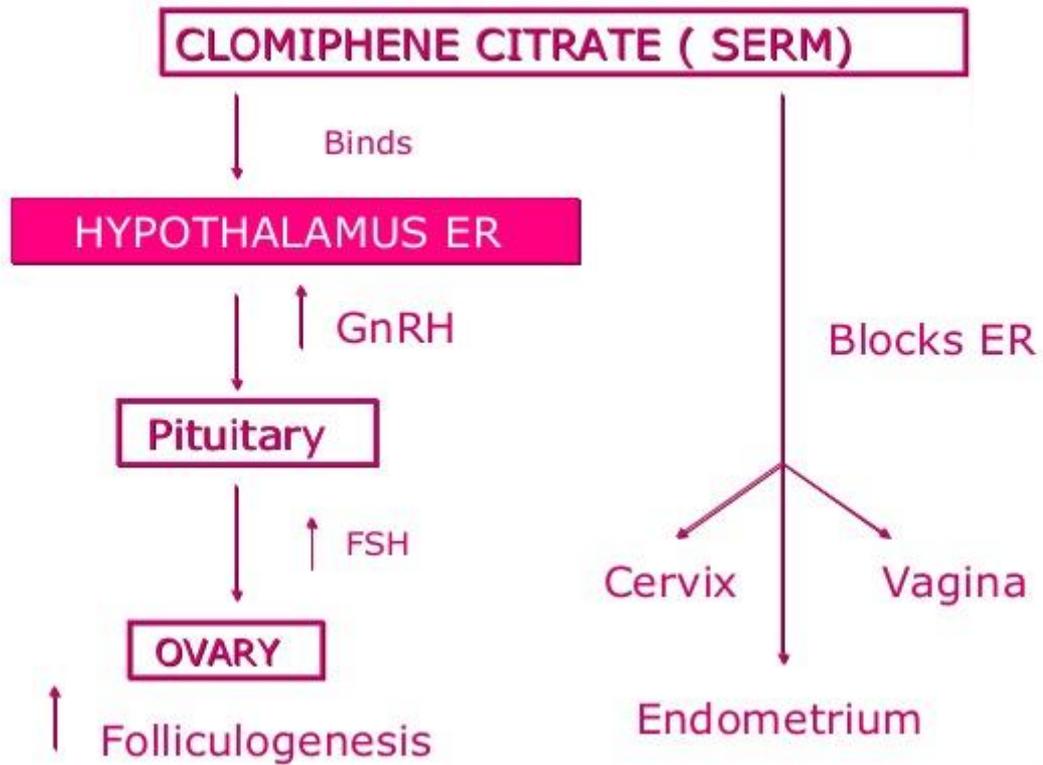
e

Zuclomifene

(Z-Clomifene)



CC is a racemic mixture of the **two stereoisomers** enclomifene and zuclomifene, with the former being the stereoisomer mainly responsible for its efficacy in ovulation induction . CC is metabolized in the liver and excreted in the stool, with a relatively long half-life of 5e7 days . The less potent stereoisomer zuclomifene remains detectable for much longer periods of time, without major clinical relevance



Use of clomiphene citrate in infertile women: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

SUMMARY

- Clomiphene citrate is an effective first-line treatment for the majority of women with anovulatory infertility.
- Clomiphene citrate treatment combined with intercourse does not increase cycle fecundity in couples with unexplained infertility compared with expectant management.
- Clomiphene citrate treatment in combination with IUI seems to increase cycle fecundity in couples with unexplained infertility compared with expectant management.
- Side effects of CC treatment generally are mild and well tolerated. The principal risk of CC treatment is an increased incidence of multifetal gestation (<10%).

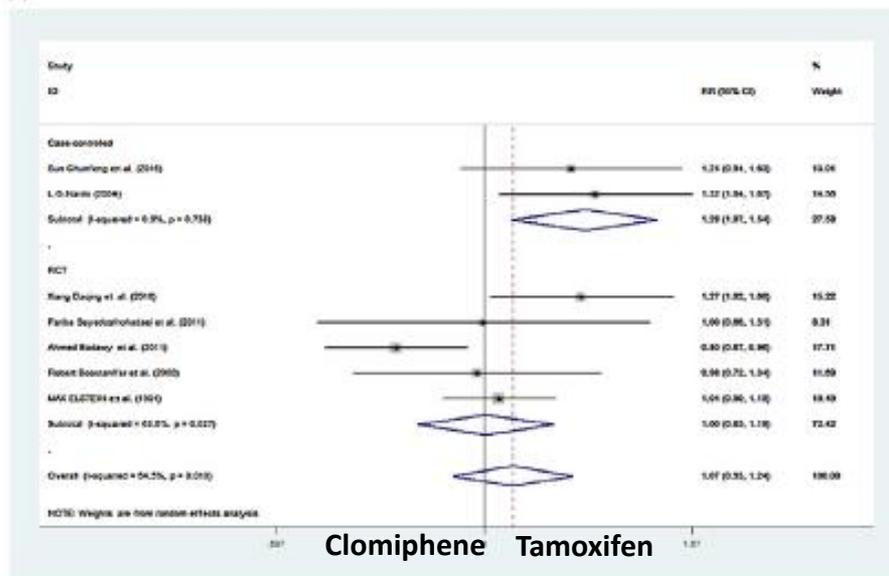
Review article

Tamoxifen versus clomiphene citrate for ovulation induction in infertile women

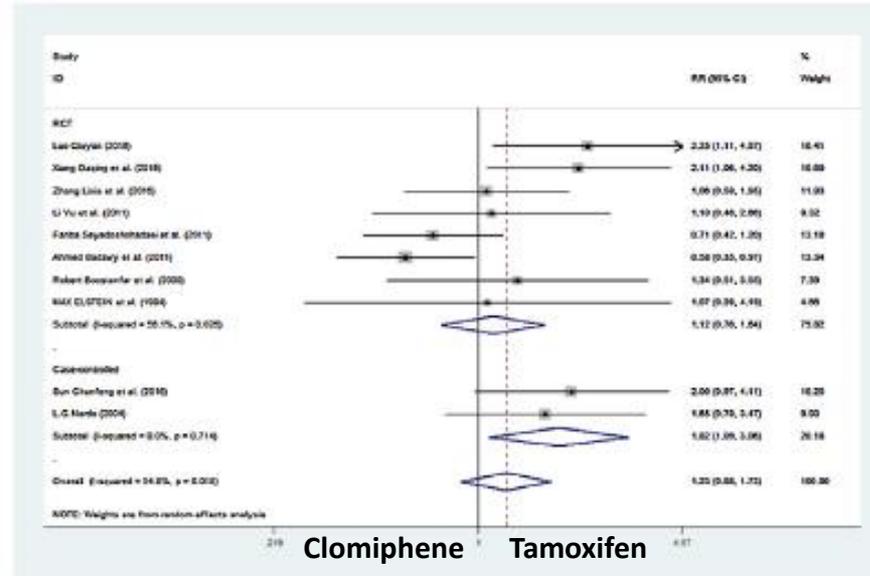
Jie Li^{a,1,*}, Li Deng^{a,1}, Yang Chen^{b,1}, Haiying Zhang^{a,*}

Forest plot of comparison of tamoxifen (TMX) with clomiphene citrate (CC) for **ovulation rate** using random models (A), **pregnancy rate** using random models (B)

A

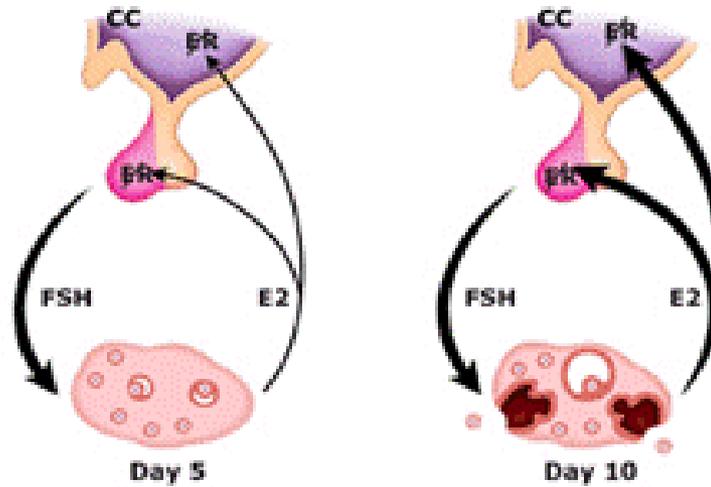


B

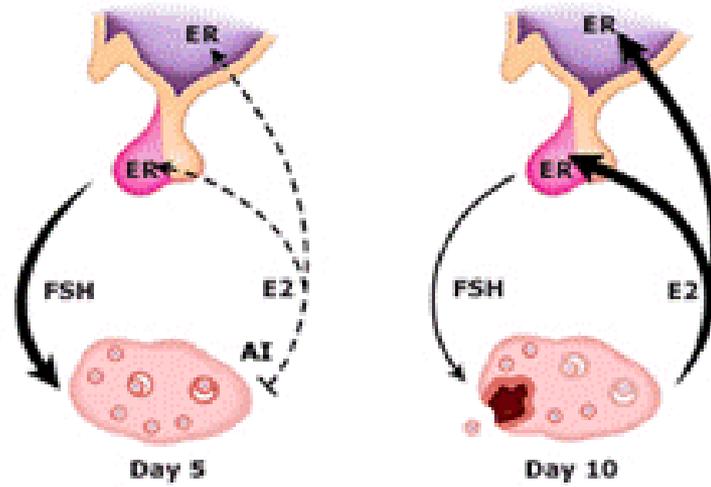


Aromatase inhibitor treatment

Clomiphene Citrate Treatment



Aromatase Inhibitor Treatment



OVULATION INDUCTION

Two mechanisms

INDIRECT ACTION

Clomiphene

Estrogens

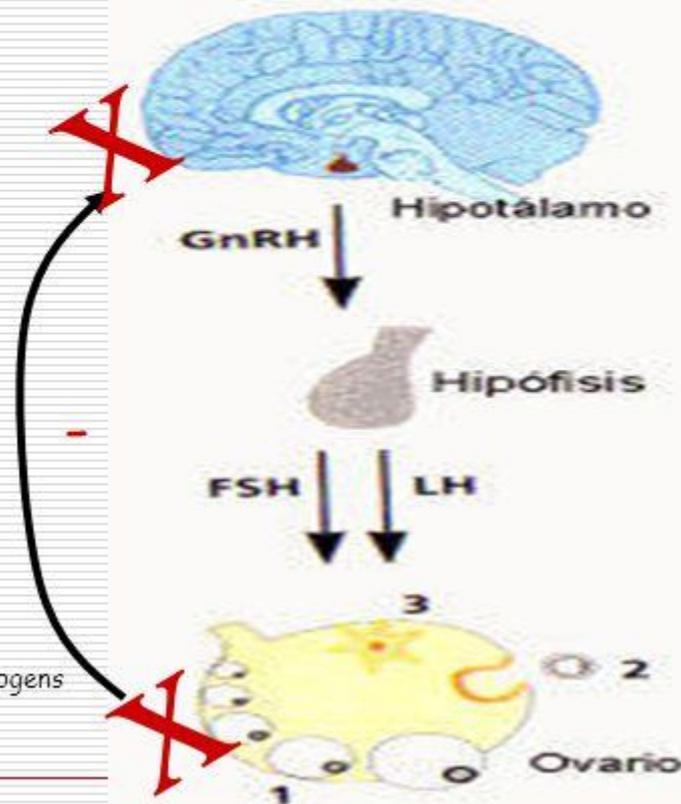
Aromatase inhibitors

↓ Decrease androstenedione conversion to estrogens

DIRECT ACTION

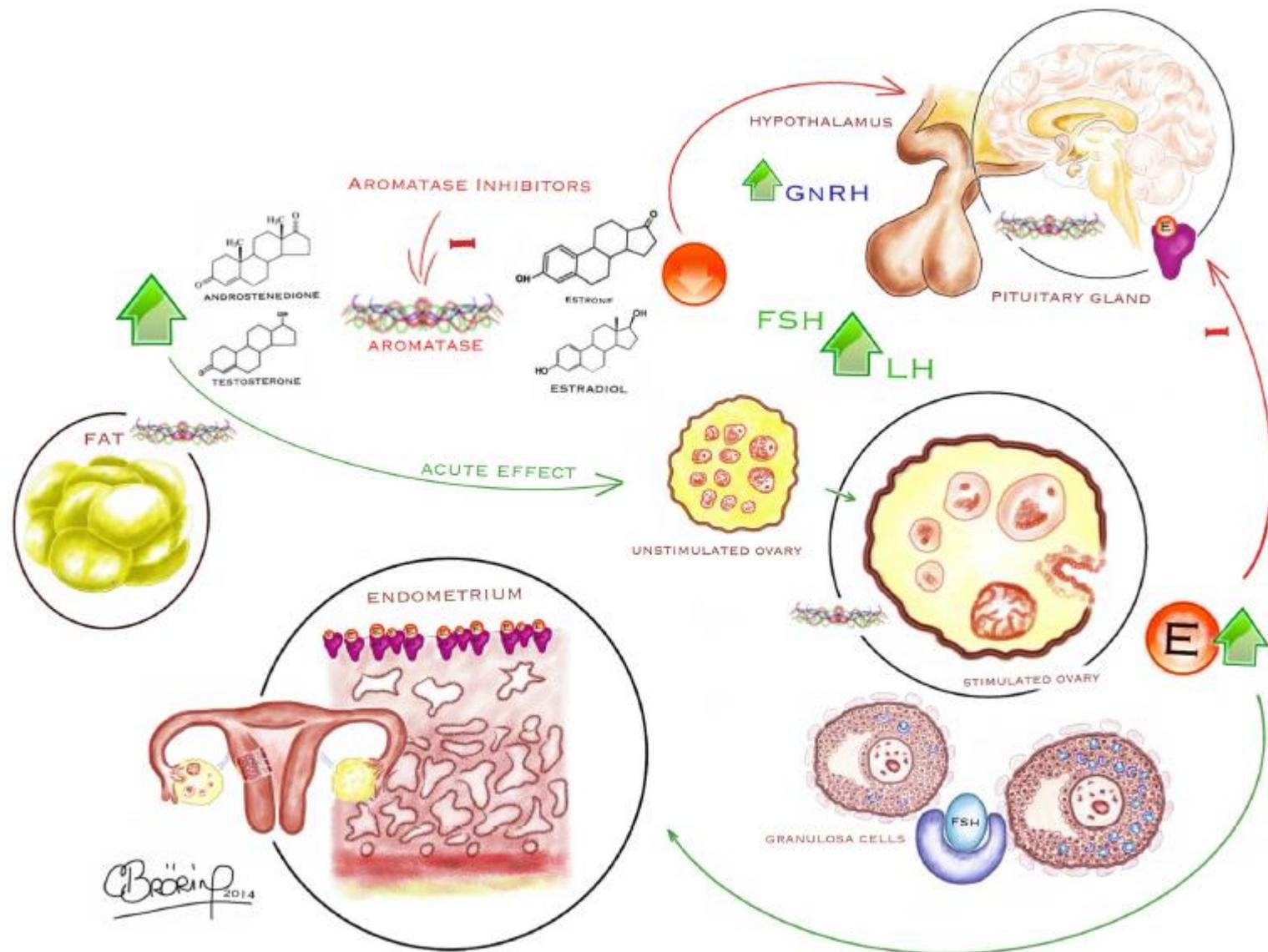
GnRH

Gonadotropins



Aromatase Inhibitors for Ovulation Induction

Stefano Palomba



Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility

M.P. Diamond, R.S. Legro, C. Coutifaris, R. Alvero, R.D. Robinson, P. Casson, G.M. Christman, J. Ager, H. Huang, K.R. Hansen, V. Baker, R. Usadi, A. Seungdamrong, G.W. Bates, R.M. Rosen, D. Haisenleder, S.A. Krawetz, K. Barnhart, J.C. Trussell, D. Ohl, Y. Jin, N. Santoro, E. Eisenberg, H. Zhang, and for the NICHD Reproductive Medicine Network*

Abstract

BACKGROUND—The standard therapy for women with unexplained infertility is gonadotropin or clomiphene citrate. Ovarian stimulation with letrozole has been proposed to reduce multiple gestations while maintaining live birth rates.

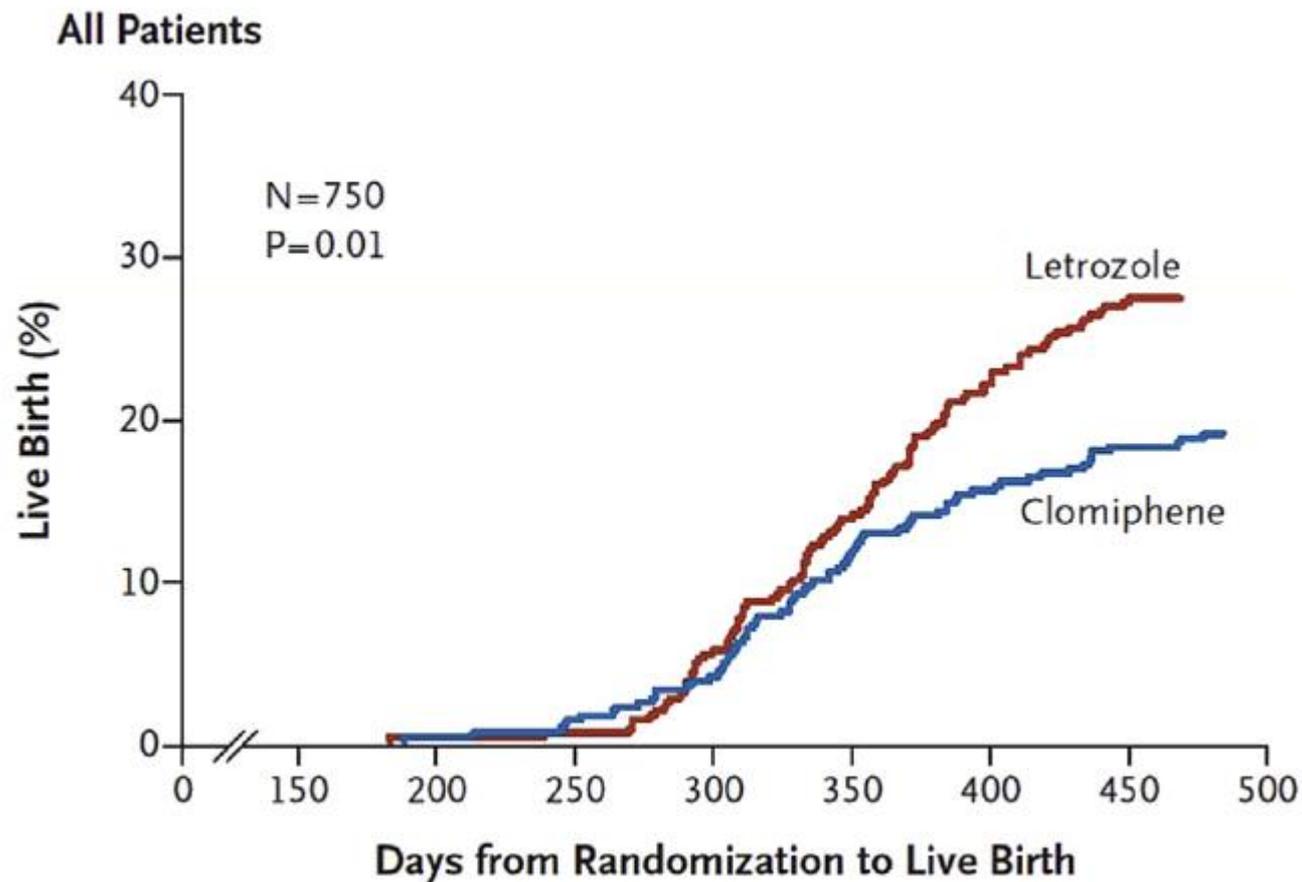
METHODS—We enrolled couples with unexplained infertility in a multicenter, randomized trial. Ovulatory women 18 to 40 years of age with at least one patent fallopian tube were randomly assigned to ovarian stimulation (up to four cycles) with gonadotropin (301 women), clomiphene (300), or letrozole (299). The primary outcome was the rate of multiple gestations among women with clinical pregnancies.

RESULTS—After treatment with gonadotropin, clomiphene, or letrozole, clinical pregnancies occurred in 35.5%, 28.3%, and 22.4% of cycles, and live birth in 32.2%, 23.3%, and 18.7%, respectively; pregnancy rates with letrozole were significantly lower than the rates with standard therapy (gonadotropin or clomiphene) ($P = 0.003$) or gonadotropin alone ($P < 0.001$) but not with clomiphene alone ($P = 0.10$). Among ongoing pregnancies with fetal heart activity, the multiple gestation rate with letrozole (9 of 67 pregnancies, 13%) did not differ significantly from the rate with gonadotropin or clomiphene (42 of 192, 22%; $P = 0.15$) or clomiphene alone (8 of 85, 9%; $P = 0.44$) but was lower than the rate with gonadotropin alone (34 of 107, 32%; $P = 0.006$). All multiple gestations in the clomiphene and letrozole groups were twins, whereas gonadotropin treatment resulted in 24 twin and 10 triplet gestations. There were no significant differences among groups in the frequencies of congenital anomalies or major fetal and neonatal complications.

CONCLUSIONS—In women with unexplained infertility, ovarian stimulation with letrozole resulted in a significantly lower frequency of multiple gestation but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT01044862.)

Pharmacology of medications used for ovarian stimulation

Alexander M. Quaas, MD ^{a, b, c, *}, Richard S. Legro, MD ^d



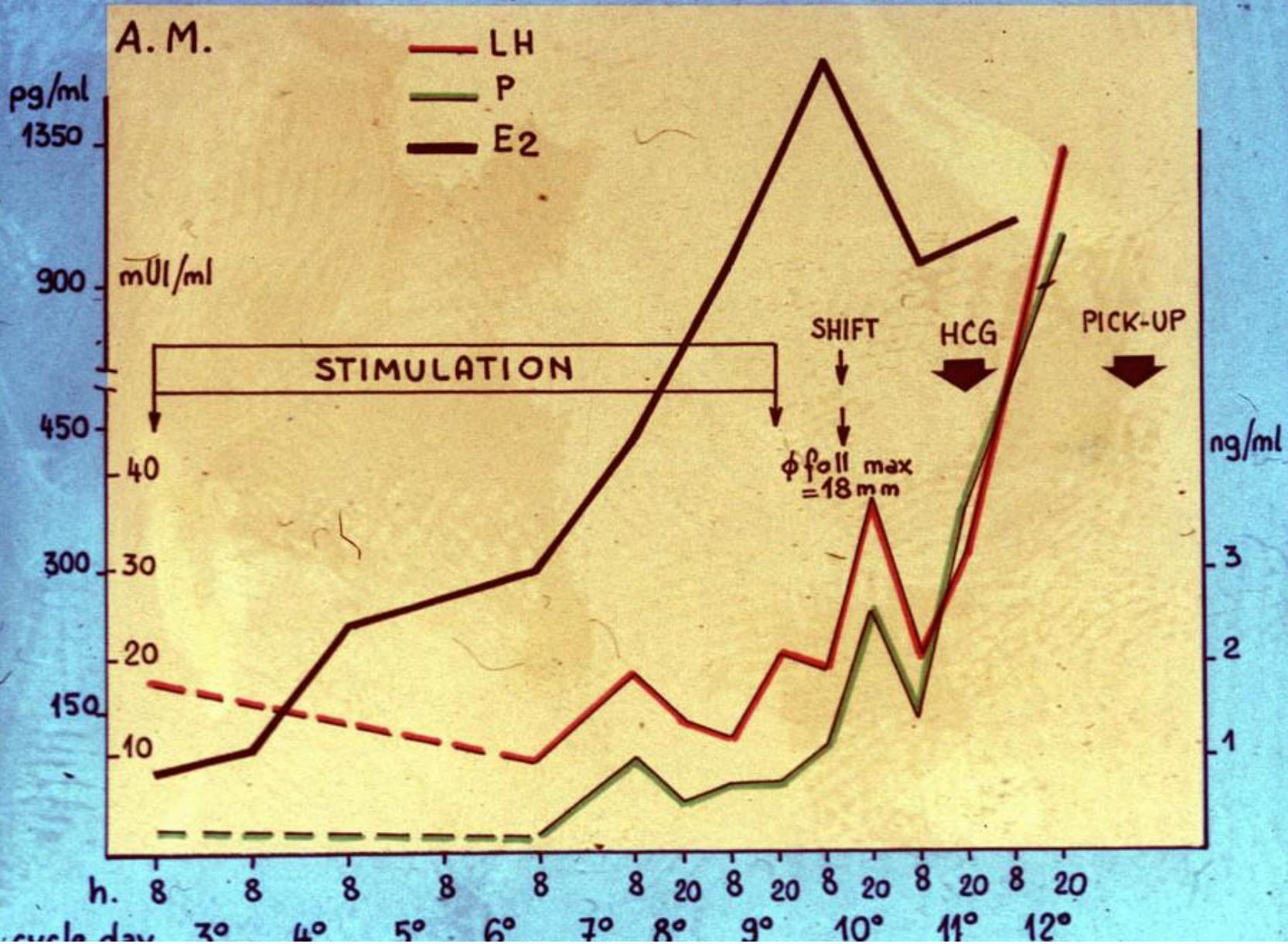
Mono-ovulation in women with polycystic ovary syndrome: a clinical review on ovulation induction

Kathrine Birch Petersen ^{a,*}, Nina Gros Pedersen ^b, Anette Tønnes Pedersen ^c,
Mette Petri Lauritsen ^d, Nina la Cour Freiesleben ^e

	Ovulation	Multiple pregnancies	Time to pregnancy	Ultrasound examinations	Side-effects	Patient compliance
Lifestyle interventions	↑					
Metformin	↑					
Clomiphene citrate	↑↑					
Letrozole	↑↑↑					
Gonadotrophins	↑↑↑					
Ovarian drilling	↑					

↑ Less likely to induce ovulation
 ↑↑ Likely to induce ovulation
 ↑↑↑ Most likely to induce ovulation

Green colour: The least discomfort / lowest risk for the patient 
 Yellow colour: Moderate discomfort / risk for the patient 
 Red colour: Inconvenience for the patient / highest risk 



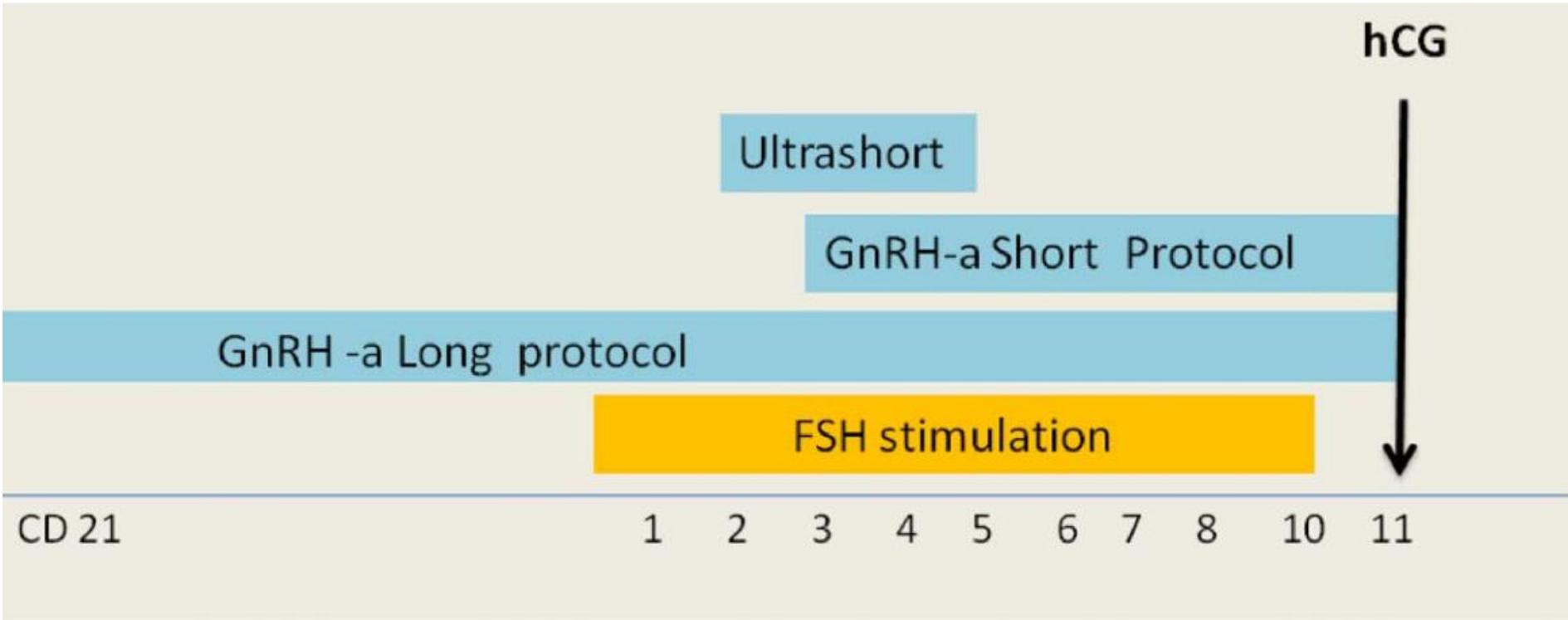
Agonisti del GnRH nella PMA

VANTAGGI

- riduzione dei cicli sospesi
- aumento del n. di follicoli reclutati
- aumento del numero e della qualità (?) degli ovociti prelevati
- sincronizzazione dei cicli

SVANTAGGI

- stimolazione ovarica più lunga e con dosaggio totale di GT più elevato
- aumento di OHSS



REVIEW

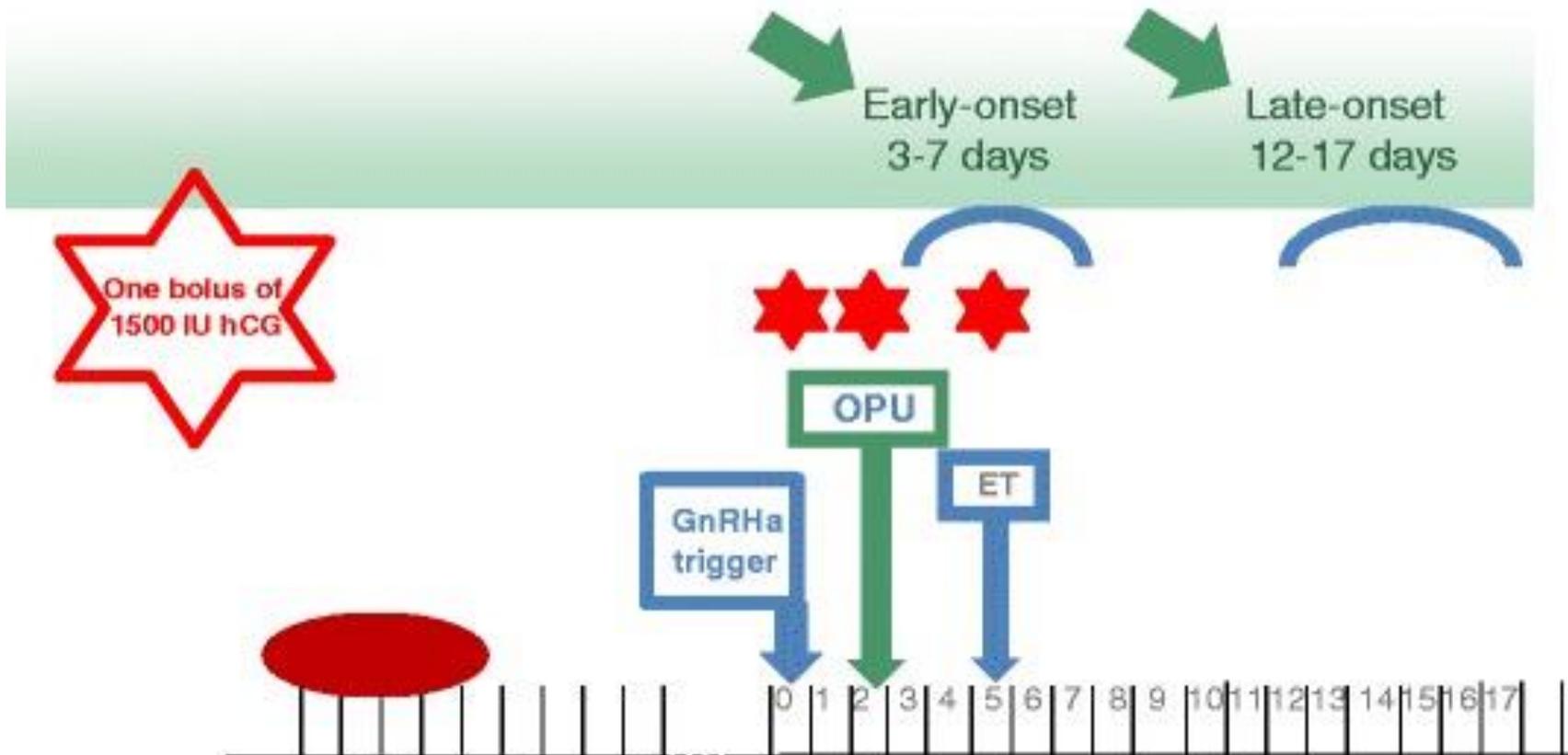
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Triggering final follicular maturation- hCG, GnRH-agonist or both, when and to whom?

Raoul Orvieto^{1,2}

OHSS-almost always develops after
hCG administration or in early pregnancy



Antagonisti del GnRH

Molecole con affinità competitiva, dose dipendente, superiore a quella della molecola endogena, per il recettore del GnRH, senza attività GnRH-mimetica.

GnRH ANTAGONISTI DOSI MULTIPLE

PROTOCOLLO FISSO

0.25 mg sc GnRH antagonista al giorno G5 o G6

PROTOCOLLO FLESSIBILE

0.25 mg sc GnRH antagonista

-Si adatta al diametro follicolare (13-14 mm)

-Si adatta al livello di E2 (400 to 600 pg/ml)

GnRH ANTAGONISTI DOSE SINGOLA

3 mg GnRH antagonista in FASE FOLLICOLARE TARDIVA (8°-9° GIORNO)

L'effetto inibitorio si manifesta per almeno 4 giorni e previene il picco di LH nell'80% dei cicli

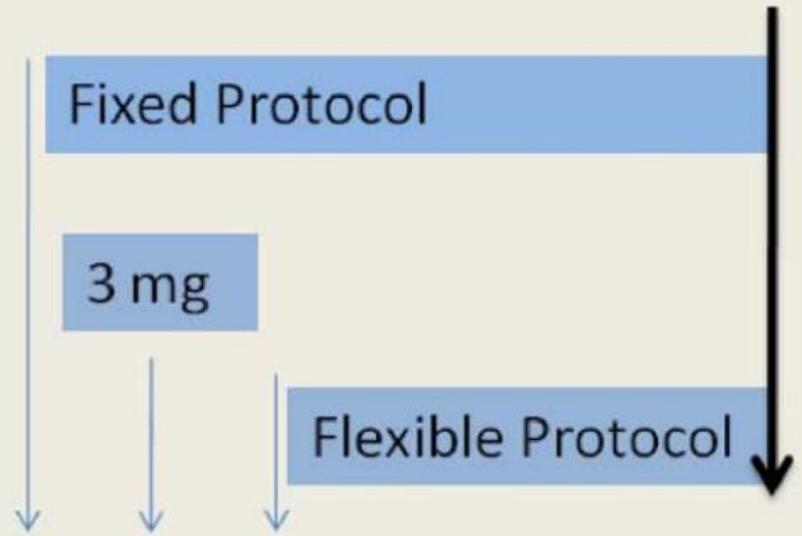
hCG

Fixed Protocol

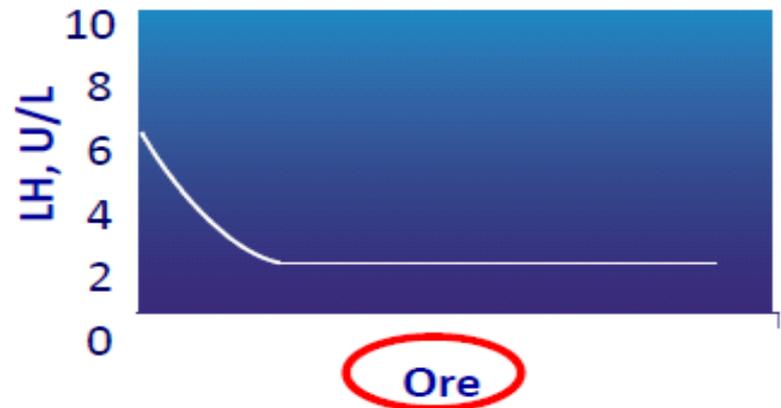
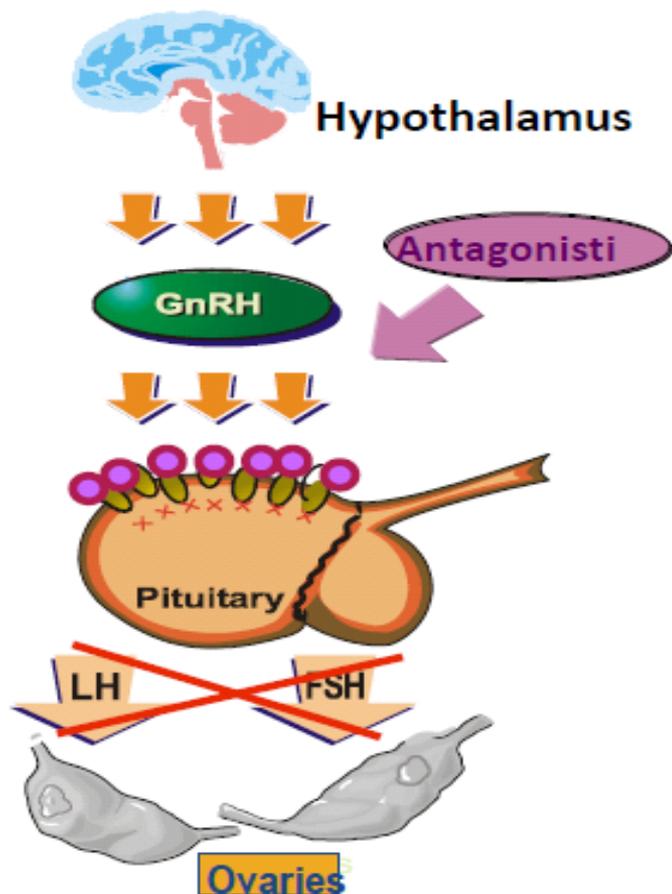
3 mg

Flexible Protocol

FSH Stimulation 1 2 3 4 5 6 7 8 9 10 11 12



GnRH ANTAGONISTI : MECCANISMO D'AZIONE

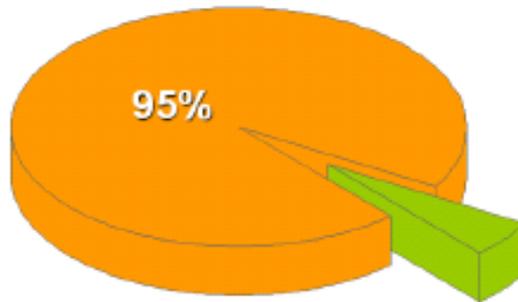


- non provocano effetto flare-up
- non provocano desensibilizzazione dei recettori ipofisari
- inibizione del rilascio di LH/FSH è quasi immediato
- il grado di soppressione è proporzionale al dosaggio

GnRH-antagonisti: vantaggi

- Blocco del picco spontaneo dell'LH
- Riduzione del periodo di trattamento
- Riduzione del numero di fiale di gonadotropine utilizzate
- Riduzione incidenza OHSS

REPORT MONDIALE
IVF WORLD MEETING IN PARIS 1995



PROPORZIONE DI CICLI IVF

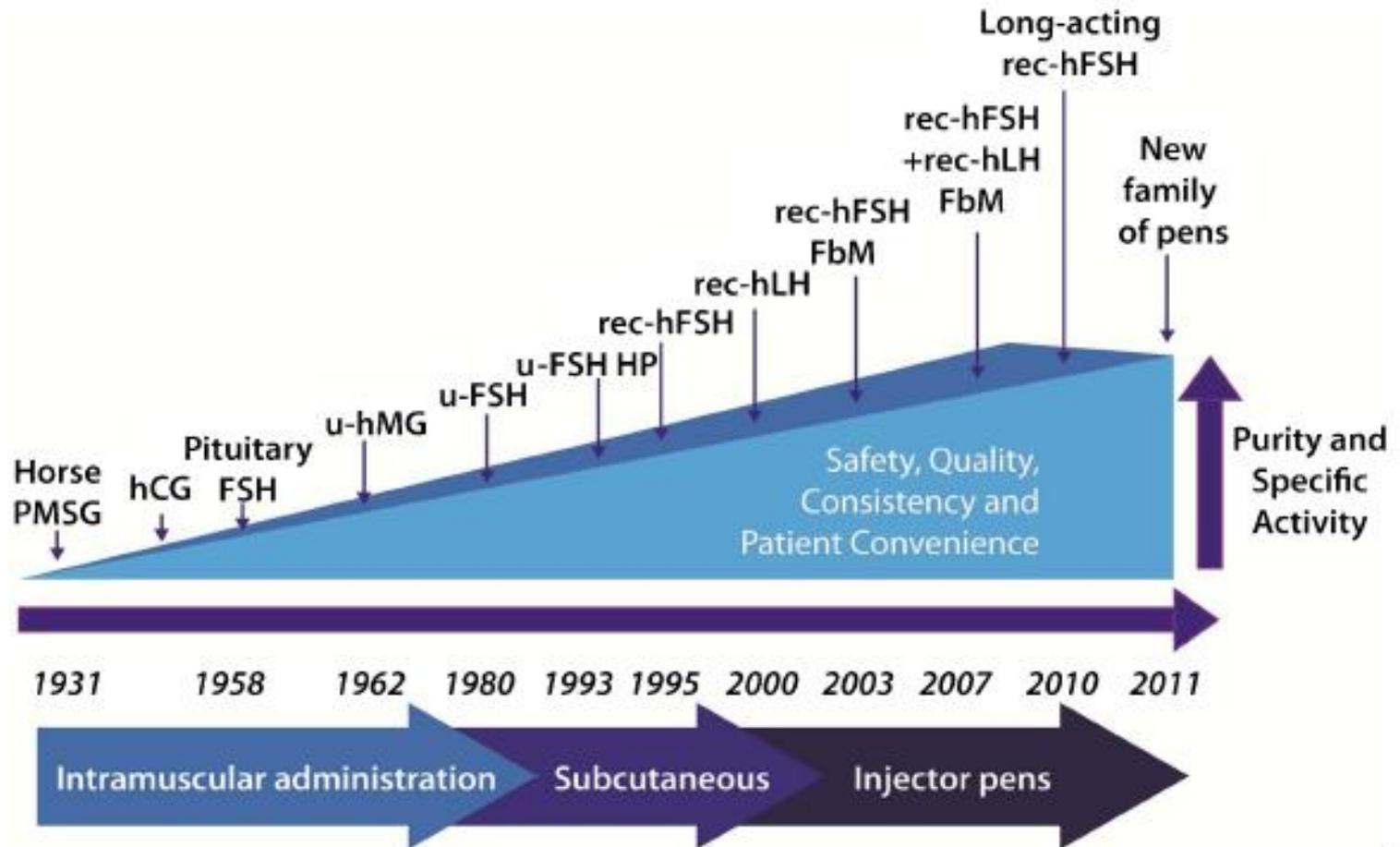


CICLI PIU' BREVI
MENO INIEZIONI

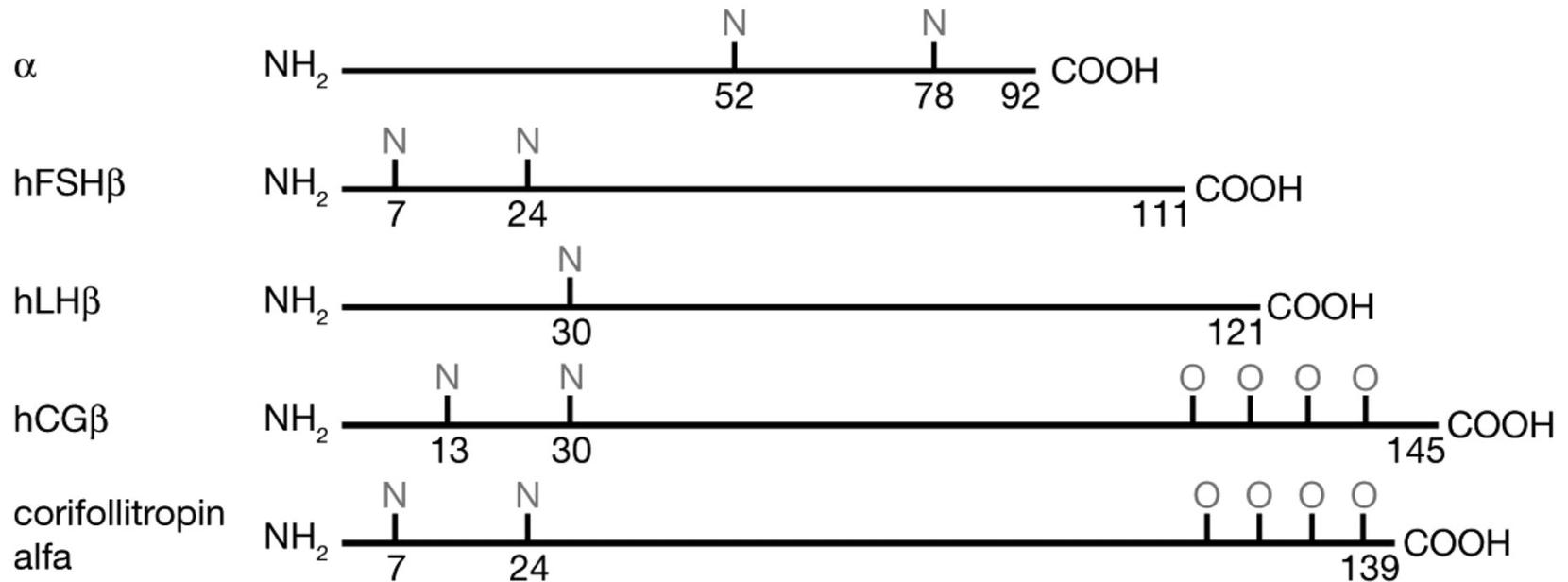
Gonadotropine

- FSH activity Human derived
 Recombinant
 Recombinant long acting
- LH activity Recombinant LH
 hCG

Exogenous Gonadotropins



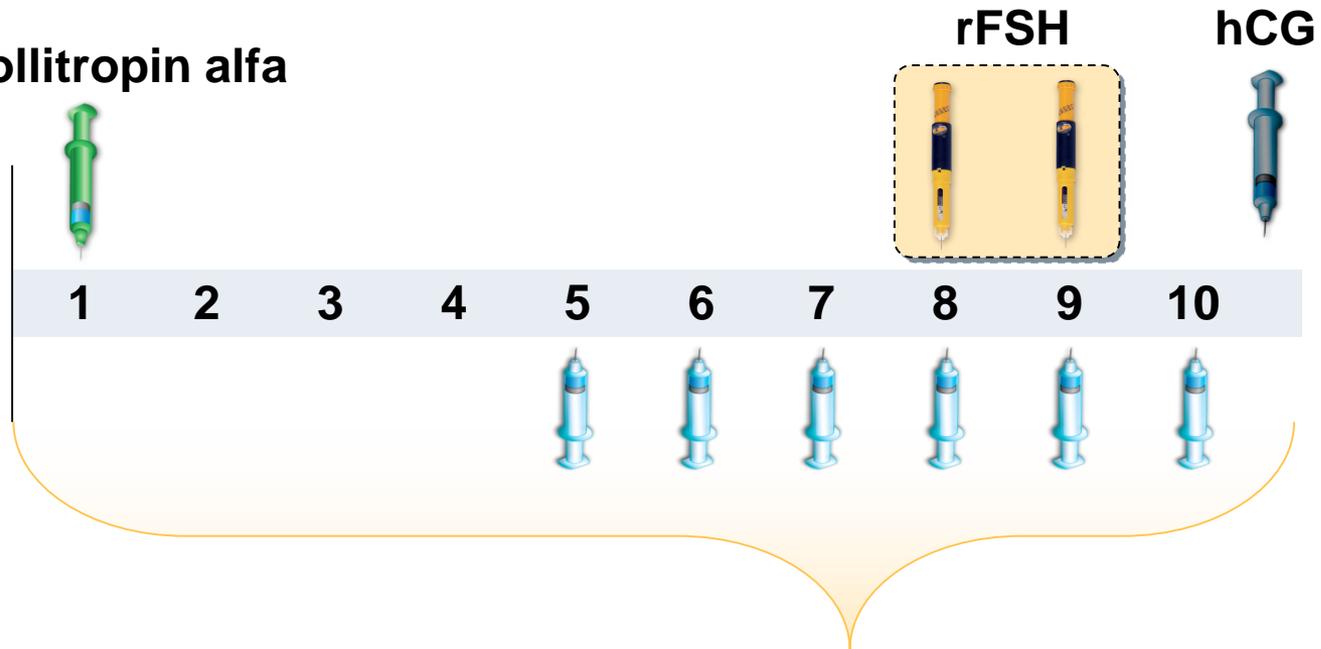
Corifollitropin α : structure



A recombinant fusion molecule of FSH and the CTP of the hCG β - subunit.

Corifollitropin α : protocol

Corifollitropin alfa



In the late 1980s and early 1990s, a widespread increase in the daily dosage of gonadotropins was introduced for multiple reasons that included:



the attempt to **increase the number of oocytes** for low responders,



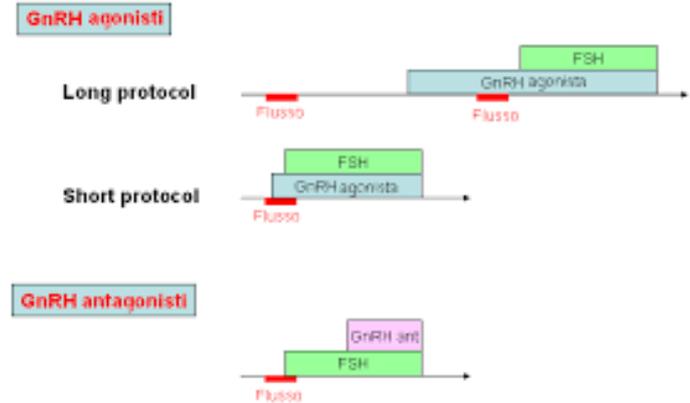
the goal of **retrieving excess oocytes** for embryo cryopreservation,



the introduction of suppression protocols with GnRH agonists that **eliminated the premature LH surge** but led to the increase in the dosage of GT required and the duration of treatment.



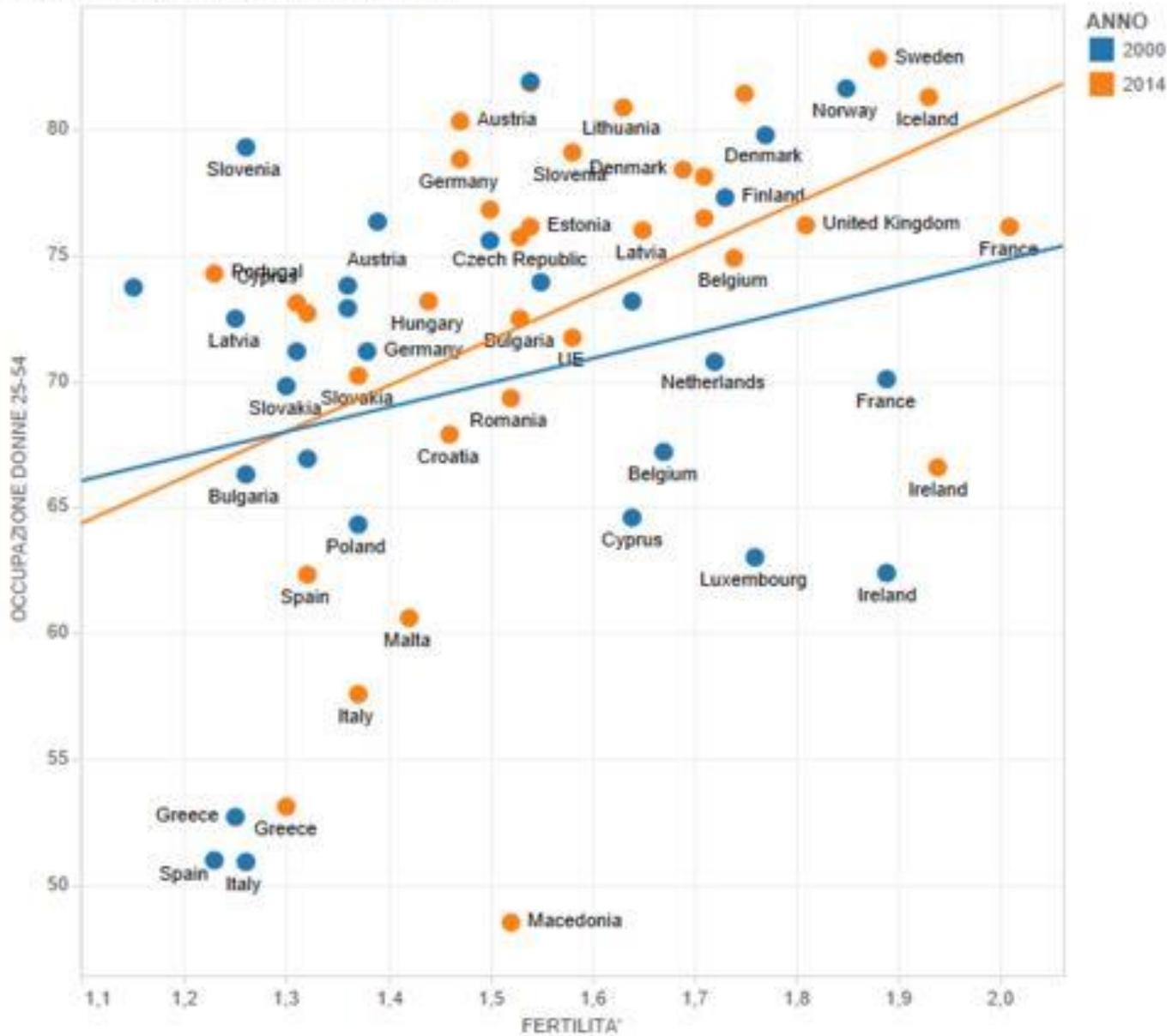
An increase in the recruitment of multiple fertilizable oocytes definitely contributed to **better success rates with IVF**, but also resulted in an increased cost of treatment and an increased incidence of multiple pregnancies and OHSS.

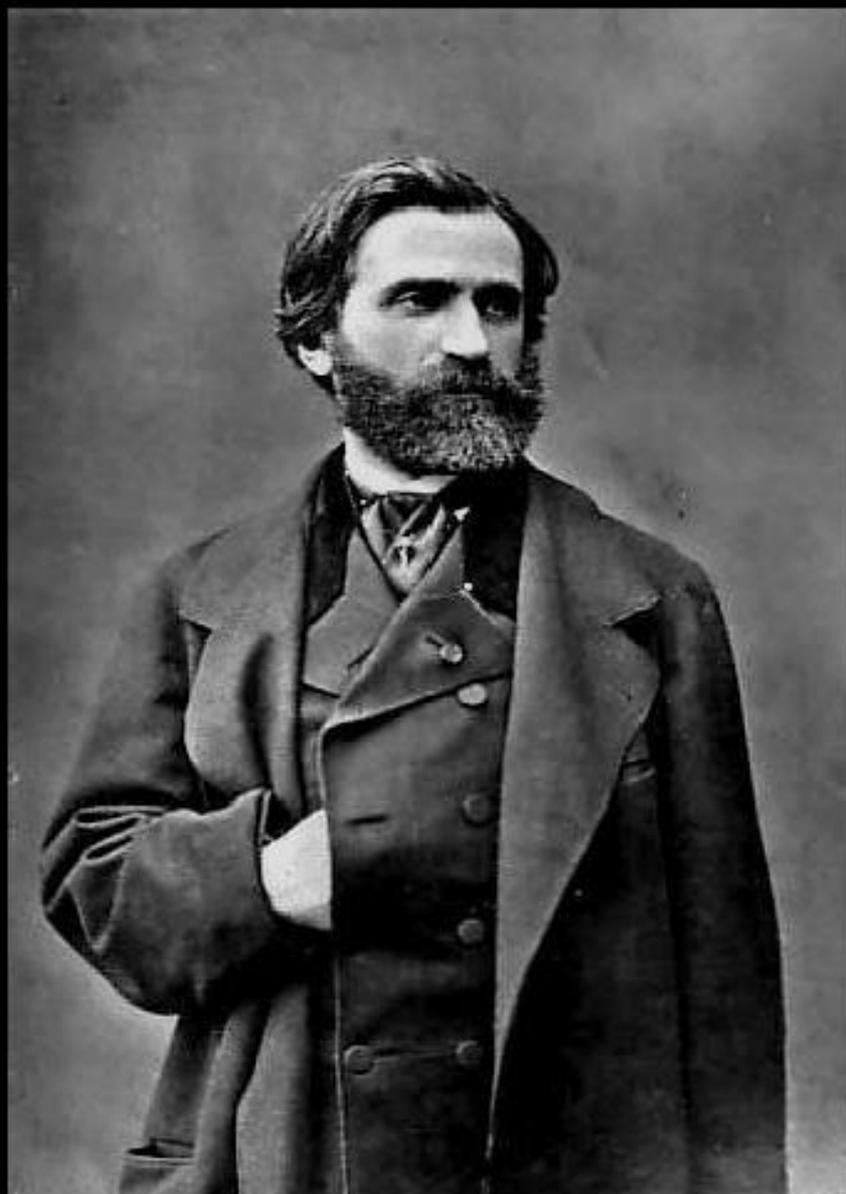


Protocollo corto con antagonista GnRH



OCCUPAZIONE DONNE E FERTILITA'

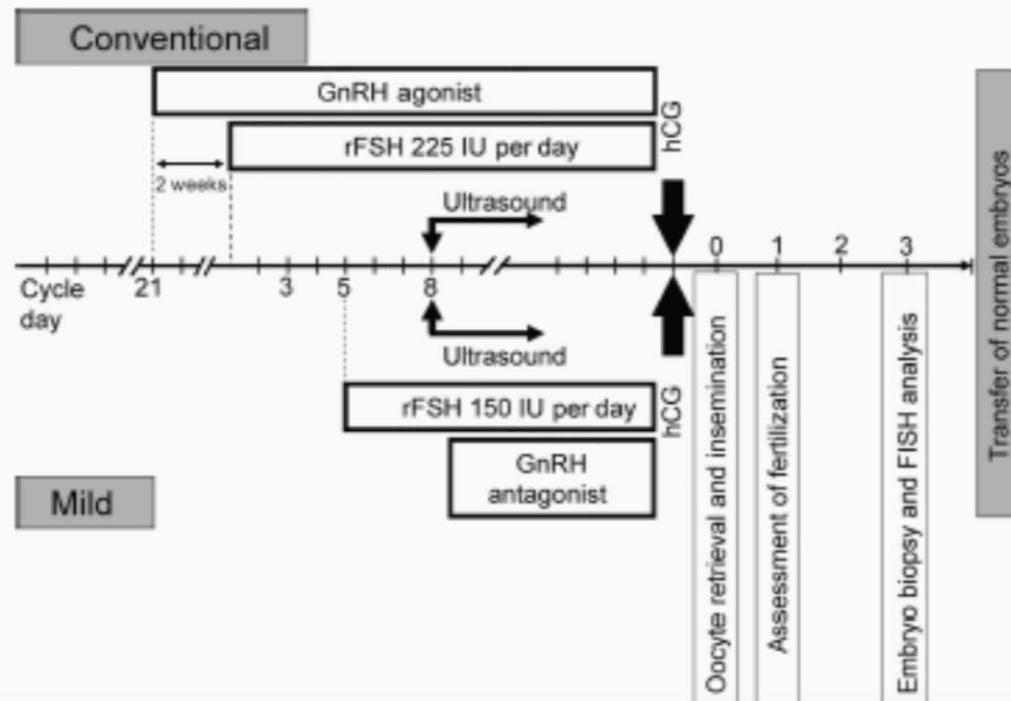




**“TORNIAMO ALL’ANTICO ,
SARA’ UN PROGRESSO”**

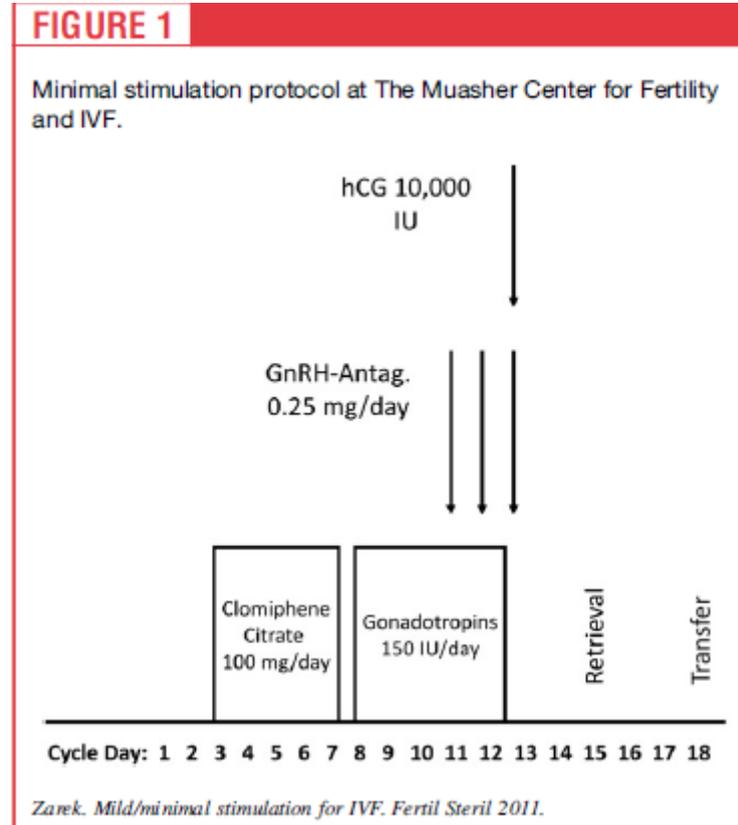
Giuseppe Verdi

Mild stimulation protocol



In mild stimulation, a dosage of 100–150 IU of gonadotropins is started in the early follicular phase with the prevention of an LH surge by the use of a GnRH antagonist after 5 to 7 days of stimulation.

Minimal stimulation protocol



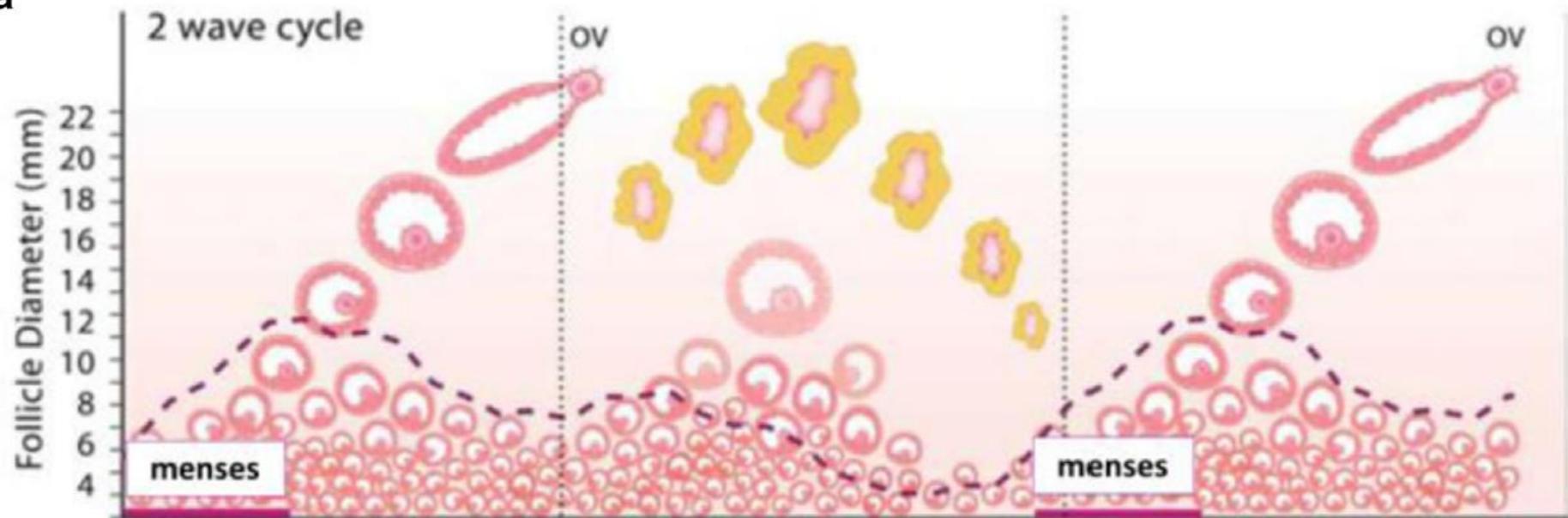
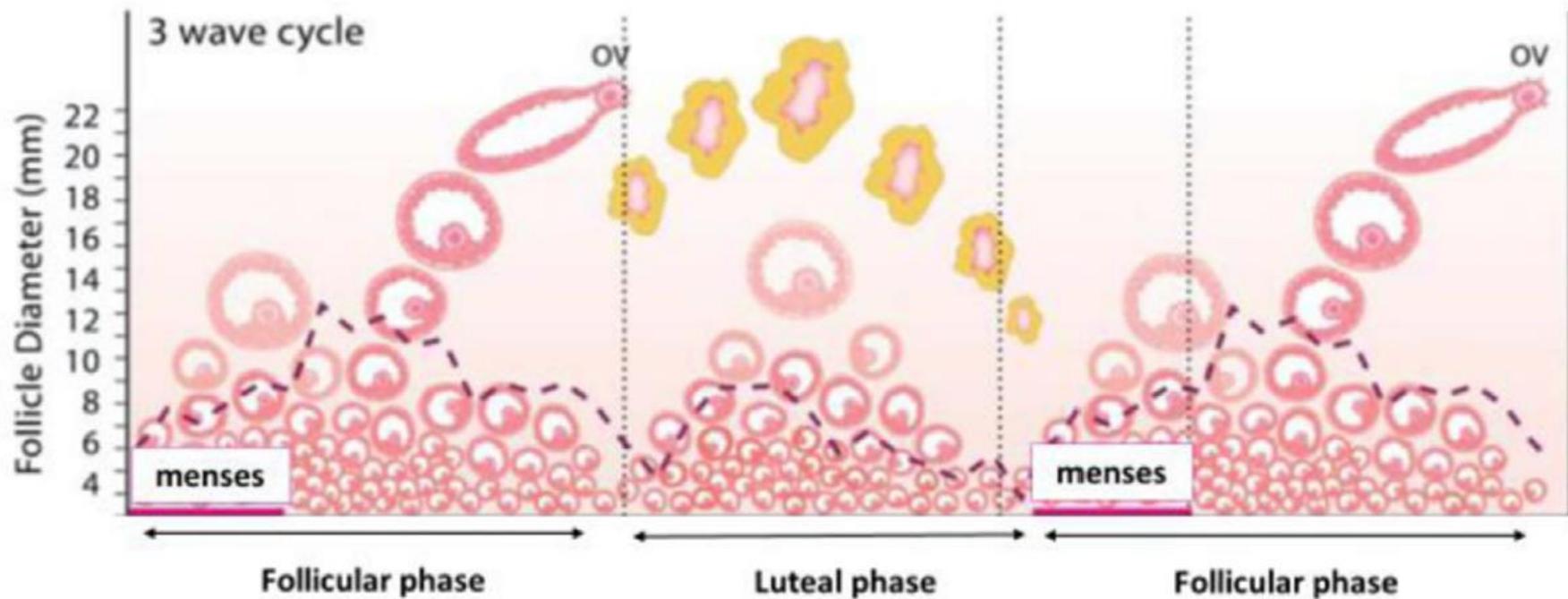
This protocol is offered to all patients, **mostly women with no insurance coverage** for the treatment, to decrease the cost and improve the patient's tolerability and acceptance of the IVF treatment.

Mild Ovarian Stimulation for in vitro Fertilization: Are We Ready to Change? A Meta-Analysis

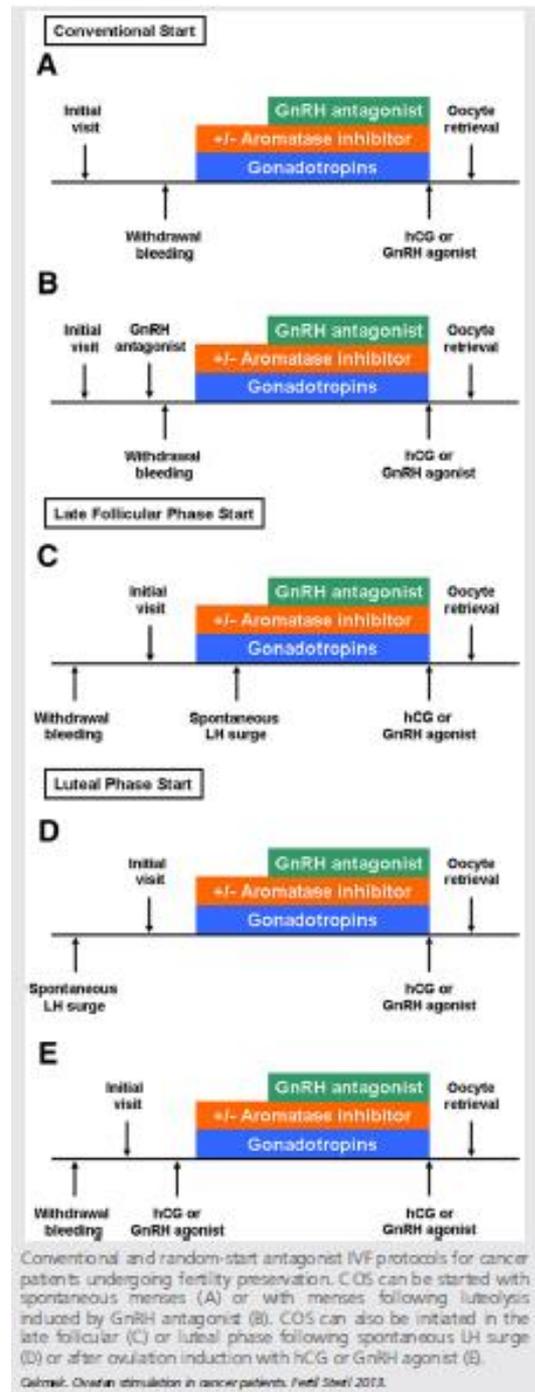
Thabo Matsaseng^a Thinus Kruger^a Wilhelm Steyn^b

In conclusion, this paper showed significantly better outcomes in terms of LBRs and OPRs per started cycle all in favour of conventional stimulation IVF, therefore currently remaining the preferred treatment of choice. However, in the limited resource setting and in a well-selected group of good prognosis patients, mild stimulation IVF may be considered a treatment option due to its potential benefits such as lower risk of OHSS, lower medication cost, less complexity in nature and lower levels of patient distress. In the future, more data on LBRs in both mild and conventional stimulation IVF is still required for proper and accurate comparison.

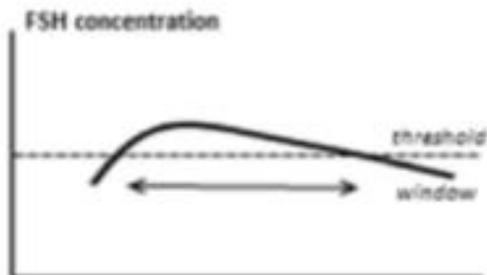
RANDOM- AND LUTEAL PHASE START OVARIAN STIMULATION PROTOCOLS

a**b**

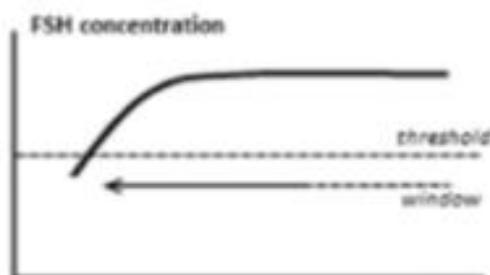
- The theory of multiple follicular waves and hence the possibility of random-start ovarian stimulation is an attractive approach for **cancer patients**.
- In cancer patients, there is no need to achieve synchrony between ovaries and endometrium as **there is no fresh embryo transfer**, thus allowing random-start stimulation protocols.
- Luteal phase- and random-start protocols have also recently been applied **outside the oncological setting**, in normal and poor responders.



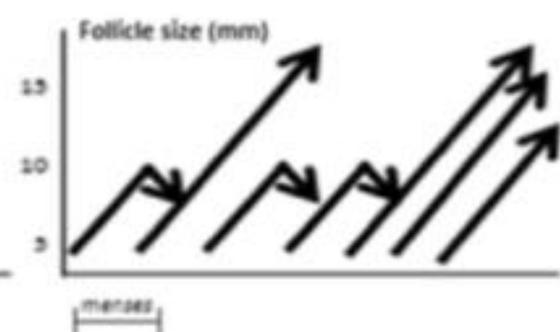
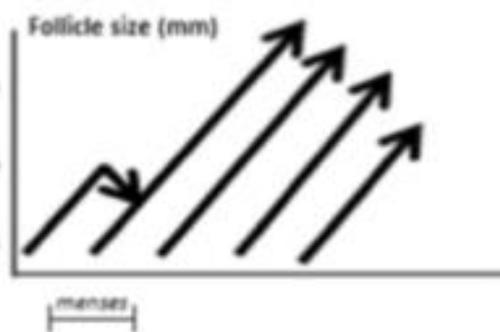
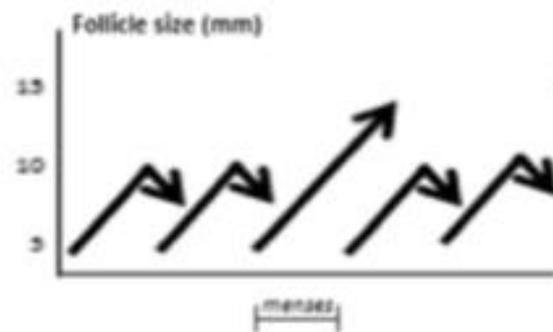
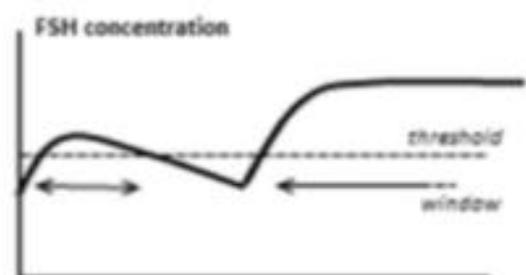
Spontaneous cycle



Conventional OS



Luteal start OS



Luteo - Follicular
Transition

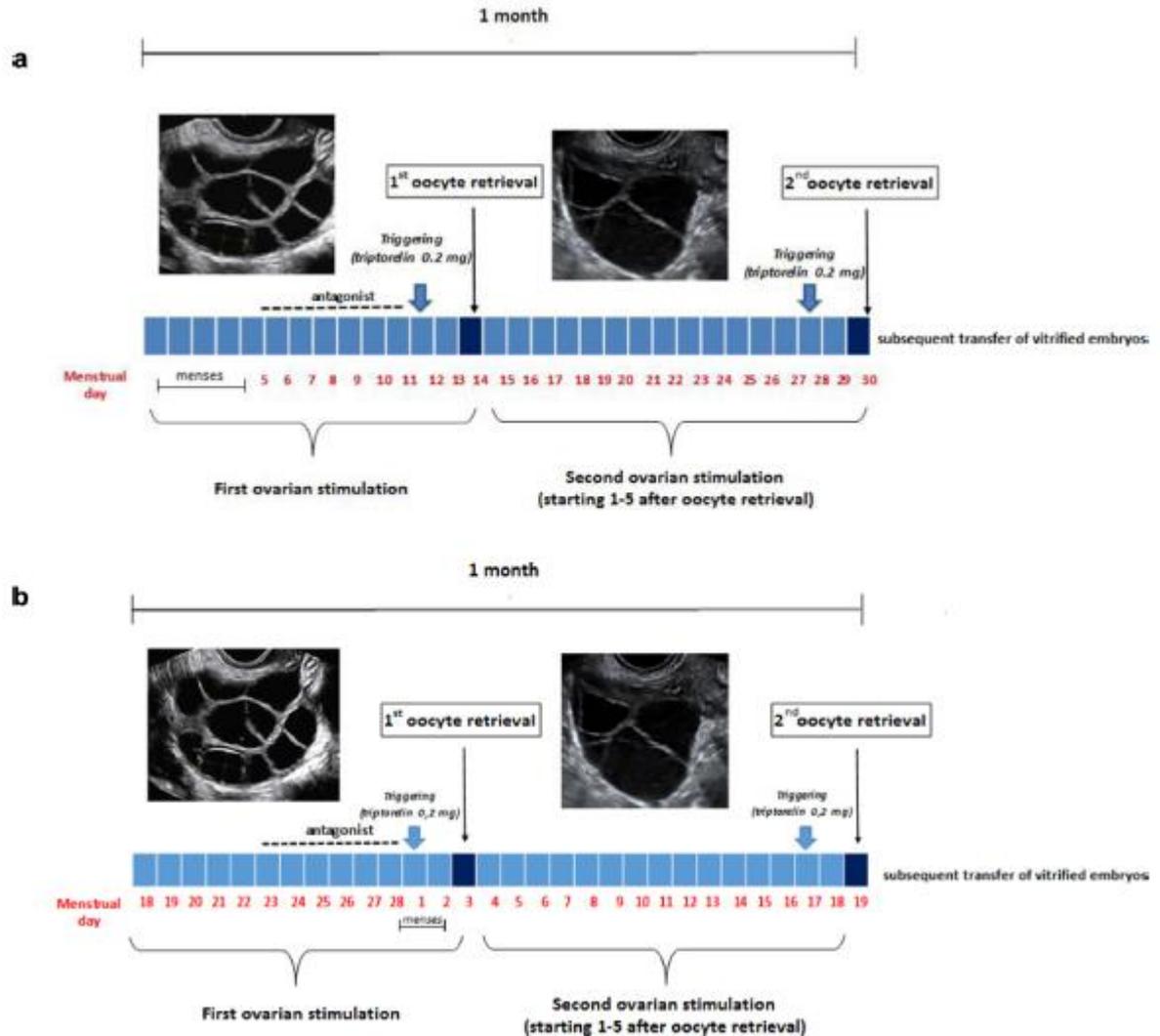
Early Follicular
Phase

Follicular
Phase

Luteal
Phase

**DOUBLE OVARIAN
STIMULATION
(DOS) REGIMEN**

DOS consists of two successive ovarian stimulations in the follicular and ensuing luteal phase with two oocyte retrievals at the end of both ovarian stimulations.



Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation

Filippo Maria Ubaldi, M.D., M.Sc.^{a,b,c} Antonio Capalbo, Ph.D.^{a,b,c} Alberto Vaiarelli, M.D., Ph.D.^{a,b}
 Danilo Cimadomo, M.Sc.^{a,b,c} Silvia Colamaria, M.D.^{a,b} Carlo Aliviggì, M.D., Ph.D.^{d,e}
 Elisabetta Trabucchi, M.D.^{a,b} Roberta Venturella, M.D.^{a,b,f} Gábor Vajta, Ph.D.^{a,b} and Laura Rienzi, M.Sc.^{a,b,c}

Data according to follicular and luteal phase stimulation.

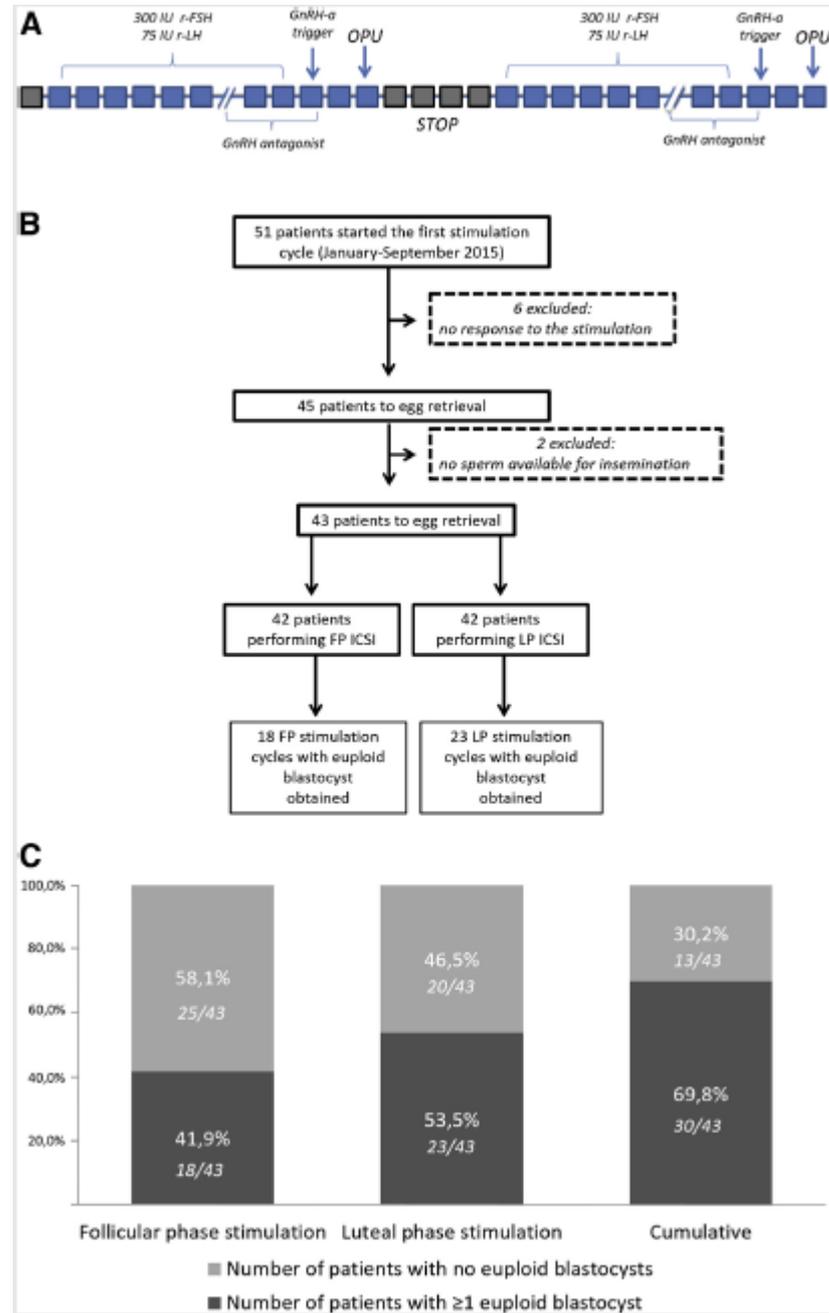
Data basis	Stimulation phase		P value
	Follicular	Luteal	
Per patient ^a			
Days of stimulation	9.6 ± 2.4 (6-14)	10.3 ± 2.5 (8-15)	NS
COCs	5.1 ± 3.4 (1-22)	5.7 ± 3.3 (1-17)	NS

Possible application areas of the DuoStim approach include :

1. all patients in whom obtaining oocytes is urgent, including those with malignant diseases or other medical indications, and
2. patients of advanced maternal age and/or reduced ovarian reserve

Note was
 COC = cumulus-oocyte complex; MII = metaphase 2; NS = not statistically significant.
^a Data are presented as mean ± standard deviation (range).

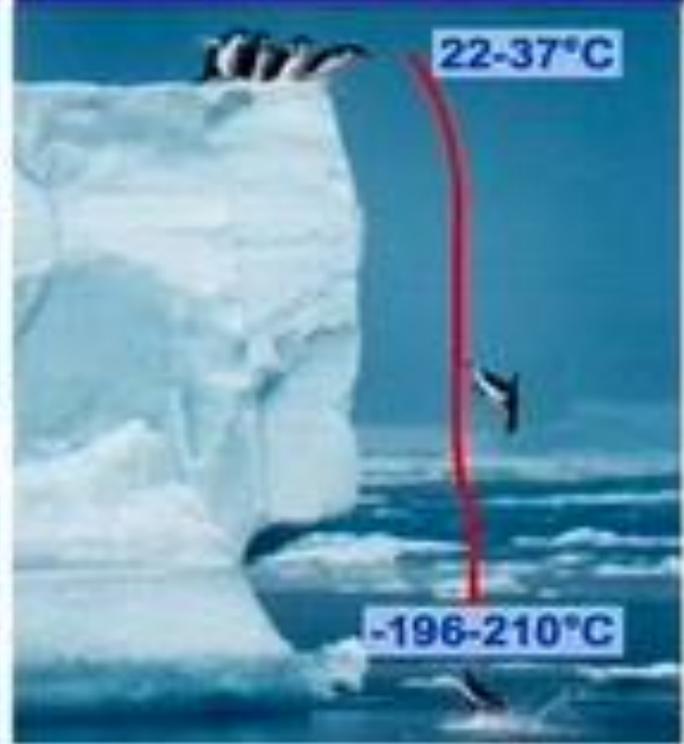
Ubaldi. DuoStim for reduced ovarian reserve. Fertil Steril 2016.



Slow freezing



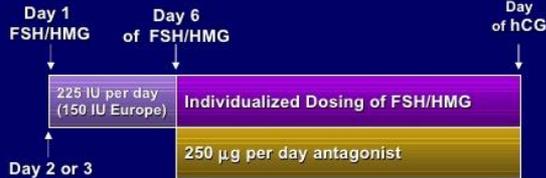
Vitrification



Because of the **asynchrony between endometrial receptivity and embryo development in cases of a 'nonconventional start' stimulation**, all the oocytes/embryos have to be cryopreserved and transferred subsequently.

Protocols for IVF

GnRH Antagonist Protocols



GnRH Agonist Protocols

7 – 8 days after estimated ovulation



OCP

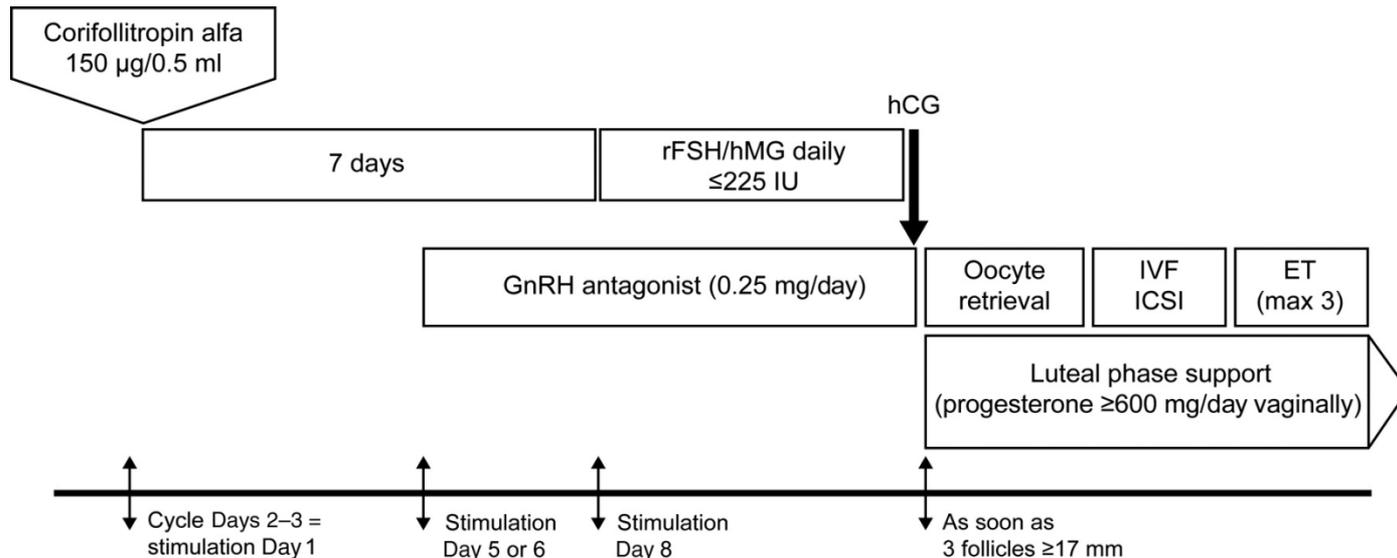
GnRH_a 1.0 mg per day up to 21 days

Down regulation

I. Individualization of stimulation protocol

- Correct prediction of ovarian response (especially extremes: poor and hyper response).
- By most sensitive markers of ovarian reserve.
- Ovarian reserve testing before the first IVF cycle categorize patients (NICE, 2013)

	Low response	High response
Total AFC	4 or less	16 or more
AMH ng/ml	0.8 or less	3.5 or more
FSH IU/L	8.9 or more	4 or less



Mutational Analysis of the Follicle-Stimulating Hormone (FSH) Receptor in Normal and Infertile Men: Identification and Characterization of Two Discrete FSH Receptor Isoforms*

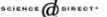
MANUELA SIMONI, JÖRG GROMOLL, WOLFGANG HÖPPNER, AXEL KAMISCHKE, THORSTEN KRAFFT, DANIEL STÄHLE, AND EBERHARD NIESCHLAG



Review

TRENDS in Endocrinology and Metabolism Vol.16 No.8 October 2005

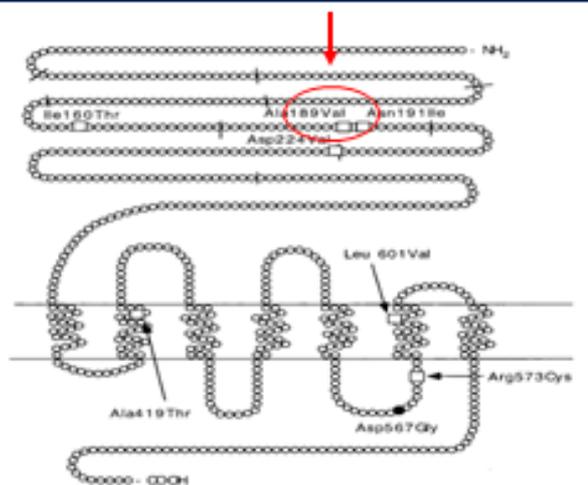
Full text provided by www.sciencedirect.com



Genetic complexity of FSH receptor function

Jörg Gromoll and Manuela Simoni

FSHR STRUTTURA e MUTAZIONI



- MUTAZIONI INATTIVANTI
- MUTAZIONE ATTIVANTE
- ▬ SEPARAZIONE ESONI

Ala 189 Val frequente in Finlandia

SINDROME DISGENESIA OVARICA

46,XX
normale sviluppo genitali

Nei maschi Ala 189 Val:

1. Normale virilizzazione ma
2. grado variabile di fertilità fino ad azoospermia

1. Arresto maturazione follicolare
2. Ovaie fibrose
3. Amenorrea primaria

Isoforms and single nucleotide polymorphisms of the FSH receptor gene: implications for human reproduction

M.Simoni¹, E.Nieschlag and J.Gromoll

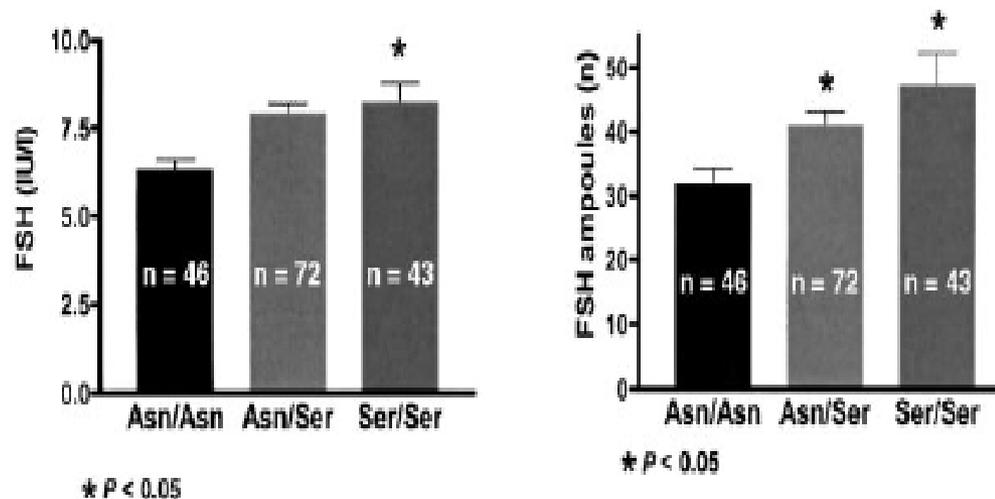


Figure 2. Serum day 3 FSH levels (left panel) and number of FSH ampoules (75 IU each) required in a controlled ovarian stimulation trial involving 161 ovulatory women subdivided into three groups according to the FSH receptor genotype at position 680 (modified from Perez Mayorga *et al.*, 2000). Perez Mayorga, M., Gromoll, J., Behre, H.M., Gassner, C., Nieschlag, E. and Simoni, M. Ovarian response to FSH stimulation depends on the FSH receptor genotype *J. Clin. Endocrinol. Metab.*, 85, 3365–3369 (2000) copyright owned by The Endocrine Society.

Italian Bar

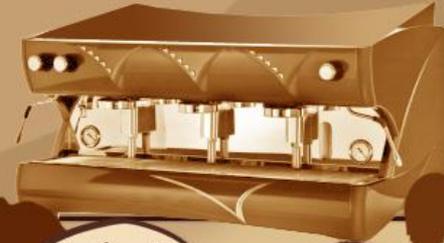
Bored from the usual espresso...
Here are 50 italian ways to drink a coffee!!

CAFFÈ ITALIANO



espresso	ristretto	lungo	al ginseng	d'orzo	lungo con cacao	lungo corretto	schiumato	shakerato con bayles	all'anice	marocchino con cioccolato bianco
macchiato chiaro	macchiato freddo	marocchino	criollo	doppio lungo	doppio ristretto				dek macchiato	
doppio	shakerato	CAFFÈ SOSPESO	mokaccino	irish coffee					doppio in tazza grande	macchiato con panna montata
corretto	moka	decaffeinato	cappuccino	in crema					corto	corto macchiato
cappuccino estivo	al pepe	allo zenzero	viennese	ice caffè	imperiale	bicerin	alla parigina	in tazzina di vetro con manico in ferro	corto con fettina d'arancia	
alla turca	con ghiaccio servito a parte		americano	con cioccolato	del marinato	ristretto corretto	miele e cannella	macchiato scuro		

...look at how many different coffees italians drink...



The present and future state of hormonal treatment for male infertility

Peter Y.Liu and David J.Handelsman¹

Table III. Empirical gonadotrophin therapy

Study	FSH dose (IU 3 times/week)	Treatment group (pregnancies/n)	Placebo group (pregnancies/n)	Odds Ratio (95% CI)
Kamischke <i>et al.</i> (1998)	150–300	2/31	2/30	0.97 (0.13, 7.22)
Knuth <i>et al.</i> (1987)	150	2/17	0/20	9.38 (0.56, 157.45)
Matarras <i>et al.</i> (1997)	150	26/58	29/78	1.37 (0.69, 2.73)
All studies	150–300	30/106	31/128	1.46 (0.77, 2.76)

Quantitative pooling of all available data showed no significant effect (OR 1.46; 95% CI 0.77-2.76) on pregnancy rates in 234 couples.

Serum Inhibin B and Follicle-Stimulating Hormone Levels as Tools in the Evaluation of Infertile Men: Significance of Adequate Reference Values from Proven Fertile Men

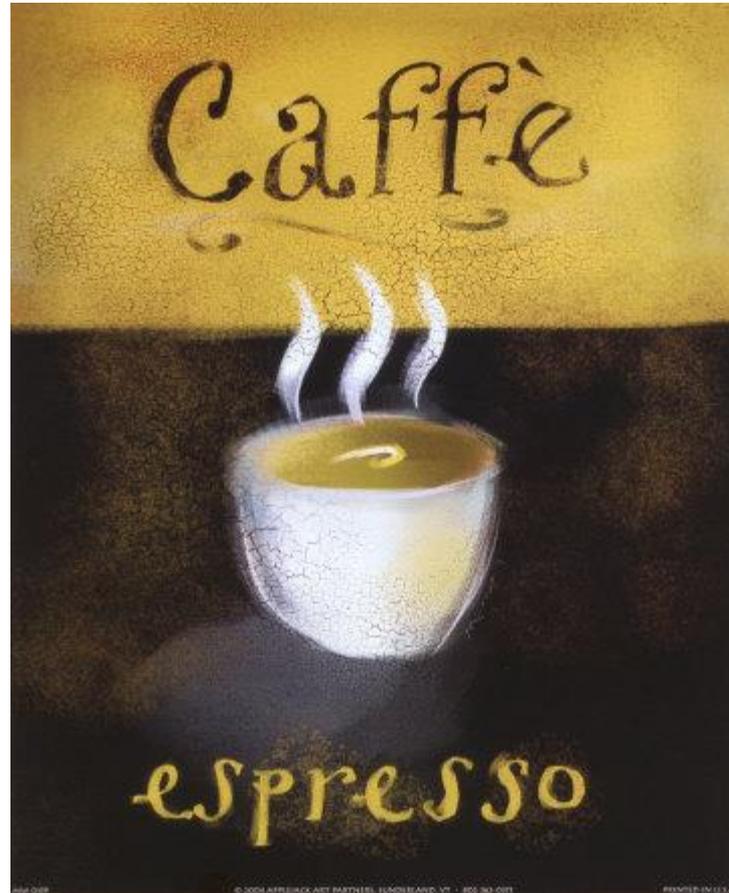
ANNA-MARIA ANDERSSON, JØRGEN H. PETERSEN, NIELS JØRGENSEN, TINA K. JENSEN, AND NIELS E. SKAKKEBÆK

TABLE 1. Characteristics of the study subjects [median (2.5–97.5 percentiles)]

	General population	Fertile men	Idiopathic infertile men
n	307	303	289
Age (yr)	30 (21–40)	31 (25–42)	33 (26–48)
BMI (kg/m ²)		24.2 (19.4–31.1)	25.3 (19.4–34.5)
Sperm concentration (million/ml)		67 (22–287)	1.8 (0.0–17.0)
Total sperm concentration (million)		237 (46–926)	5.7 (0.0–77)
Inhibin B (pg/ml)	169 (43–393)	223 (105–439)	111 (ND–308)
 FSH (IU/liter)	3.64 (1.36–14.82)	3.05 (1.23–7.89)	7.98 (1.87–38.45)
Inhibin B/FSH ratio	48 (4–241)	70 (15–303)	14 (0–133)

ND, Not detectable.

Il limite inferiore del range del FSH non discrimina i soggetti fertili dagli infertili ipo-ipo



Treatment with human, recombinant FSH improves sperm DNA fragmentation in idiopathic infertile men depending on the FSH receptor polymorphism p.N680S: a pharmacogenetic study

Manuela Simoni^{1,2,3}, Daniele Santi^{1,2,*}, Luciano Negri⁴, Ivan Hoffmann⁵, Monica Muratori⁶, Elisabetta Baldi⁶, Marta Cambi⁶, Marios Marcou⁵, Thomas Greither⁵, Enrica Baraldi⁷, Simonetta Tagliavini⁷, Daniela Carra⁷, Francesco Lombardo⁸, Loredana Gandini⁸, Francesco Pallotti⁸, Csilla Krausz⁶, Giulia Rastrelli⁶, Alberto Ferlin⁹, Massimo Menegazzo⁹, Elisa Pignatti^{1,3}, Francesca Linari^{1,2}, Marco Marino^{1,3}, Renzo Benaglia⁴, Paolo E. Levi-Setti^{4,†}, and Hermann M. Behre^{5,†}

REVIEW

Spiritual aspects of qualitative studies

Joana Romeiro MSc,
Professor¹  | Vivian
Midwifery²  | Fiona
MSc, RM, Senior Lecturer

Spiritual aspects of
qualitative studies
recognise the
standing needs of
individuals living with
infertility
limited.



Synthesis of

D, MSc, RN, Assistant
Professor in
 | Jenny Hall EdD,

many individuals
not always
the understanding
of spiritual
importance of liv-
ing between
ground to be

BASTA FB...

ME NAMOSE!

ROMA