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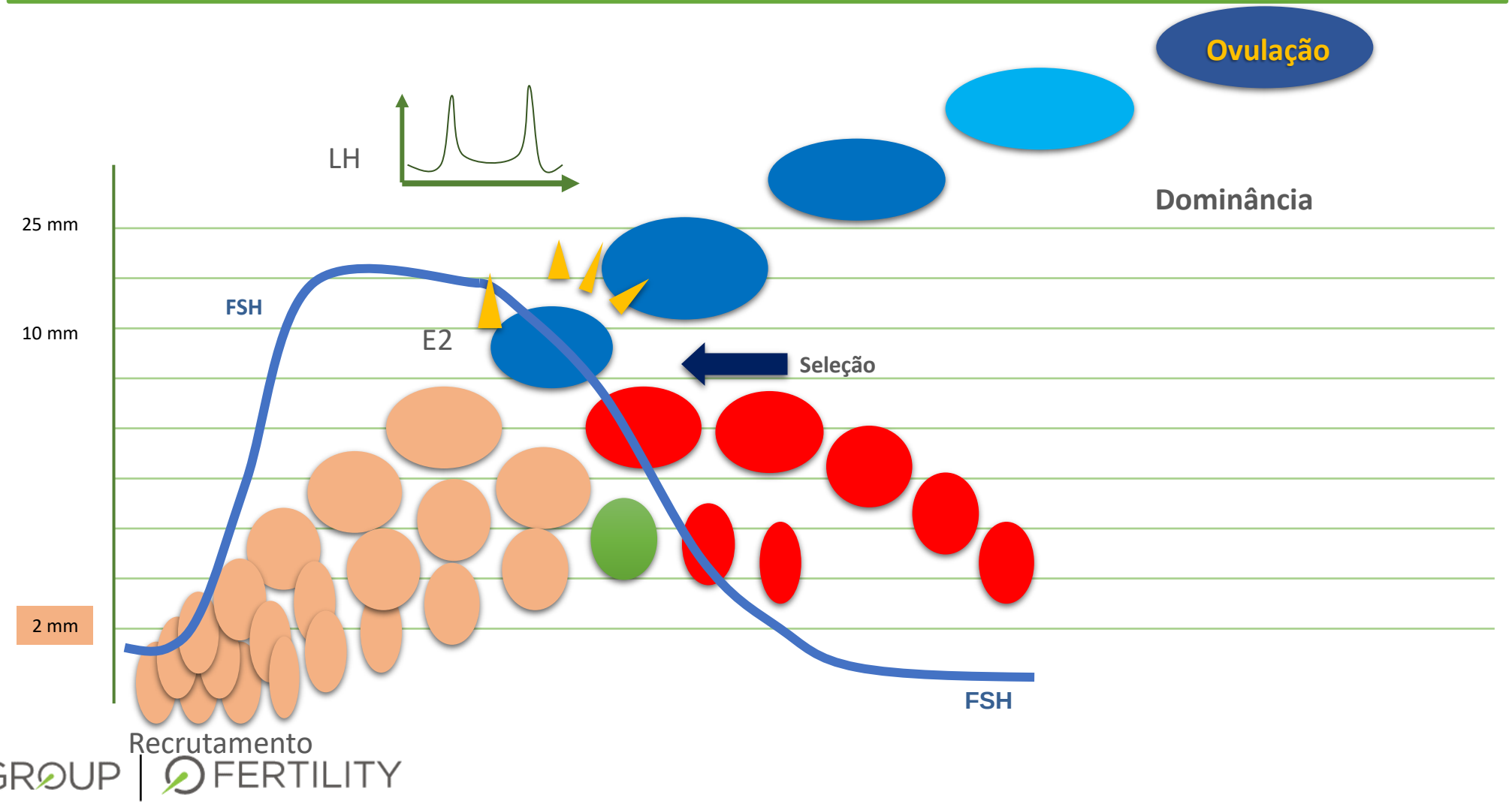
Estimulação Ovariana em R.A. Estratégias para Baixa Respondedora

Edson Borges Jr.

FERTGROUP | FERTILITY

25 ANOS Instituto Sapientiae

Coorte de crescimento folicular



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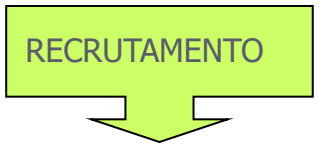
Indução da Ovulação

- Desenvolvimento folicular induzido

Indução da Ovulação

- Desenvolvimento folicular induzido



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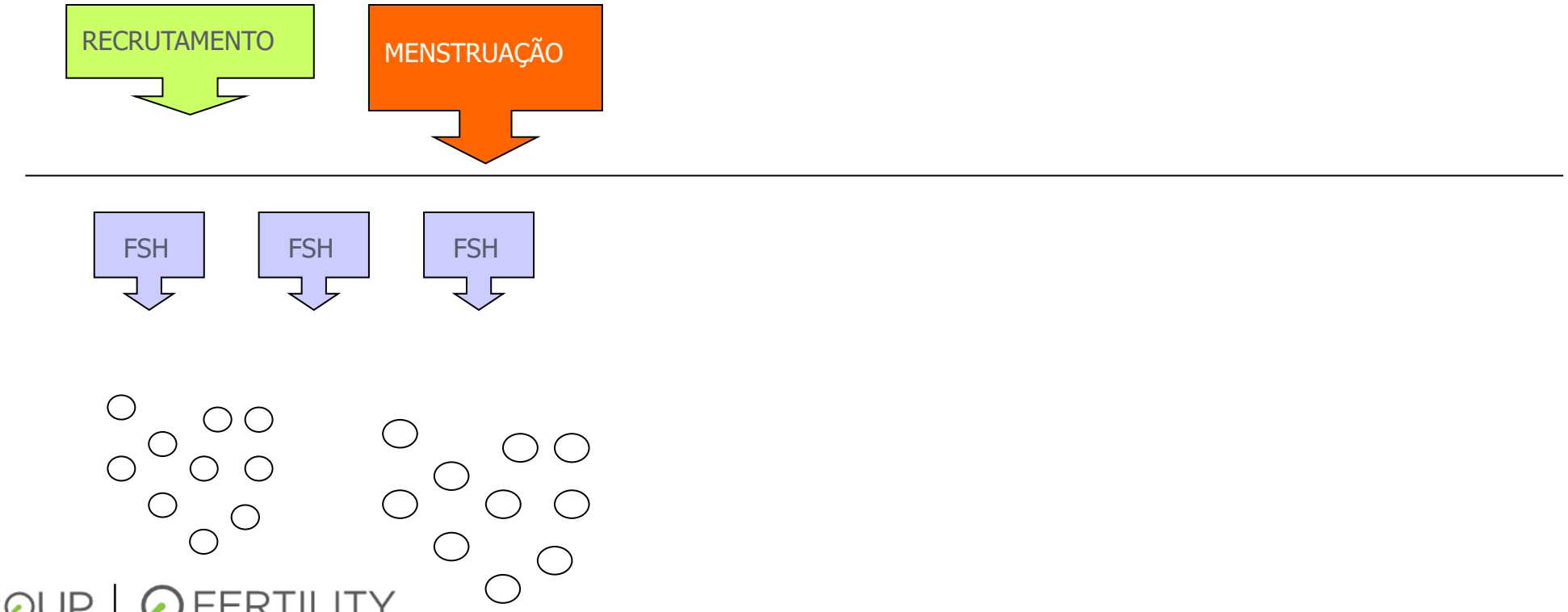
Indução da Ovulação

- Desenvolvimento folicular induzido



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Indução da Ovulação

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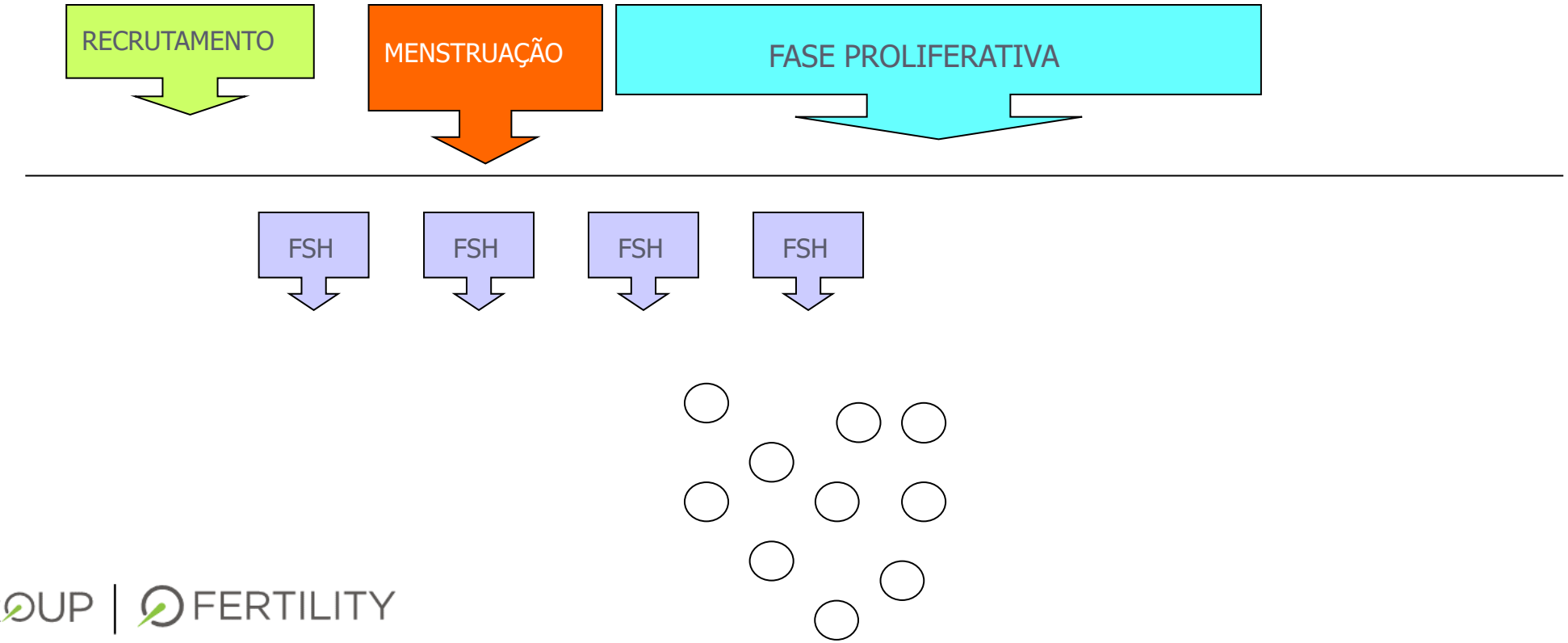

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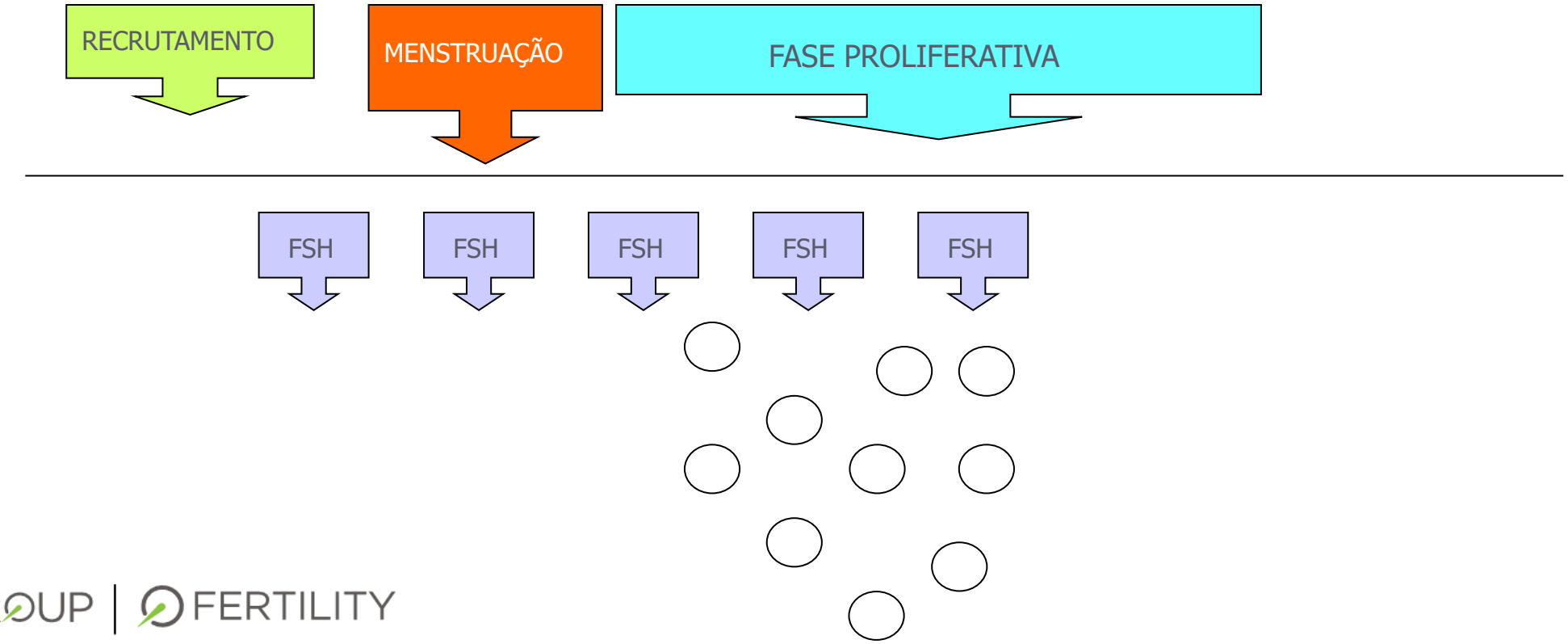
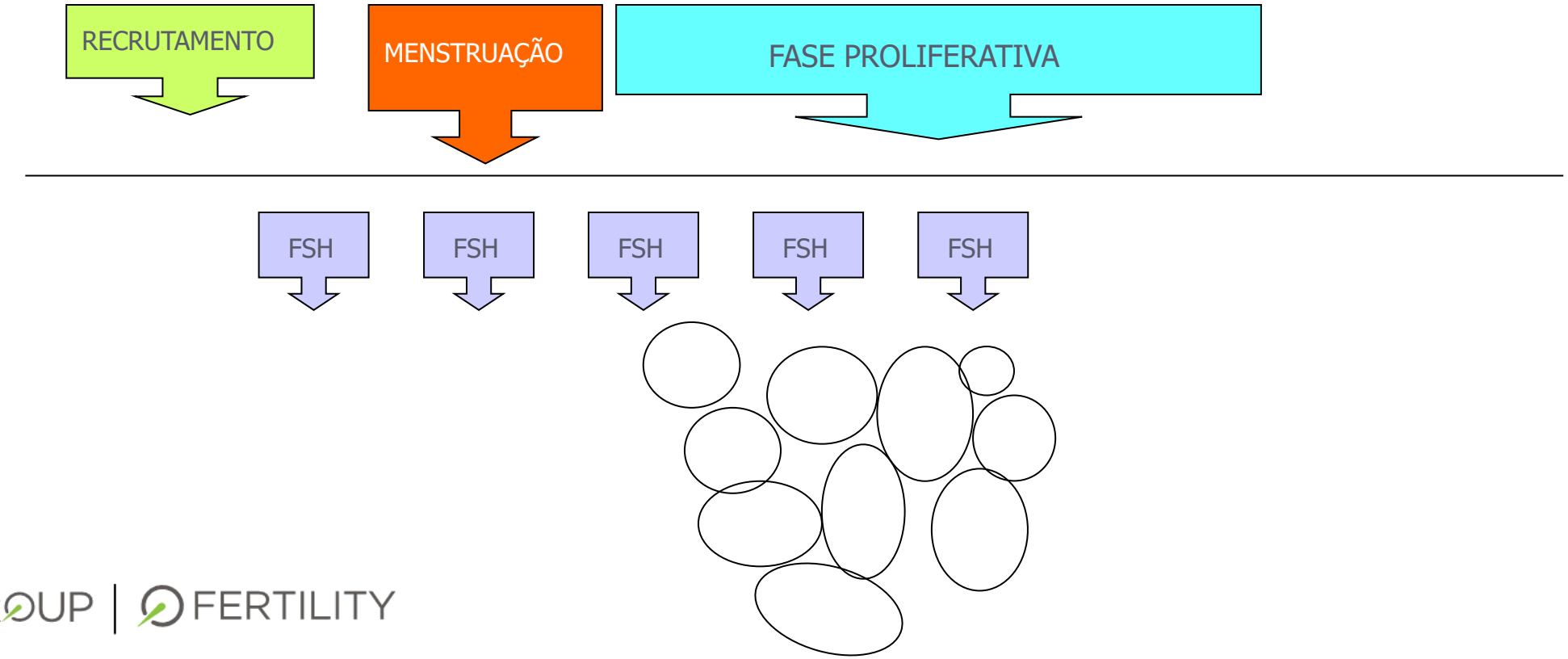


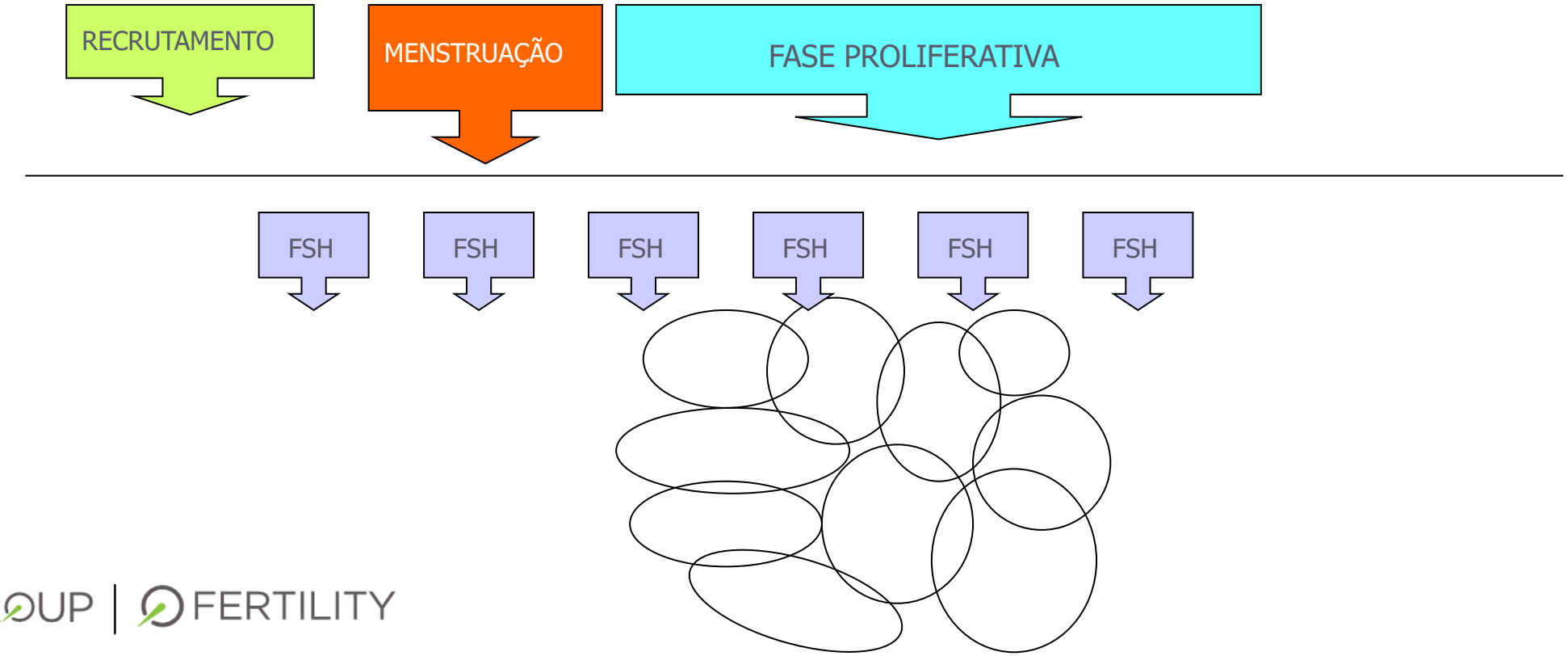
Indução da Ovulação

- Desenvolvimento folicular induzido



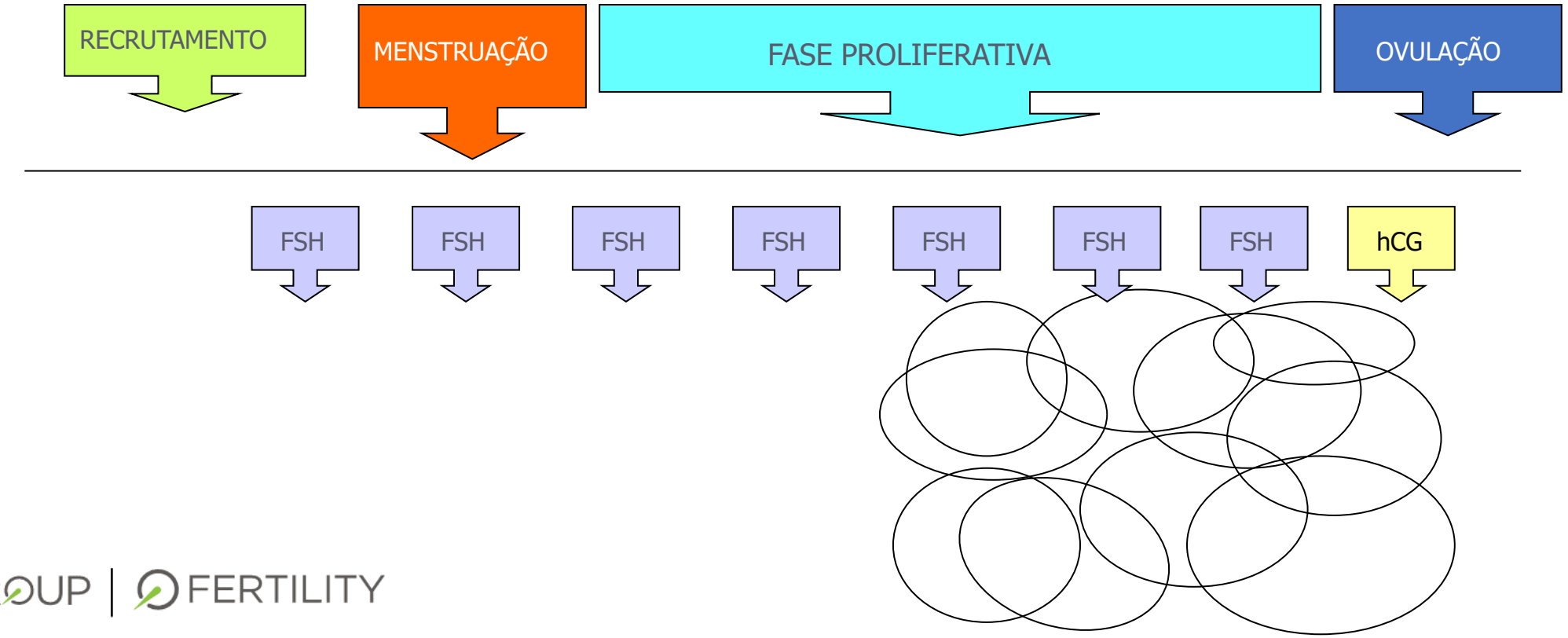
Indução da Ovulação

- Desenvolvimento folicular induzido



Indução da Ovulação

- Desenvolvimento folicular induzido



Gonadotropinas / Análogos GnRH

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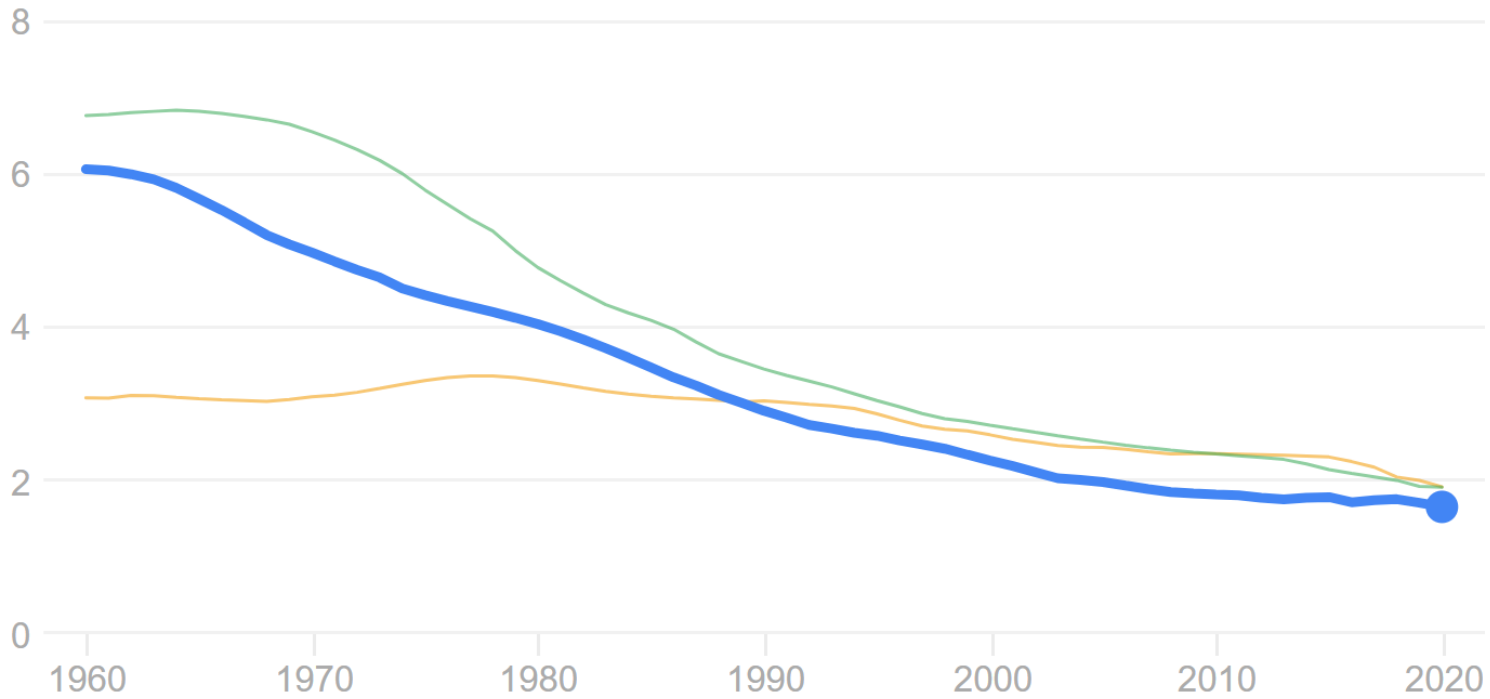
1,65 nascimentos por mulher (2020)



Fontes: Banco Mundial

Feedback

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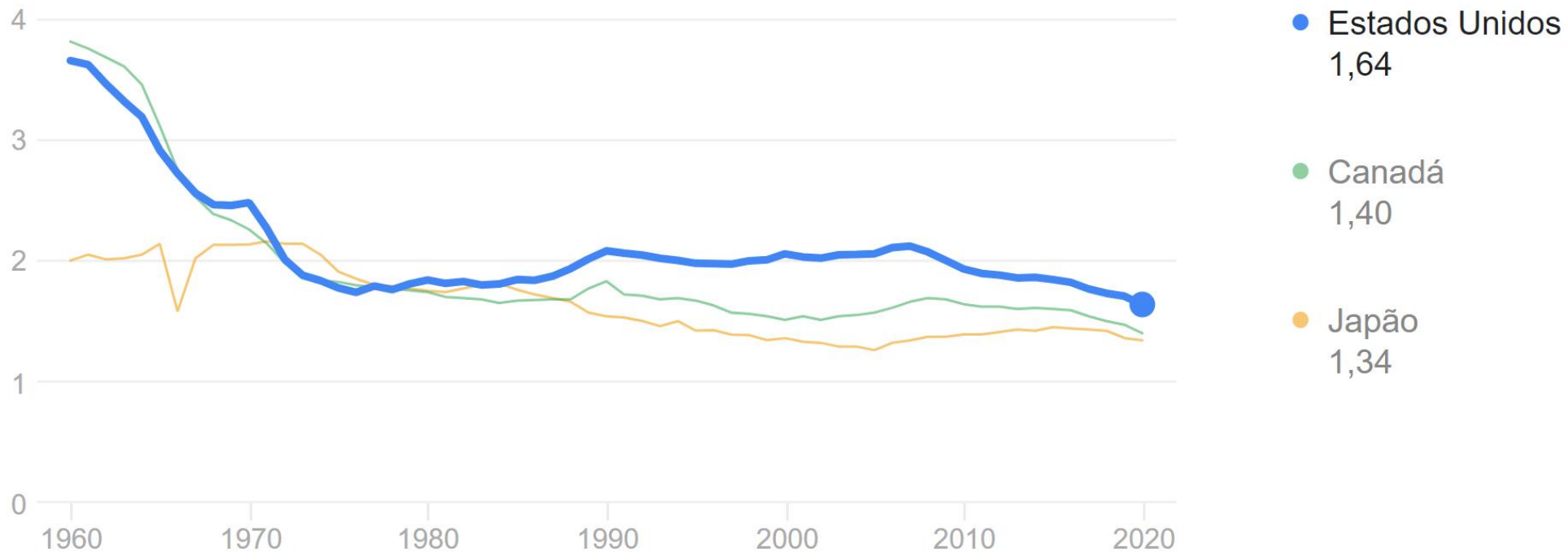
1,64 nascimentos por mulher (2020)



Fontes: Banco Mundial

Feedback

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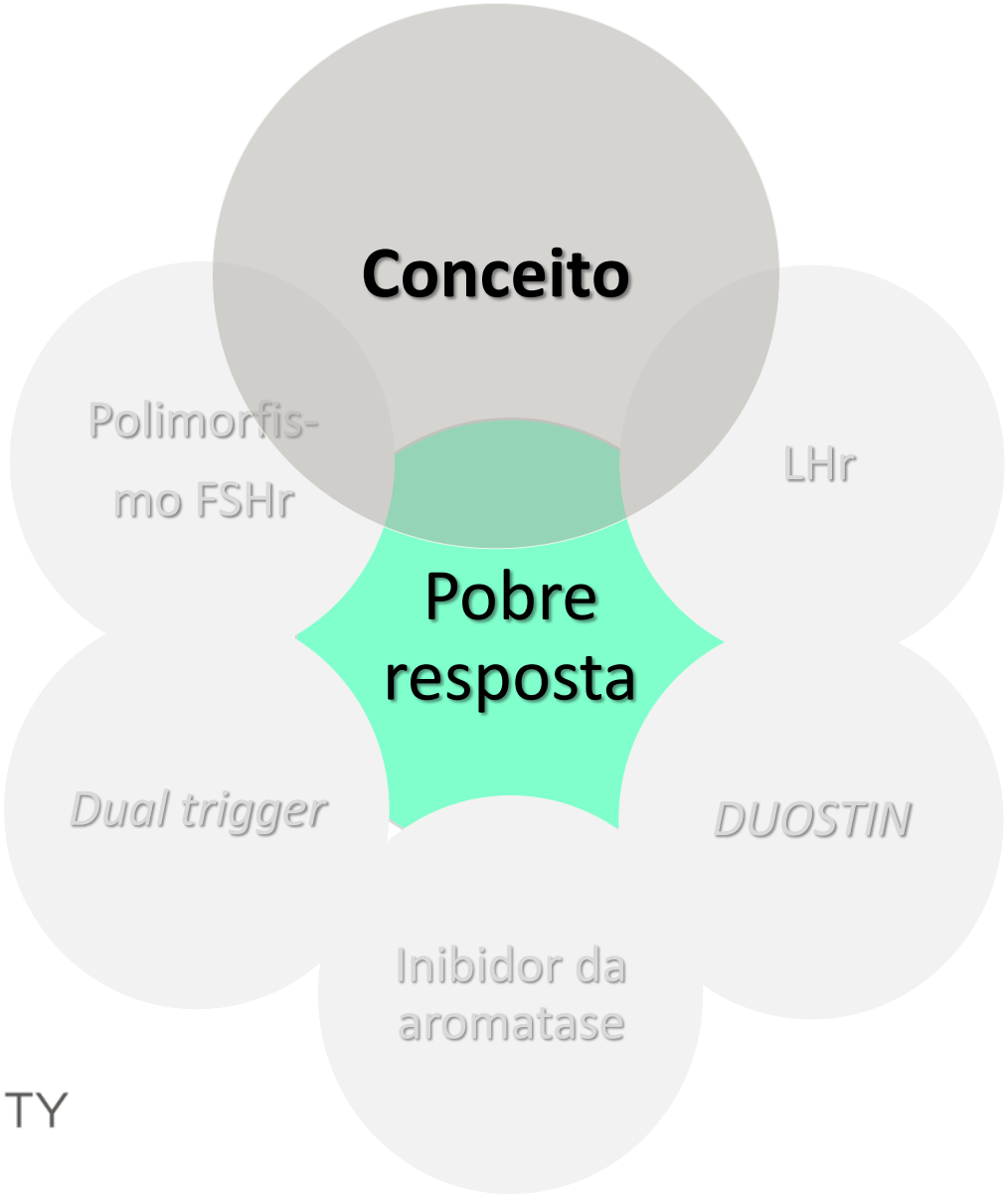
AGENDA

- Conceito
- Uso de LHr
- DUOSTIN – dupla estimulação
- Uso de inibidor da aromatase
- Dual trigger
- Polimorfismo FSHr



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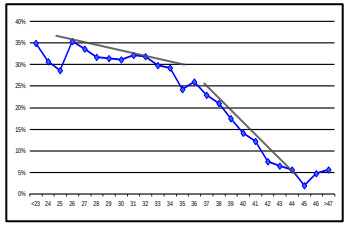
Estimulação ovariana: *pobre resposta*

O que sabemos:

- Redução progressiva e mais acelerada dos folículos após 35-37 anos
- 10% das mulheres < 40 anos têm redução prematura dos folículos



- 10-24% dos ciclos de FIV
- Causas prováveis: cromossômicas adquiridas, alterações genéticas, iatrogênicas

Porém:
SEM CAUSA APARENTE na maioria das vezes

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Estimulação ovariana: *pobre resposta*

How to define, diagnose and treat poor responders? Responses from a worldwide survey of IVF clinics

Reproductive BioMedicine Online (2015) 30, 581–592

Pasquale Patrizio [a,*], Alberto Vaiarelli [b], Paolo E Levi Setti [c], Kyle J Tobler [d], Gon Shoham [e], Milton Leong [f], Zeev Shoham [g,h]

Table 1 Geographical distribution of respondents to the survey.

Continent	*Number of centres*	*Number of respondent-cycles (%)*
Europe	72	41,400 (33)
Asia	34	24,300 (19)
USA and Canada	40	22,700 (18)
South America	30	13,200 (11)
Australia and New Zealand	9	13,800 (11)
Africa	11	9300 (7)
Total	196	124,700 (100)

The present study shows that:
The definition of poor responders is still subjective

Estimulação ovariana: *pobre resposta*

A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel?

Fertility and Sterility® Vol. 96, No. 5, November 2011
y, M.D., Ph.D.

Systematic review identified 47 RCT that used:

- 41 different descriptions for POR,
- each definition used by no more than three trials

Estimulação ovariana: *pobre resposta*

Human Reproduction, Vol.26, No.7 pp. 1616–1624, 2011
Advanced Access publication on April 19, 2011 doi:10.1093/humrep/der092

human reproduction

ESHRE PAGES

ESHRE consensus on the definition of 'poor response' to ovarian stimulation for *in vitro* fertilization: the Bologna criteria†

A.P. Ferraretti[1,*], A. La Marca[2], B.C.J.M. Fauser[3], B. Tarlatzis[4], G. Nargund[5], and L. Gianaroli[1] on behalf of the ESHRE working group on Poor Ovarian Response Definition‡

[1]S.I.S.Me.R Reproductive Medicine Unit, Via Mazzini 12, 40138 Bologna, Italy [2]Mother-Infant Department, University Hospital Policlinico di Modena, Modena, Italy [3]Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, Utrecht, The Netherlands [4]Unit for Human Reproduction, Papageorgiou General Hospital, Thessaloniki, Greece [5]Department of Obstetrics and Gynecology, St George's Hospital, London, UK

Dois de três criterios:

- Idade materna ≥40 anos ou outro fator de risco para baixa resposta (Sindrome Turner, mutações do X-frágil, história de quimioterapia, etc.)
- Episódio anterior de má resposta (≤3 oocitos com protocolo convencional de estimulação)
- Teste anormal para reserva ovariana (AFC 5 – 7 folículos ou AMH 0.5 – 1.1 ng/ml)

ESHRE Bologna criteria for poor ovarian response (POR)

Two of the three criteria are required

1. Advanced maternal age (≥40 years) or any other POR risk factor
2. A previous incident of POR
3. A low ovarian reserve test in terms of antimüllerian hormone (AMH) and antral follicle count (AFC)

Combines very different patient profiles in the same group
does not account for hypo-response to ovarian stimulation

POSEIDON classification for low prognosis women

Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number

GROUP 1

Young patients <35 years with adequate ovarian reserve parameters (AFC ≥ 5; AMH ≥ 1.2 ng/ml) and with an unexpected poor or suboptimal ovarian response

Subgroup 1a: < 4 oocytes
Subgroup 1b: 4-9 oocytes retrieved

GROUP 2

Older patients ≥ 35 years with adequate ovarian reserve parameters (AFC ≥ 5; AMH ≥ 1.2 ng/ml) and with an unexpected poor or suboptimal ovarian response

Subgroup 2a: < 4 oocytes
Subgroup 2b: 4–9 oocytes retrieved

GROUP 3

Young patients (< 35 years) with poor ovarian reserve pre-stimulation parameters

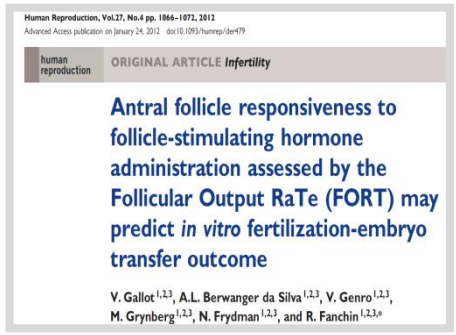
(AFC < 5; AMH < 1.2 ng/ml)

GROUP 4

Older patients (≥ 35 years) with poor ovarian reserve pre-stimulation parameters

(AFC < 5; AMH < 1.2 ng/ml)

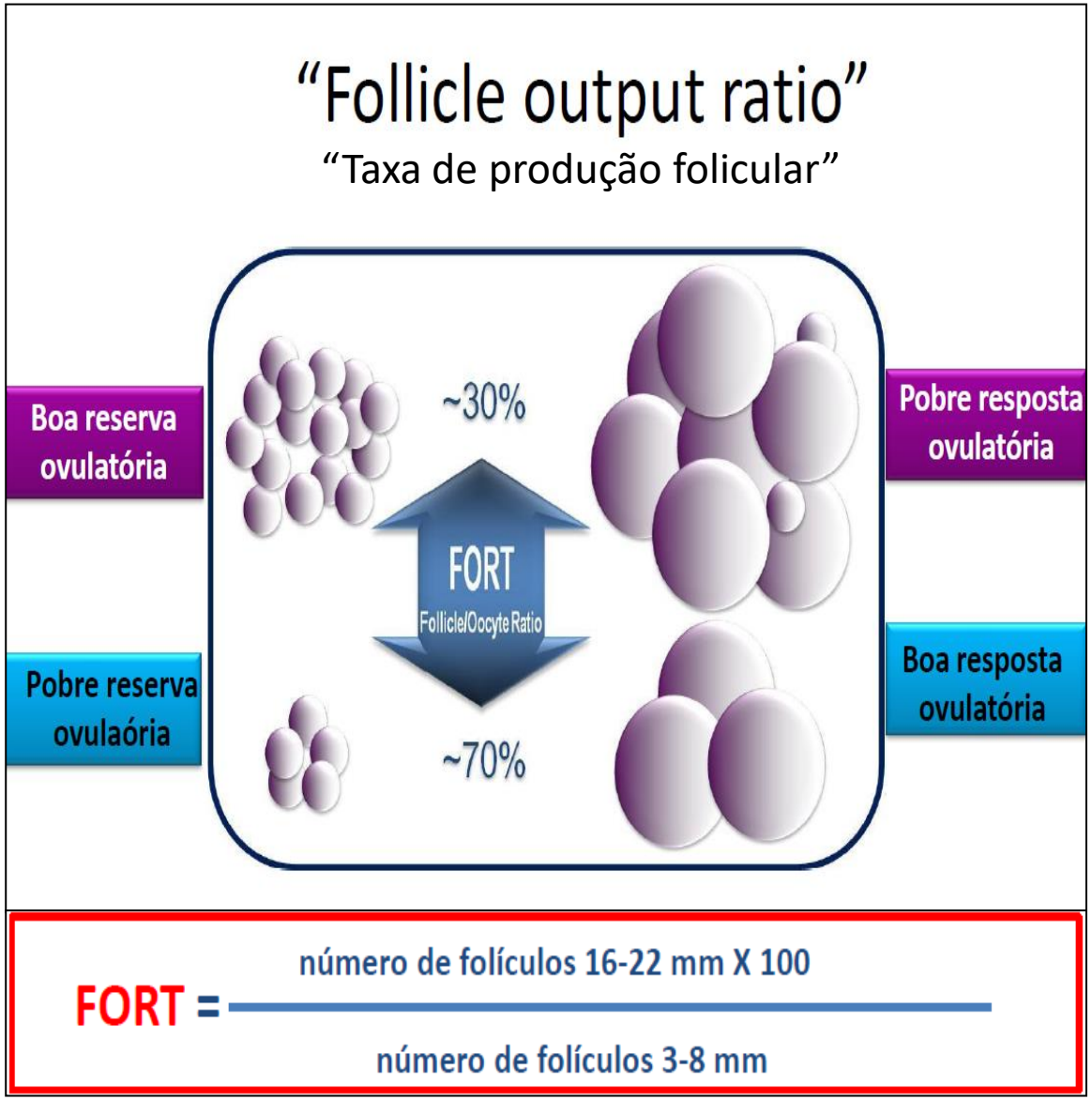
Estimulação ovariana: *pobre resposta*


Human Reproduction, Vol.27, No.4 pp. 1066–1072, 2012
Advanced Access publication on January 24, 2012 doi:10.1093/humrep/der479

human reproduction ORIGINAL ARTICLE *Infertility*

Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the Follicular Output RaTe (FORT) may predict *in vitro* fertilization-embryo transfer outcome

V. Gallot[1,2,3], A.L. Berwanger da Silva[1,2,3], V. Genro[1,2,3], M. Grynberg[1,2,3], N. Frydman[1,2,3], and R. Fanchin[1,2,3,*]



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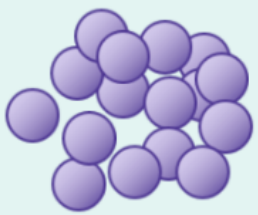
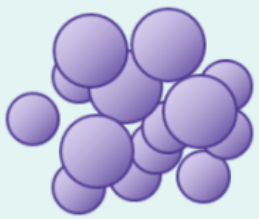
Measuring ovarian response to ovarian stimulation

LOW Follicle Output RaTe (FORT) with standard doses of FSH

Polygenic trait



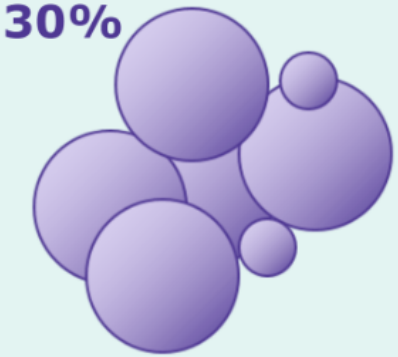
Day stimulation 5–8



What to do?
Increase FSH?
Add LH?

Poor!

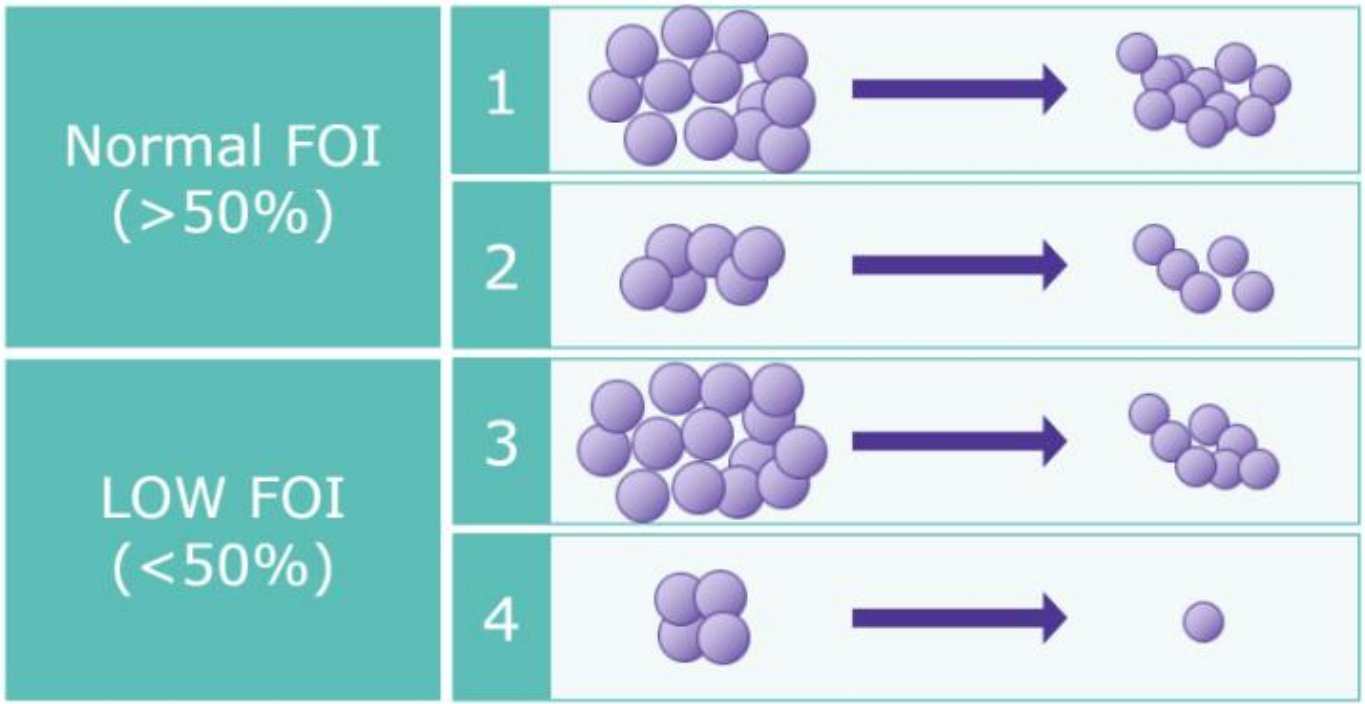
~30%



Hyposensitivity to FSH
(15% of women with good ovarian reserve)

FOI as a practical indicator of hypo-response

Follicle-to-Oocyte Index (FOI)* = Oocyte Number/Antral Follicle Count x100



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

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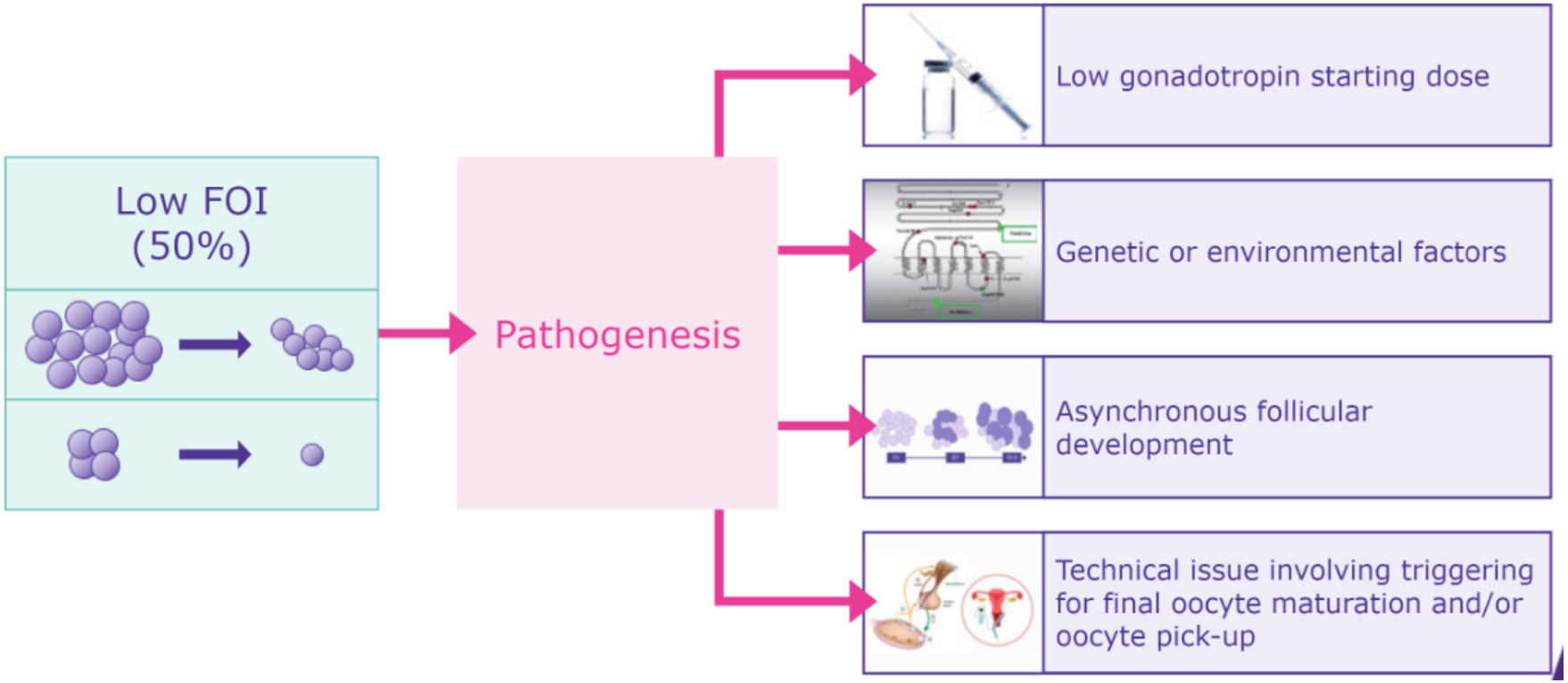
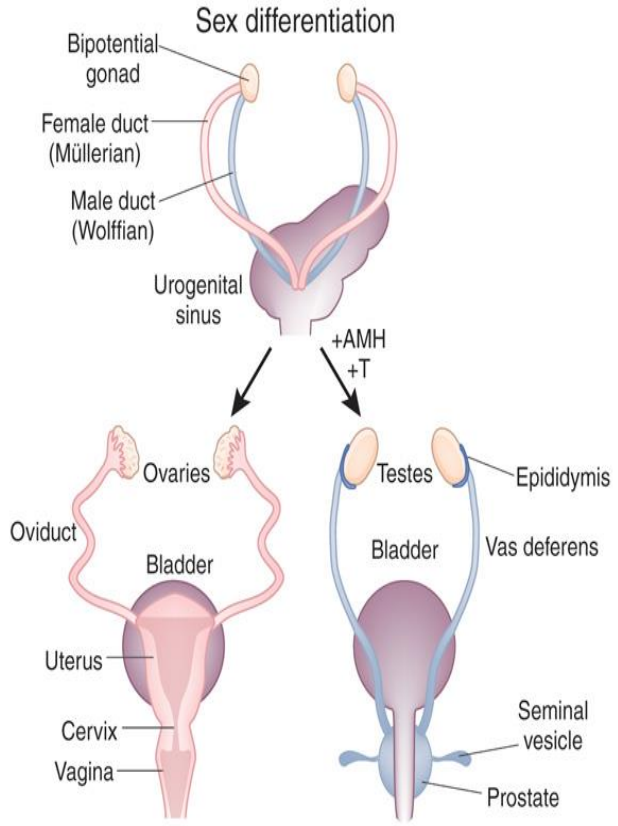
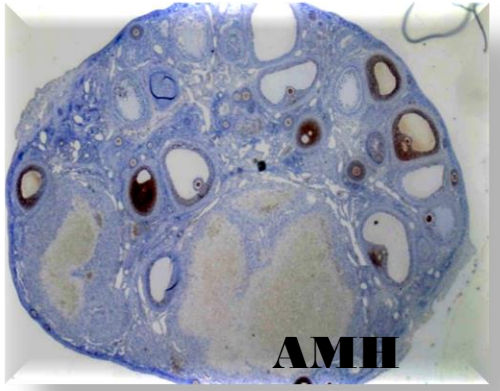
Possible causes of low FOI

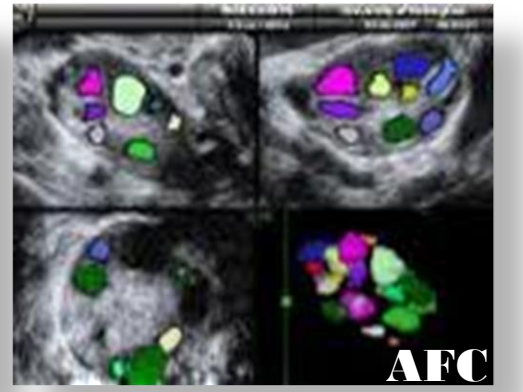


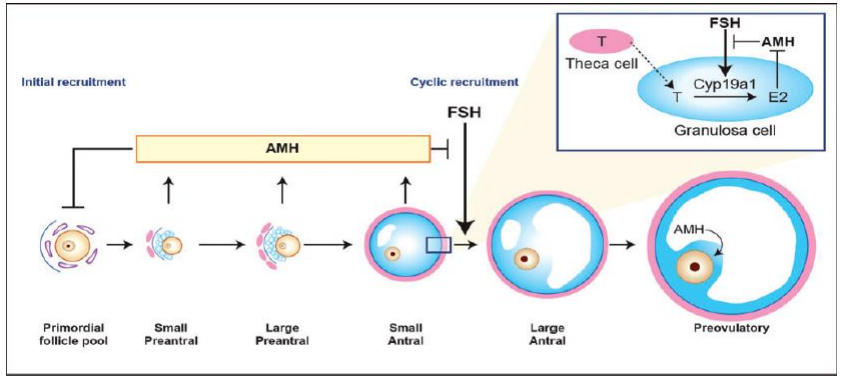
AMH and AFC: Best predictors of ovarian response



Katie Vicari







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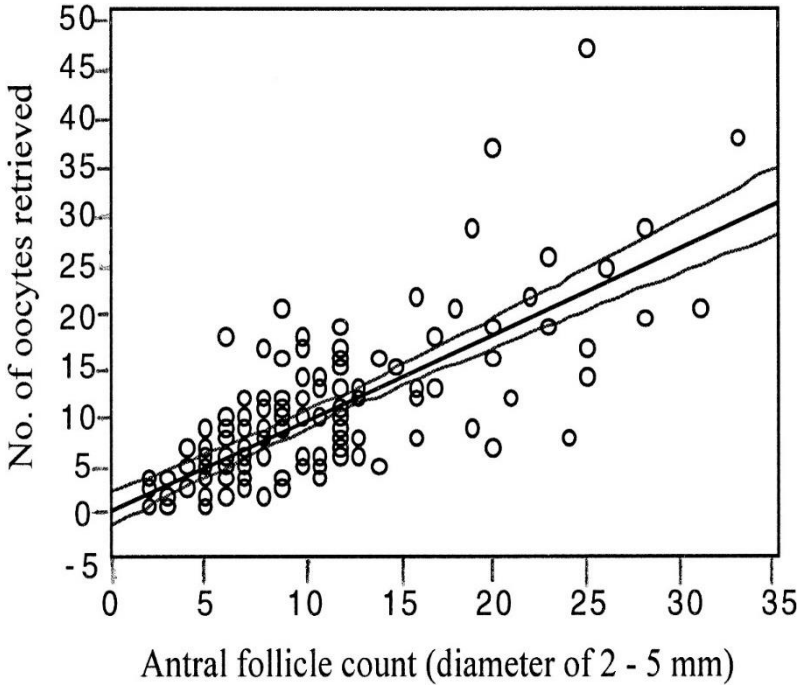
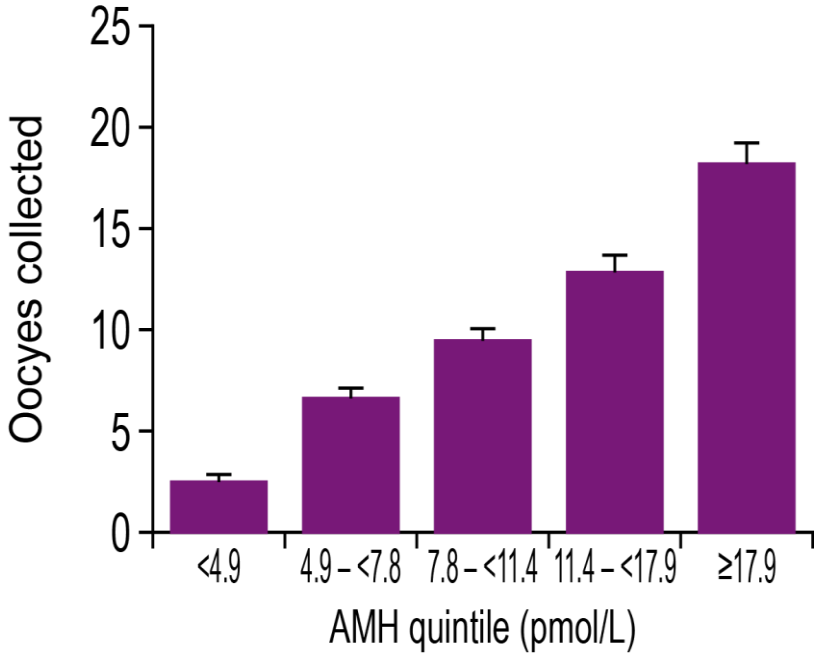
Both predict oocyte yield





Chang et al *Fertil Steril* 1998
Nelson et al *Hum Reprod 2007*

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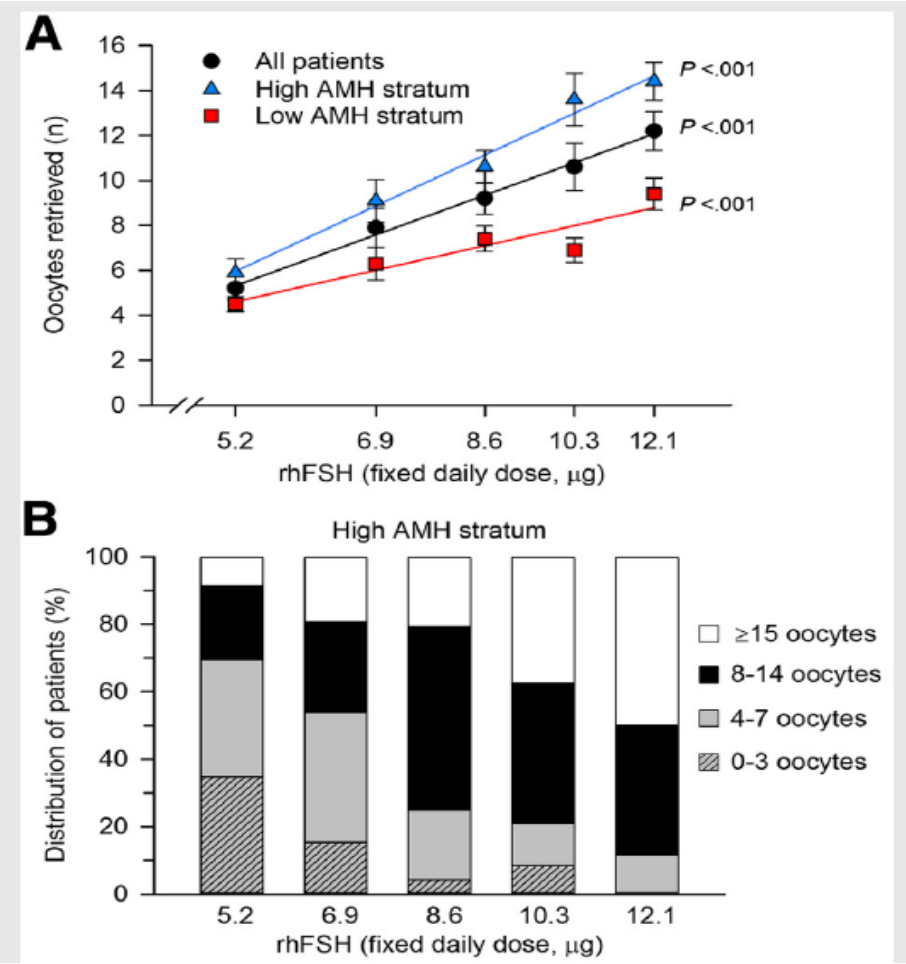
AMH predict oocyte yield according rFSH dose



Arce, J-C, Fertil Steril, Vol 102 No. 6, Dec 2014

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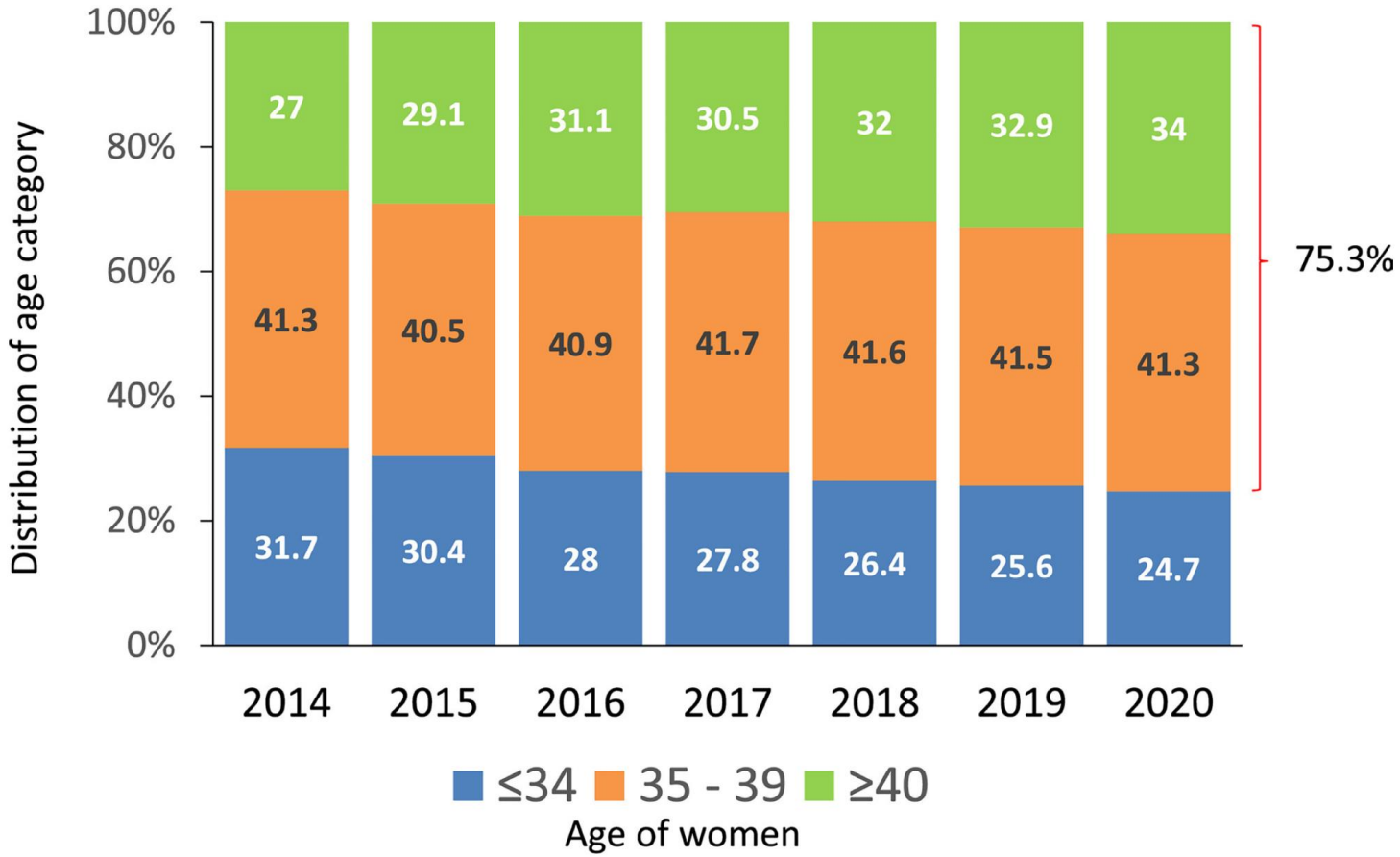
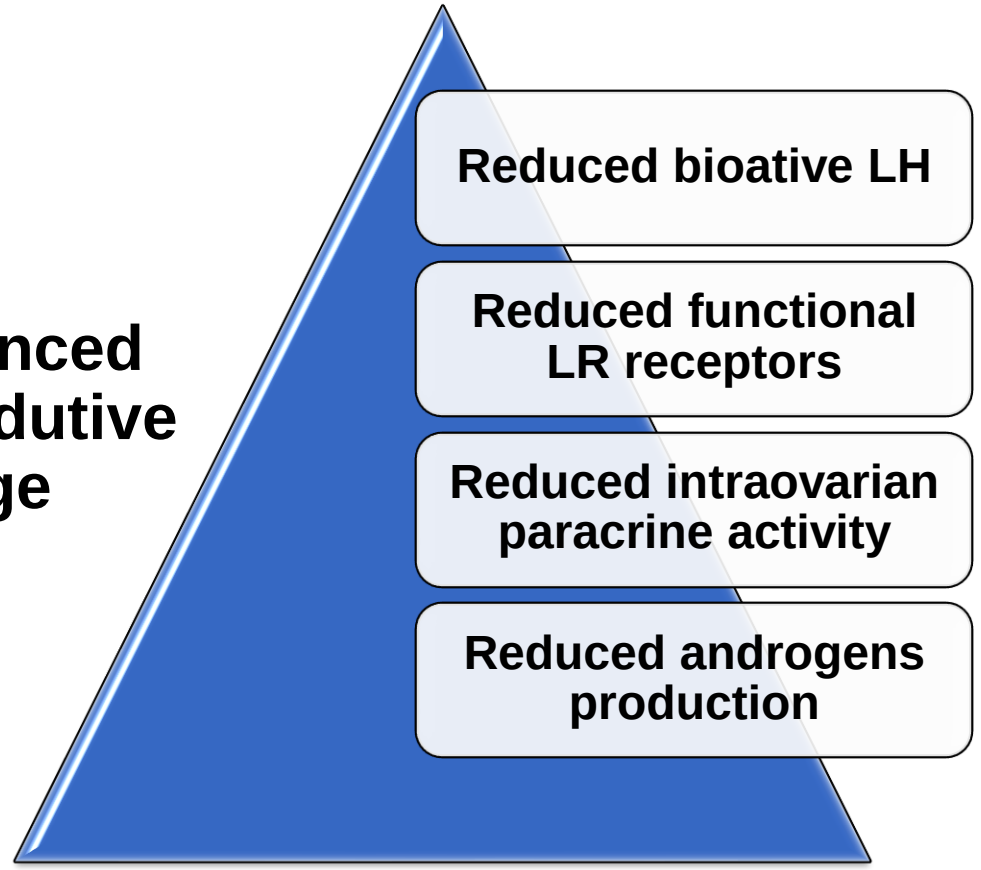
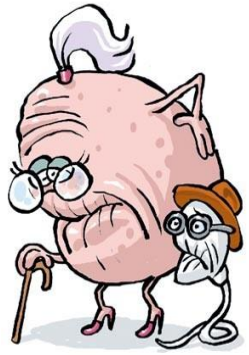


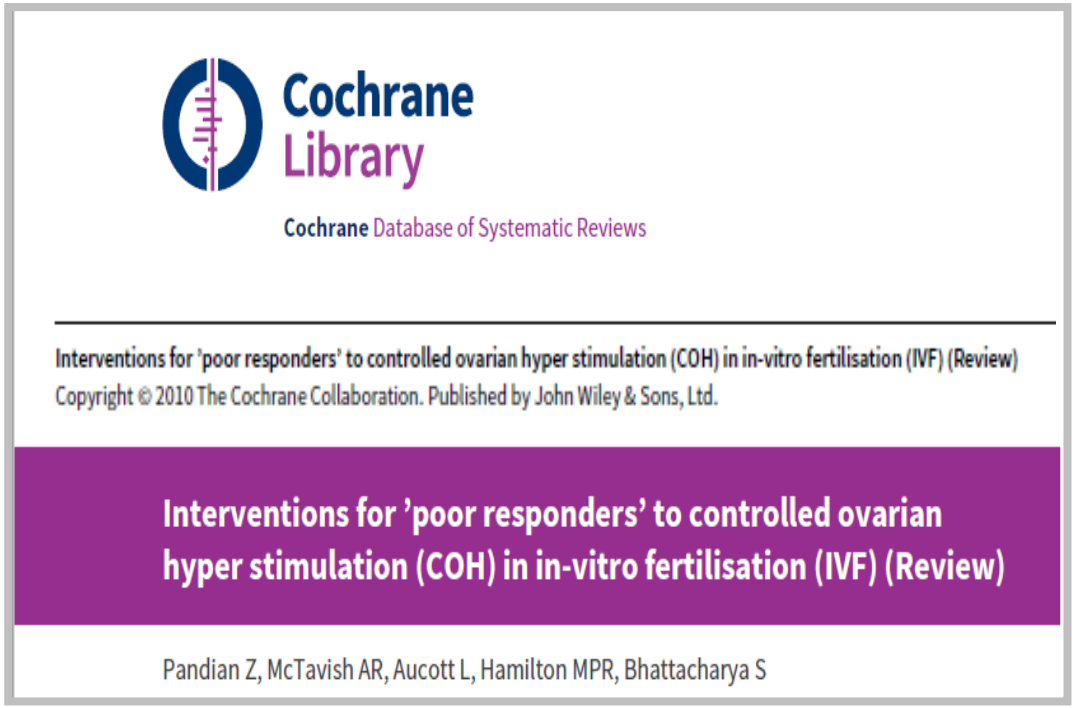
Figure 3. Age distribution of female partner in fresh IVF and intracytoplasmic sperm injection (IVF/ICSI) in Latin America, 2014—2020.

Advanced Reprodutive Age



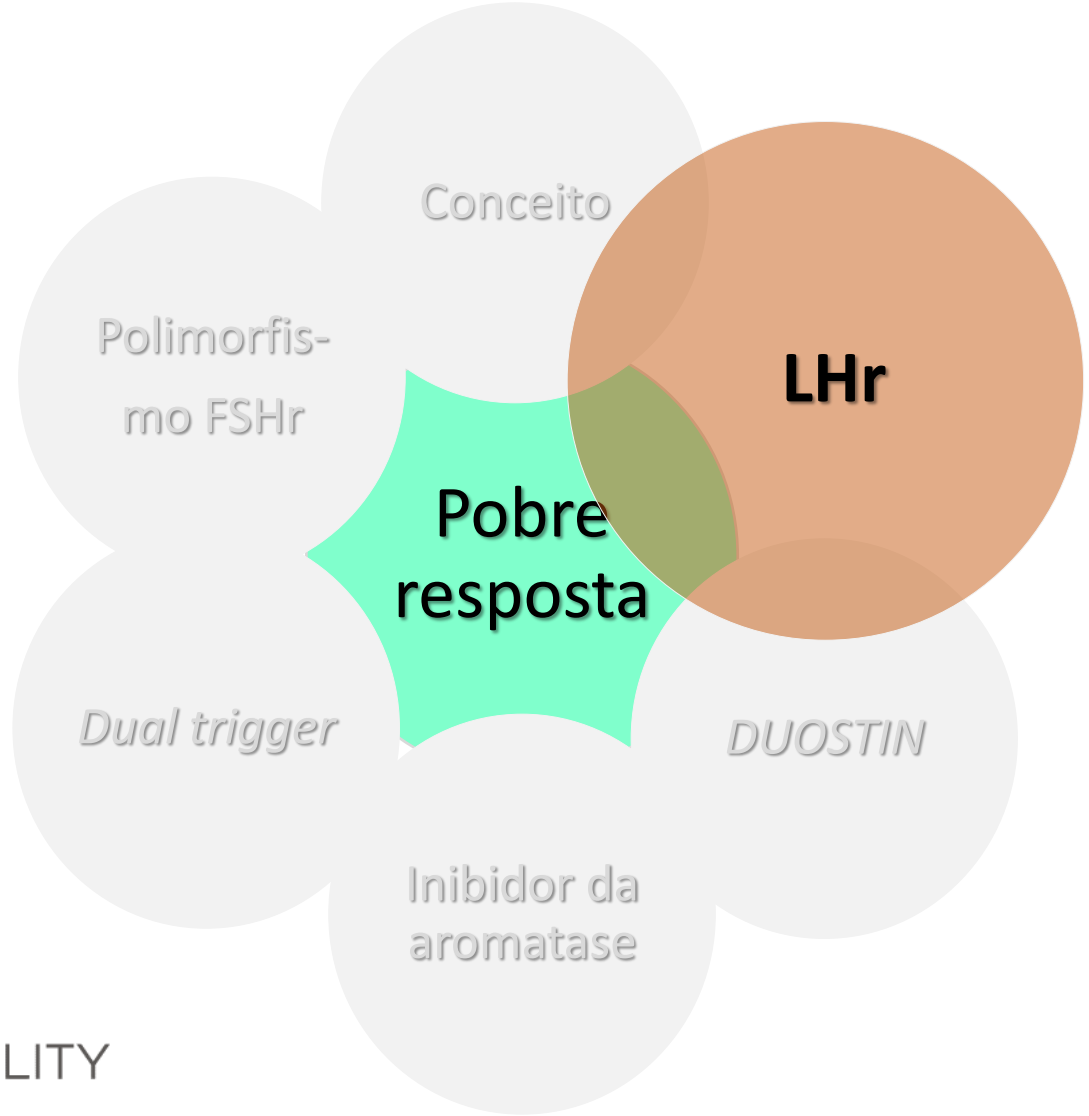


Estimulação ovariana: *pobre resposta*



There is ***insufficient evidence*** to support the routine use of any particular intervention either:

- ***pituitary down regulation,***
- ***ovarian stimulation or***
- ***adjuvant therapy***



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Lehert *et al. Reproductive Biology and Endocrinology* 2014, **12**:17
http://www.rbej.com/content/12/1/17

RESEARCH Open Access

Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis

Philippe Lehert[1,2*], Efstratios M Kolibianakis[3], Christos A Venetis[3], Joan Schertz[4], Helen Saunders[5,6], Pablo Arriagada[5,6], Samuel Copt[5,7] and Basil Tarlatzis[3]

- 40 RCTs (6443 patients) were included in the analysis.
- Data were available from 43 studies (r-hFSH plus r-hLH, n = 3113; r-hFSH, n = 3228) in the intention-to-treat (ITT) population

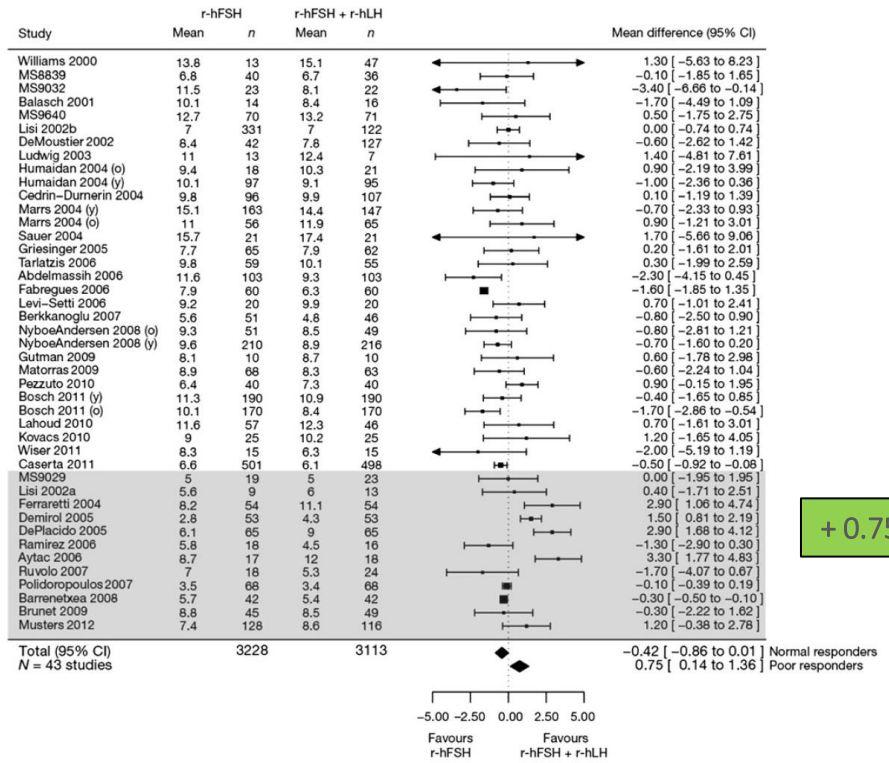


Figure 2 Forest plot of the number of oocytes retrieved in normal versus poor responders (intention-to-treat population). Studies are listed by first author's last name followed by the year of publication. Some studies were divided by subgroup designations: y, young/normal or o, advanced maternal age. The grey-shaded box designates studies of patients with a poor ovarian response. CI, confidence interval; MS, Merck Serono S.A. – Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; r-hFSH, recombinant human follicle-stimulating hormone; r-hLH, recombinant human luteinizing hormone.

+ 0.75 ovocitos; IC 95% 0.14-1.36)

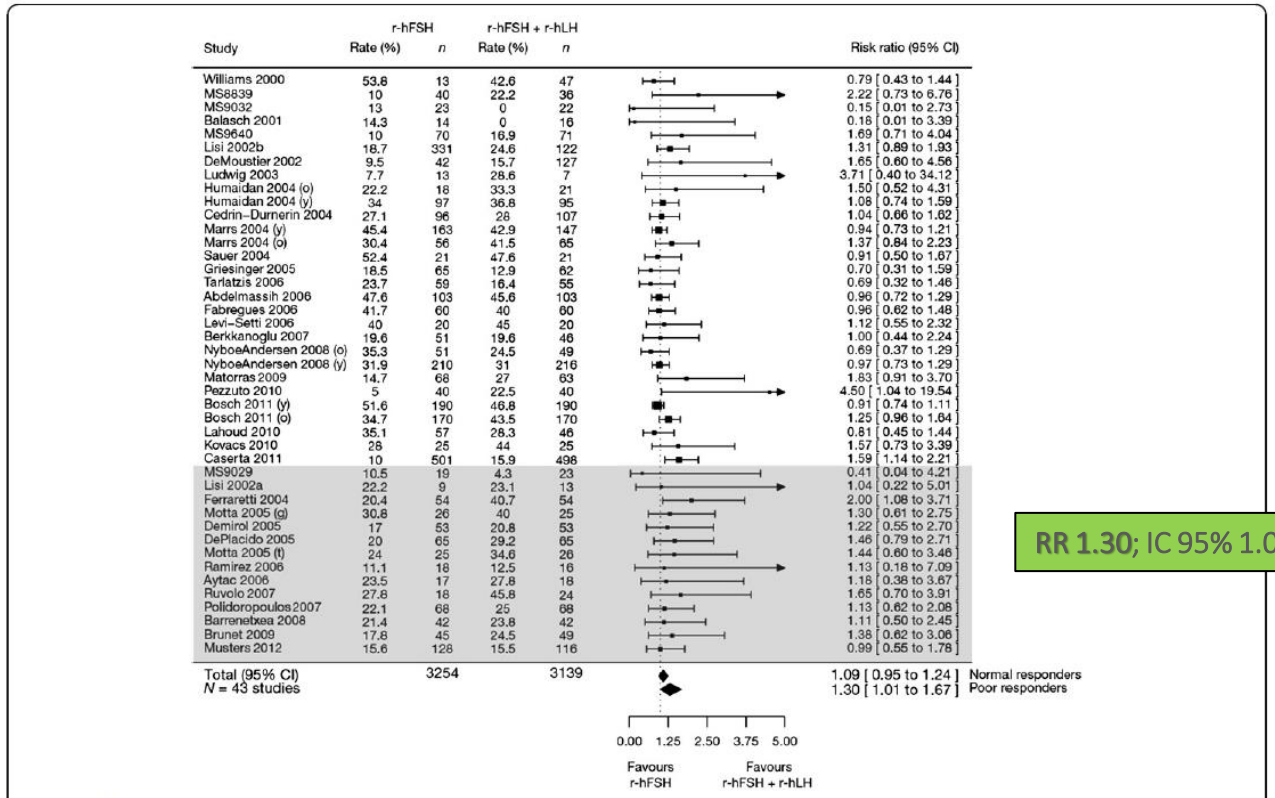
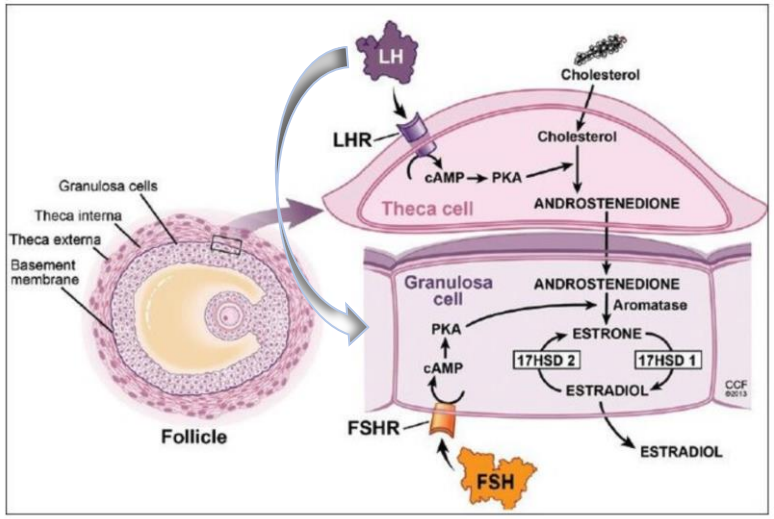


Figure 3 Forest plot of the clinical pregnancy rate for normal versus poor responders (intention-to-treat population). Studies are listed by first author's last name followed by the year of publication. Some studies were divided by subgroup designations: y, young/normal or o, advanced maternal age; g, GnRH agonist or t, GnRH antagonist. The grey-shaded box designates studies of patients with a poor ovarian response. CI, confidence interval; MS, Merck Serono S.A. – Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; r-hFSH, recombinant human follicle-stimulating hormone; r-hLH, recombinant human luteinizing hormone.

RR 1.30; IC 95% 1.01–1.67)

LH receptors



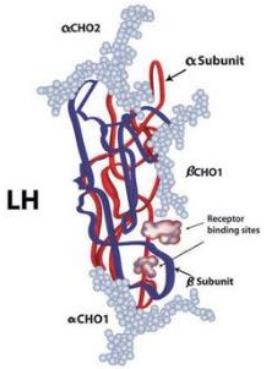
LH receptors are also expressed on GCs, especially after follicular selection, and their expression is 10 times higher in the GCs of preovulatory follicles than in antral follicles 3–10mmin diameter.

MOLECULAR MEDICINE REPORTS 12: 4219-4229, 2015

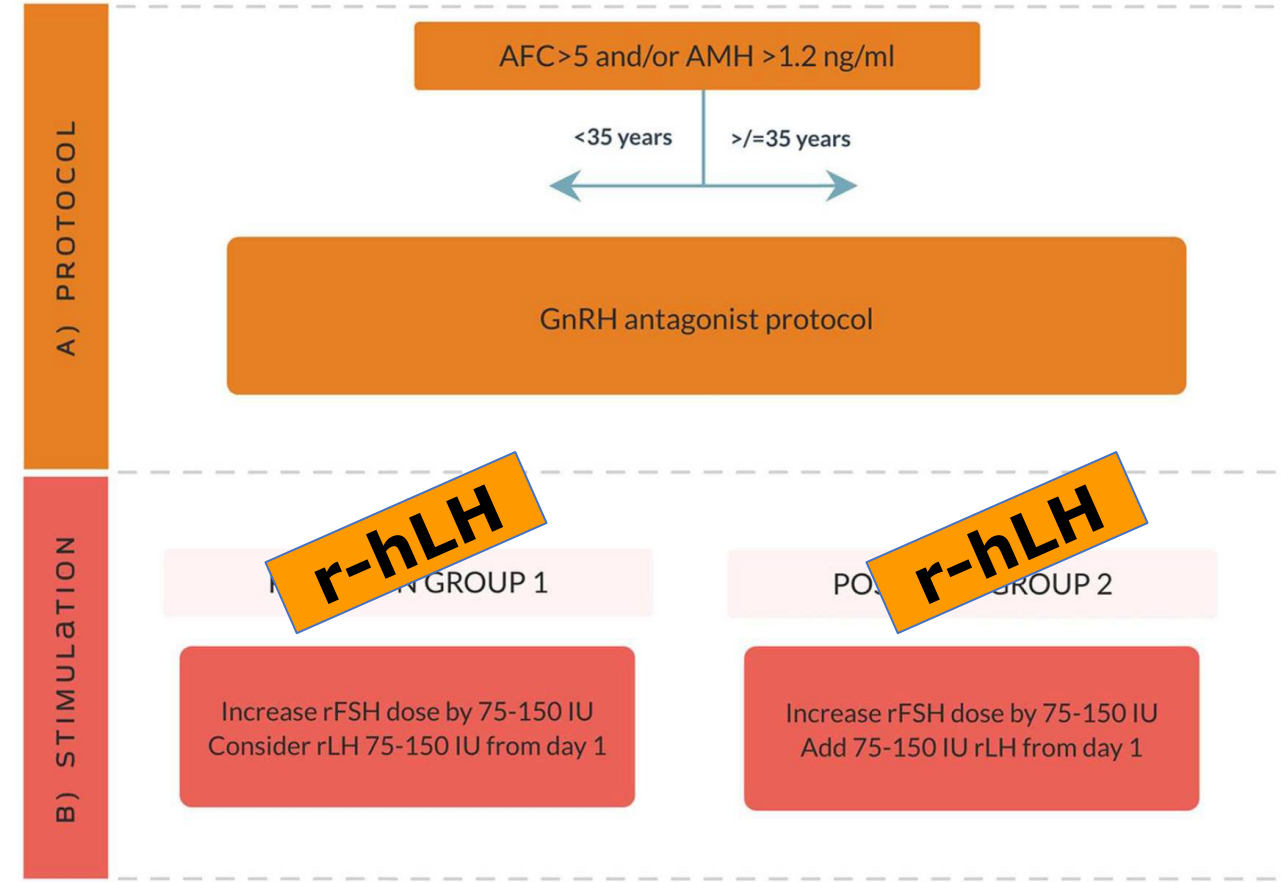
Recombinant LH supplementation during IVF cycles with a GnRH-antagonist in estimated poor responders: A cross-matched pilot investigation of the optimal daily dose and timing

SALVATORE GIZZO, ALESSANDRA ANDRISANI, MARCO NOVENTA, SERENA MANFÈ, ALESSANDRA OLIVA, MICHELE GANGEMI, GIOVANNI BATTISTA NARDELLI and GUIDO AMBROSINI

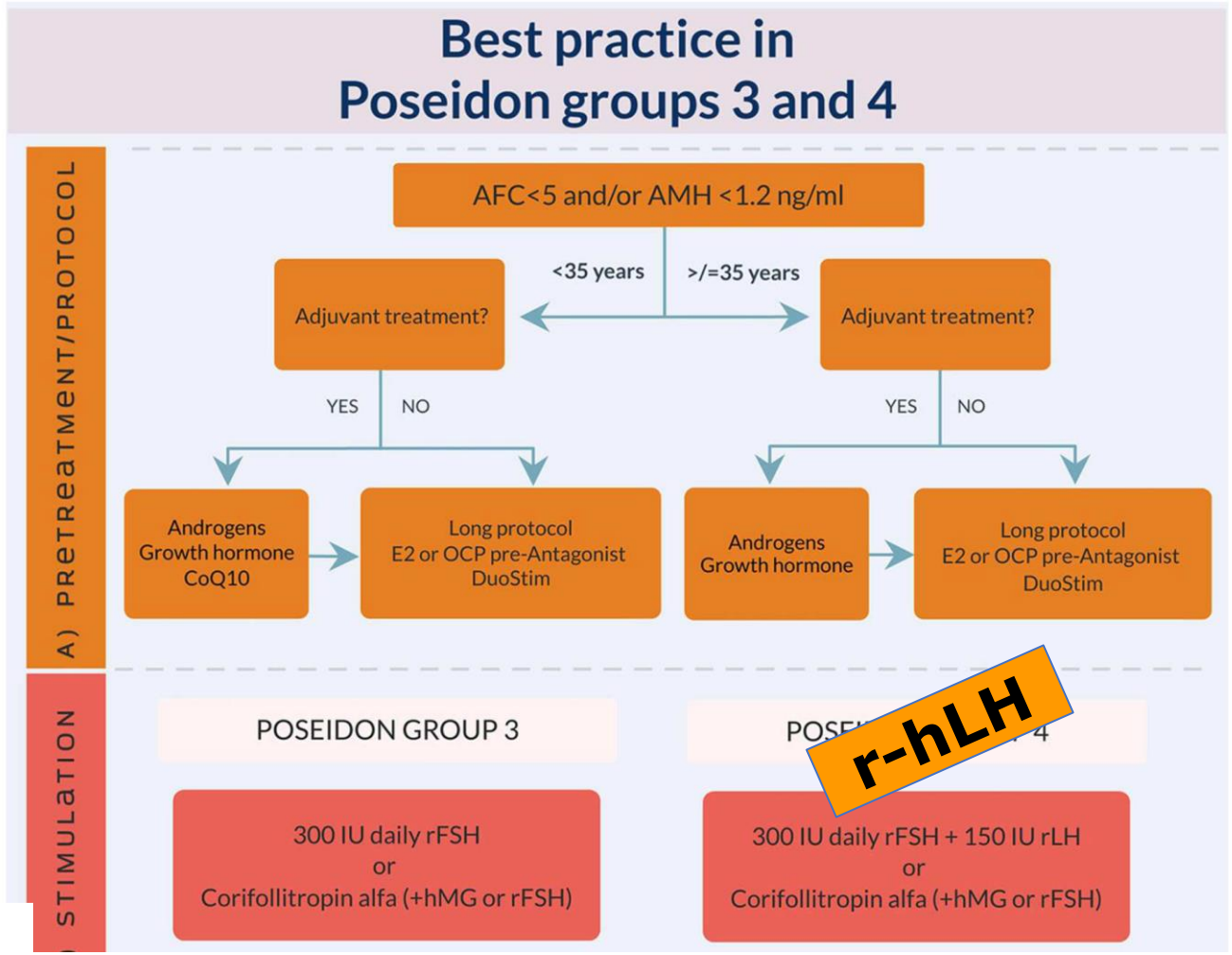
- The ovarian responses are affected by the timing of administration more than the total-dose of rLH;
- The optimal window to administer rLH appears to be the mid-to-late follicular phase,
- LH supplementation at GnRH-ant administration compensates for the severe drop in levels of endogenous LH due to administration of the antagonist itself. In addition, it produces a gonadotrophic environment more similar to the physiological environment.

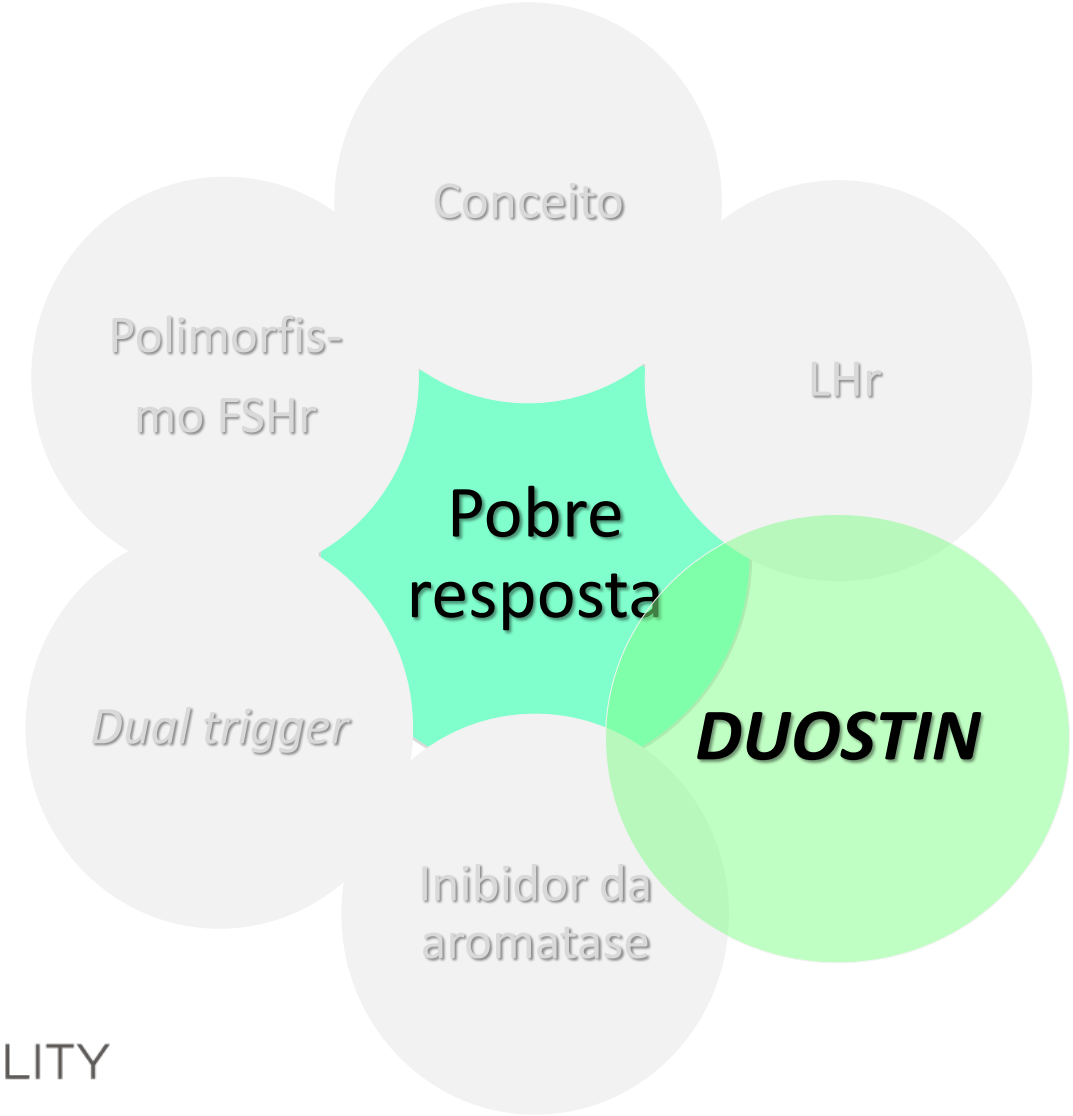


Best practice in Poseidon groups 1 and 2



Best practice in Poseidon groups 3 and 4

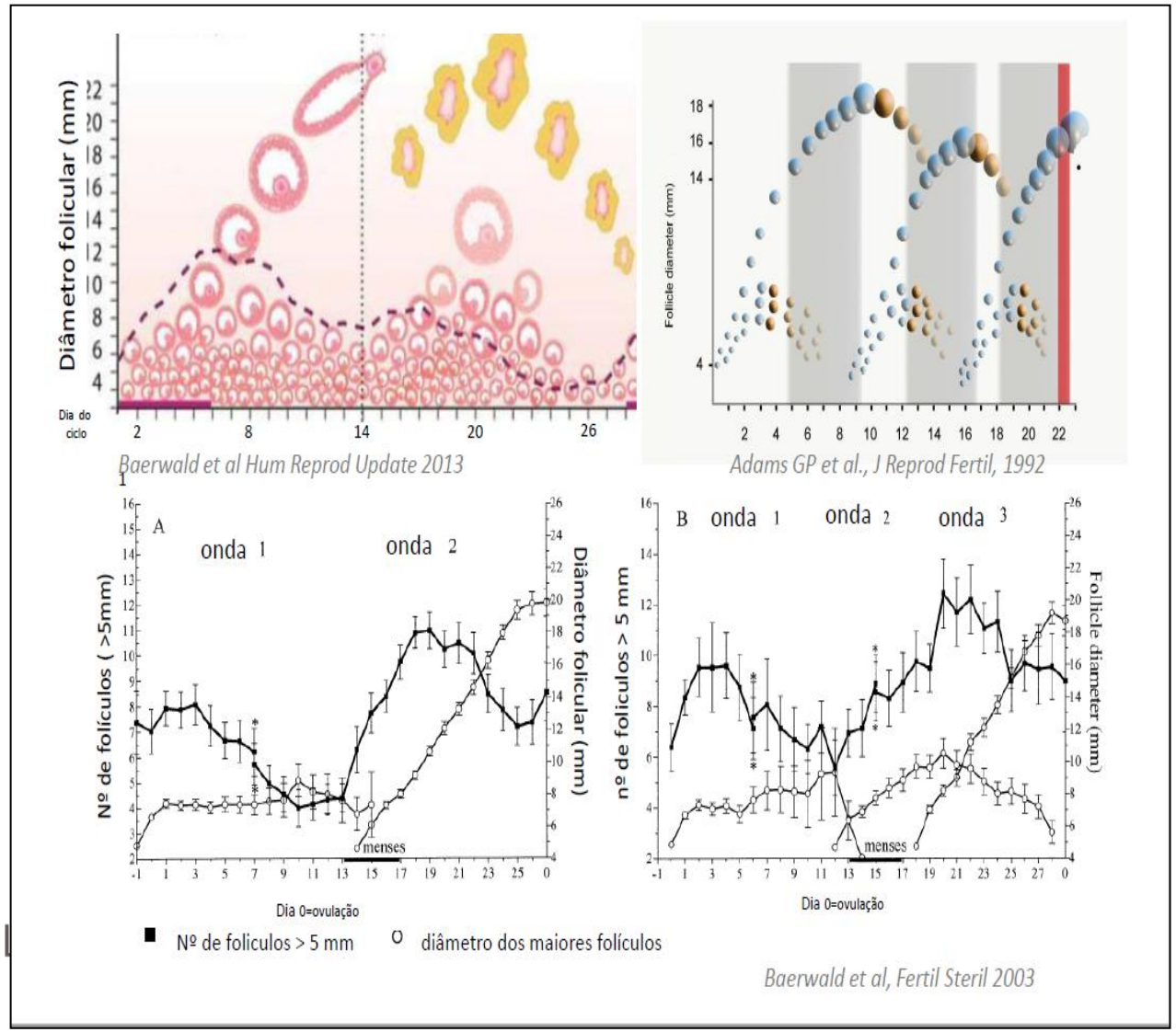




FERTGROUP | FERTILITY

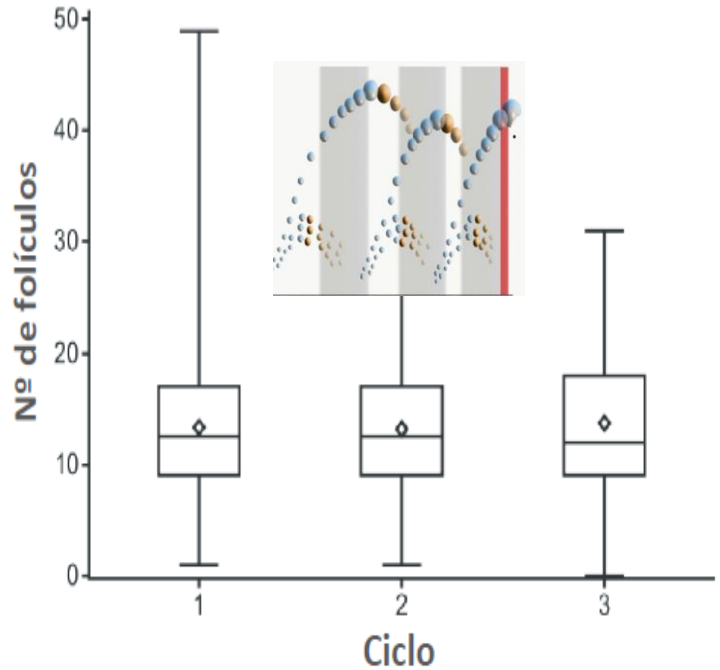
Estimulação ovariana: *pobre resposta*

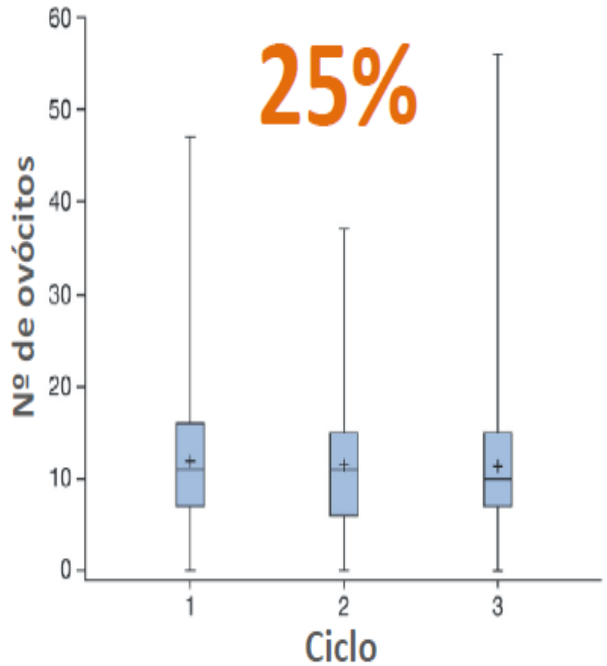
Dinâmica de recrutamento folicular



FERTGROUP | FERTI

- N = 176
- 3 ciclos – exatamente a **mesma** medicação e dose, na **mesma** paciente





Rombauts L, *et al. Fertil Steril* 2015;104:884–90

Estimulação ovariana: *pobre resposta*

DUOSTIN - Dupla estimulação

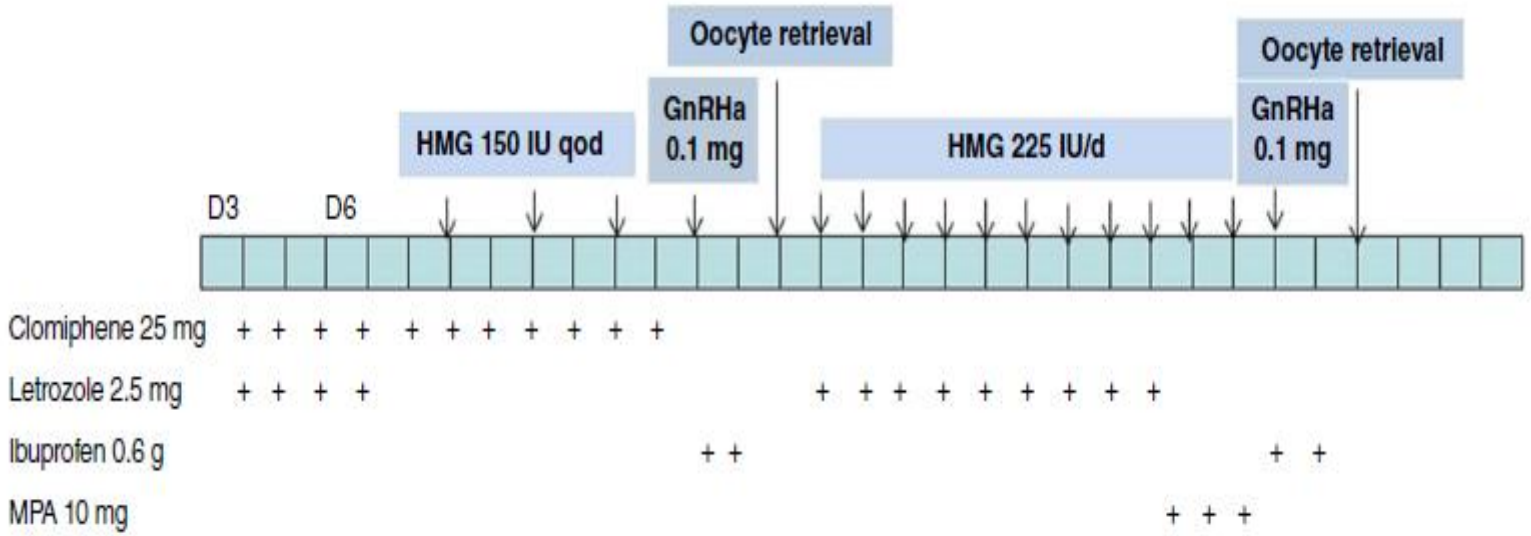
- Maior possibilidade de obtenção de ovócitos / embriões
- Menor tempo de tratamento
- Menos estresse a paciente
- Melhores resultados comparados a estímulos independentes?

Estimulação ovariana: *pobre resposta*

Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

Reproductive BioMedicine Online (2014) 29, 684–691

Yanping Kuang [a,b,*], Qiuju Chen [a,b], Qingqing Hong [a,b], Qifeng Lyu [a,b], Ai Ai [a,b], Yonglun Fu [a,b], Zeev Shoham [c]



Estimulação ovariana: *pobre resposta*

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CONCEITOS:

- ***Ibuprofeno:*** prevenir ruptura folicular
- **MPA:** para estimulações mais longas, evitando punção durante a menstruação
- ***Citrato de clomifeno (CC) e letrozole (Let):*** ações sinérgicas
  - CC (anti-estrogênico): aumento FSH hipofisário por diminuir ação estrogênica
  - Let (inibidor da aromatase): liberação hipotalâmica/hipofisária do feedback negativo dos estrógenos e aumenta os andrógeno foliculares

Estimulação ovariana: *pobre resposta*

Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

Reproductive BioMedicine Online (2014) 29, 684–691

Yanping Kuang [a,b,*], Qiuju Chen [a,b], Qingqing Hong [a,b], Qifeng Lyu [a,b], Ai Ai [a,b], Yonglun Fu [a,b], Zeev Shoham [c]

Pacientes (pelo menos 2 critérios):

- > 40 anos
- Tratamentos prévios < 3 ovócitos
- < 5 folículos antrais
- FSH 10-19 mUI/mL
- Cirurgia ovariana prévia

Table 3 Cryopreserved embryo transfer cycle outcomes using embryos derived from double stimulation in patients with poor ovarian response.

	Total	*Embryos from first oocyte retrival*	*Embryos from second oocyte retrival*	*Two embryos from two oocyte retrievals*
Number of patients	21	12	6	3
Cryopreserved embryo transfer cycles	23	13	7	3
Embryos warmed	43	22	15	6
Embryo transferred	41	21	14	6
Embryo survival rate (%)	41/43 (95.3)	21/22 (95.5)	14/15 (93.3)	6/6 (100)
Clinical pregnancy rate (%)	13/23 (56.5)	8/13 (61.5)	5/7 (71.4)	0/3
Implantation rate (%)	15/41 (36.6)	10/21 (47.6)	5/14 (35.7)	0/6
Spontaneous abortion rate (%)	2/13 (15.4)	1/8 (12.5)	1/5 (20.0)	0
Ongoing pregnancy rate (%)	11/23 (47.8)	7/13 (53.8)	4/7 (57.1)	0/3

Estimulação ovariana: *pobre resposta*

Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

Reproductive BioMedicine Online (2014) 29, 684–691

Yanping Kuang [a,b,*], Qiuju Chen [a,b], Qingqing Hong [a,b], Qifeng Lyu [a,b], Ai Ai [a,b], Yonglun Fu [a,b], Zeev Shoham [c]

CONCLUSÃO:

Protocolo a ser utilizado para pacientes com:

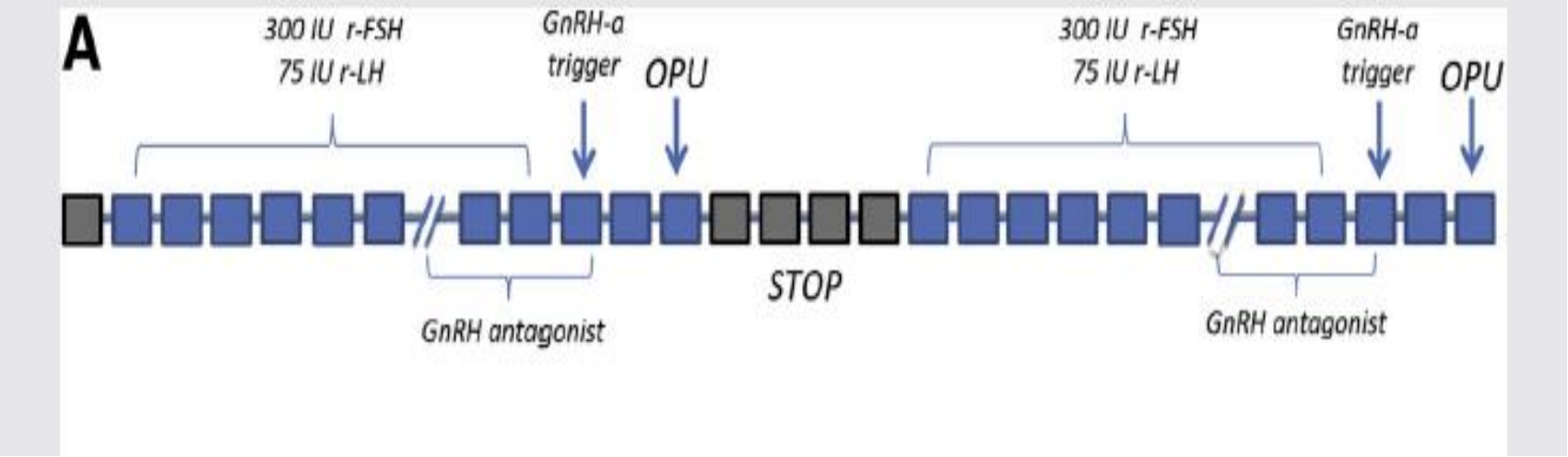
- ***falhas recorrentes de obtenção de ovócitos ou***
- ***pacientes sem embriões viáveis em estímulos ovulatórios convencionais***

Estimulação ovariana: *pobre resposta*

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,d] Silvia Colamaria, M.D.,[a,b] Carlo Alviggi, M.D., Ph.D.,[d,e] nd Laura Rienzi, M.Sc.[a,b,c]

Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282



FERTGROUP

Estimulação ovariana: *pobre resposta*

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

Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282

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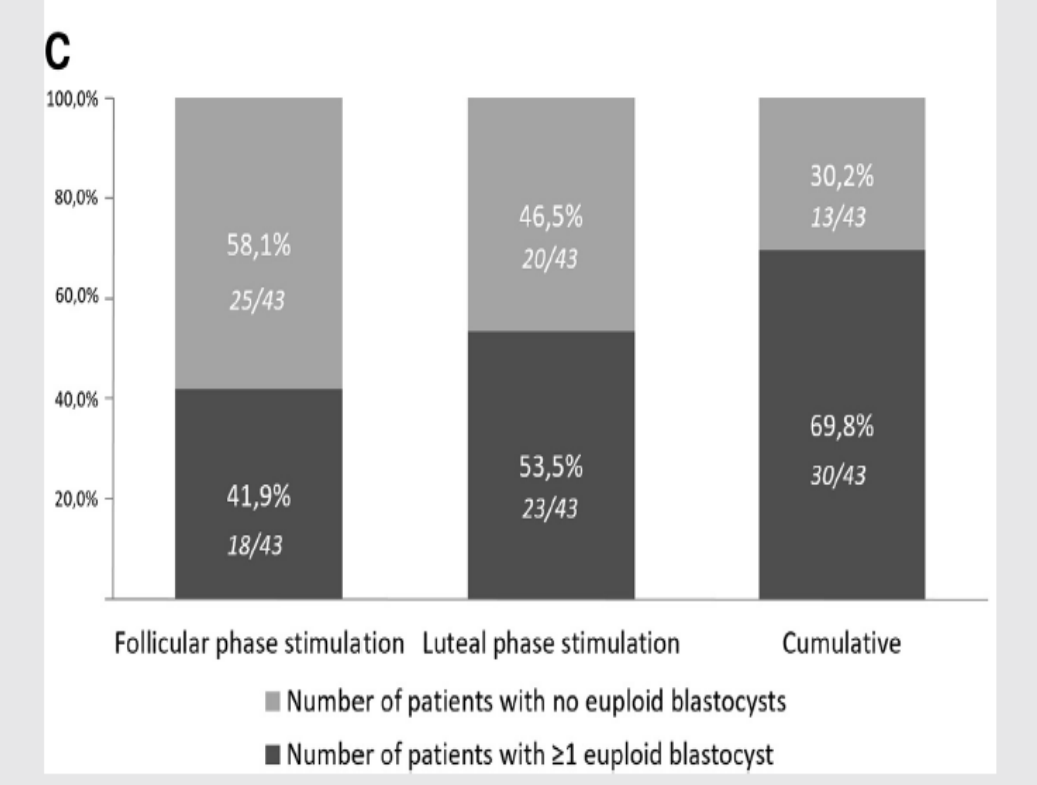
Pacientes :

- HAM < 1,5 ng/mL
- Tratamentos prévios < 3 ovócitos
- < 6 folículos antrais ou < 5 ovócitos
- PGT-A



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Estimulação ovariana: *pobre resposta*

REVIEW

Dual ovarian stimulation and random start in assisted reproductive technologies: from ovarian biology to clinical application

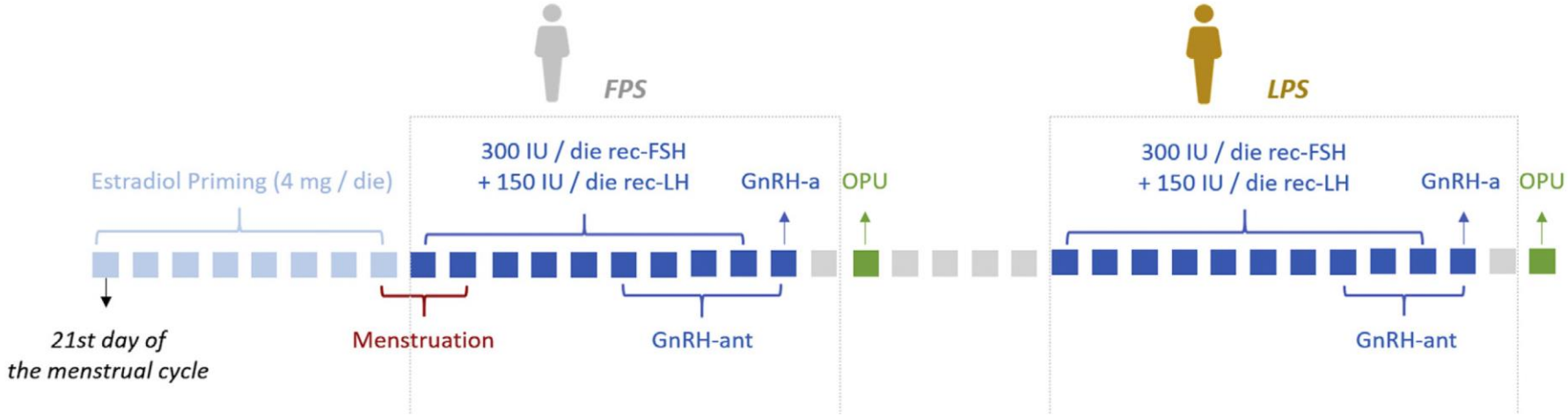
Alberto Vaiarelli[a,b], Roberta Venturella[c,d], Damiano Vizziello[e], Francesco Bulletti[f], and Filippo M. Ubaldi[a,c]

Volume 29 • Number 3 • June 2017

	FP-COS	LP-COS	*P value*	Overall
Number of patients Mean age ± SD (min–max)		153 39.5 ± 3.2 (33.0–44.0)		
Number of cycles stopped Rate – %	10 6.5%	15 9.8%	NS	25 16.3%
Number of cycles to OPU		128		
COCs – *n* (mean ± SD, min–max)	663 (5.2 ± 2.8, 1–22)	734 (5.9 ± 3.4, 1–19)	NS	1397 (5.5 ± 3.1, 1–22)
Number of cycles with at least one MII oocyte Rate – %	124 96.9%	125 97.7%	NS	128 100.0%
MII oocytes – *n* (mean ± SD, min–max) MII oocyte rate – %	486 (3.8 ± 2.2, 0–12) 73.3%	565 (4.5 ± 2.7, 0–14) 77.0%	NS NS	1051 (4.1 ± 2.5, 0–14) 75.2%
Number of cycles with at least one fertilized oocyte Rate – %	118 92.2%	120 93.8%	NS	126 98.4%
Fertilized oocytes – *n* (mean ± SD, min–max Fertilization rate – %	334 (2.6 ± 1.9, 0–9) 68.7%	433 (3.5 ± 2.5, 0–13) 76.7%	NS NS	767 (3.0 ± 2.2, 0–13) 73.0%
Number of cycles with at least one blastocysts Rate – %	95 74.2%	98 76.6%	NS	119 93.0%
Blastocysts – *n* (mean ± SD, min-max Blastocyst rate – %	161 (1.3 ± 1.1, 0–5) 48.2%	214 (1.7–1.7, 0–9) 49.4%	NS NS	375 (1.5 ± 1.4, 0–9) 48.9%
Number of cycles with at least one euploid blastocyst Rate – %	43 33.6%	54 42.2%	NS	77 60.2%
Euploid blastocyts – *n* (mean ± SD, min–max Euploidy rate – %	61 (0.5 ± 0.8, 0–3) 37.9%	81 (0.6 ± 1.0, 0–5) 37.9%	NS NS	142 (0.5 ± 0.9, 0–5) 37.9%

FERTGR

COC, cumulus–oocyte complexes; FP-COS, follicular phase controlled ovarian stimulation; GENERA, Ginecologia ENdocrinologia Embriologia Riproduzione Assistita; LP-COS, luteal phase controlled ovarian stimulation; MII, metaphase II; OPU, oocyte pickup.



Main differences between the two ovarian stimulation strategies adopted (DuoStim and conventional) in patients fulfilling the Bologna criteria during the observational period.

Characteristic	DuoStim (N = 100)	Conventional COS (N = 197)	*P* value
Patients performing two ovarian stimulations, n, %	100/100, 100%	17/197, 9%	< .01
Days between first and second oocyte retrieval, mean ± SD (min-max)	15.8 ± 2.6 (11-23)	141.4 ± 83.6 (30-330)	< .01
Patients with at least one euploid blastocyst obtained, n, %	31/100, 31% After FPS: 14 After LPS: 19 After both: 2	40/197, 20% After 1st COS: 38 After 2nd COS: 2 After both: 0	.05
Patients with at least one live birth obtained, n, %	15/100, 15%	16/197, 8%	.07

Note: COS = controlled ovarian stimulation; FPS = follicular phase stimulation; LPS = luteal phase stimulation; SD = standard deviation; SET = single embryo transfer.

Vaiarelli. DuoStim in "Bologna" poor responders. Fertil Steril 2019.

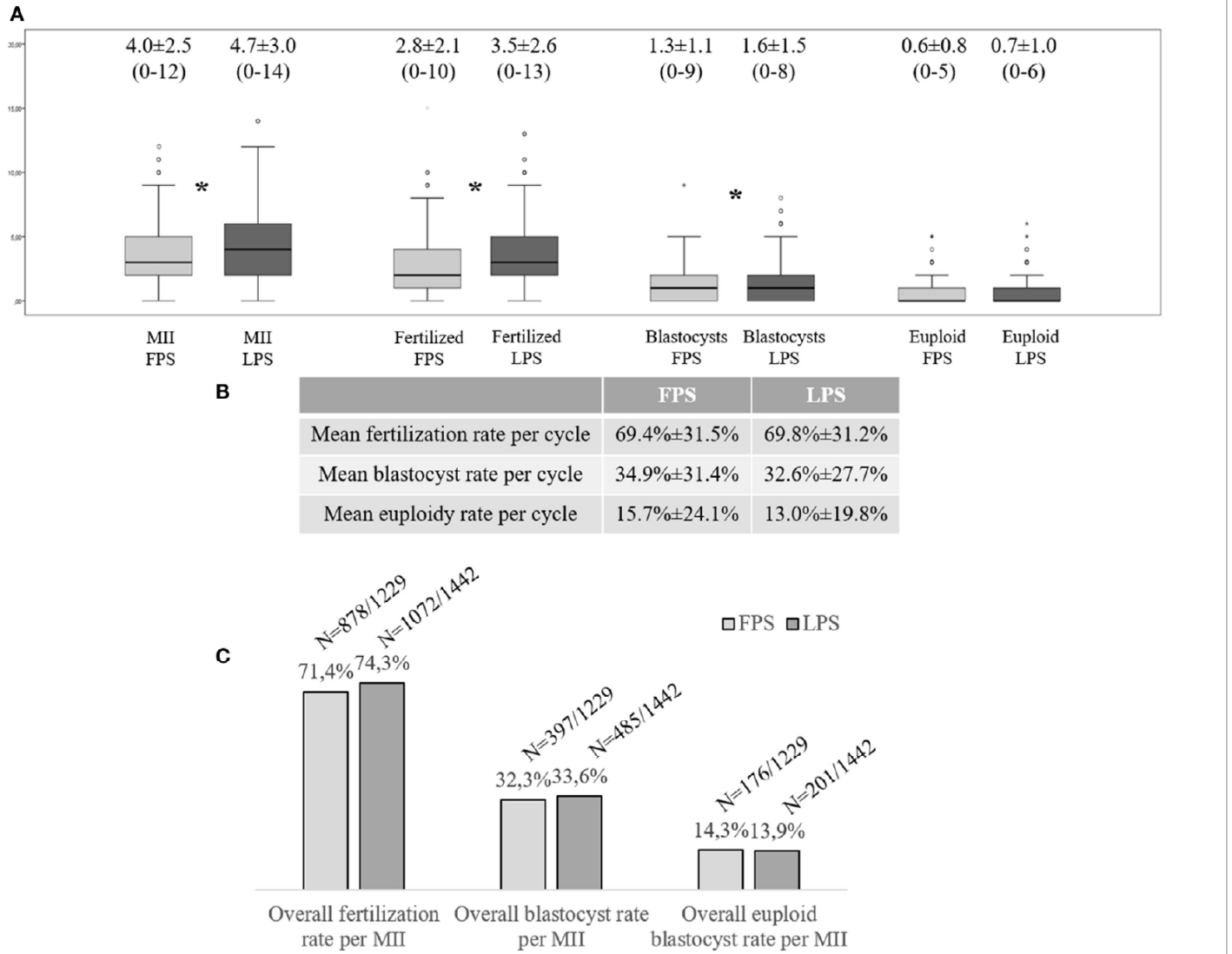


FIGURE 1 | Multicenter clinical experience at the G.EN.E.R.A. centers for reproductive medicine (Rome, Naples, Marostica, and Umbertide) with the application of a DuoStim approach. **(A)** Mean number of metaphase (MII) oocytes, fertilized embryos, blastocysts, and euploid blastocysts obtained per cycle after follicular phase stimulation (FPS) and luteal phase one (LPS); **(B)** Mean embryological results calculated per MII oocyte retrieved and inseminated in FPS- and LPS-derived cycles; **(C)** Overall embryological results of the MII oocytes collected after FPS and LPS, respectively. The stars identify statistically significant differences. The non-Gaussian distribution of the data was assessed through the Shapiro–Wilk test. Wilcoxon signed-rank test and Fisher's exact test were used to test for significant differences between FPS- and LPS-derived data.

OXFORD

human reproduction

Human Reproduction, 2024, **00(0)**, 1–10

https://doi.org/10.1093/humrep/dead276

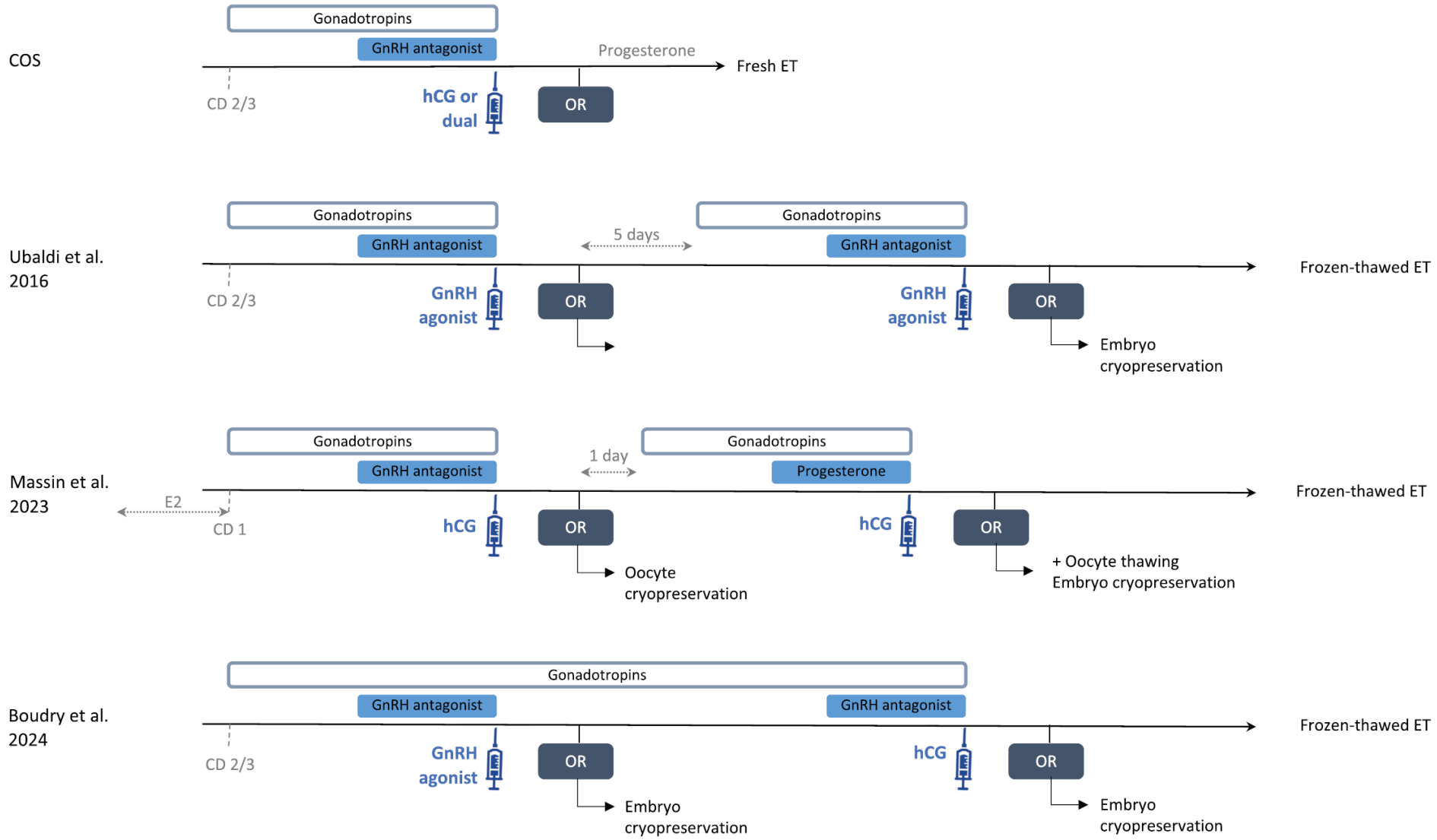
Original article

Infertility

Does dual oocyte retrieval with continuous FSH administration increase the number of mature oocytes in low responders? An open-label randomized controlled trial

L. Boudry [1,*], I. Mateizel [1], K. Wouters [1], E. Papaleo [2], S. Mackens [1], M. De Vos [1], A. Racca [3], T. Adriaenssens[4], H. Tournaye [1], and C. Blockeel [1]

FERTGROUP | FERTILITY


COS
Gonadotropins
GnRH antagonist
Progesterone
Fresh ET
CD 2/3
hCG or dual
OR
Ubaldi et al. 2016
Gonadotropins
GnRH antagonist
5 days
Gonadotropins
GnRH antagonist
Frozen-thawed ET
CD 2/3
GnRH agonist
OR
GnRH agonist
OR
Embryo cryopreservation
Massin et al. 2023
Gonadotropins
GnRH antagonist
1 day
Gonadotropins
Progesterone
Frozen-thawed ET
E2
CD 1
hCG
OR
hCG
OR
Oocyte cryopreservation
+ Oocyte thawing
Embryo cryopreservation
Boudry et al. 2024
Gonadotropins
GnRH antagonist
GnRH antagonist
Frozen-thawed ET
CD 2/3
GnRH agonist
OR
hCG
OR
Embryo cryopreservation
Embryo cryopreservation

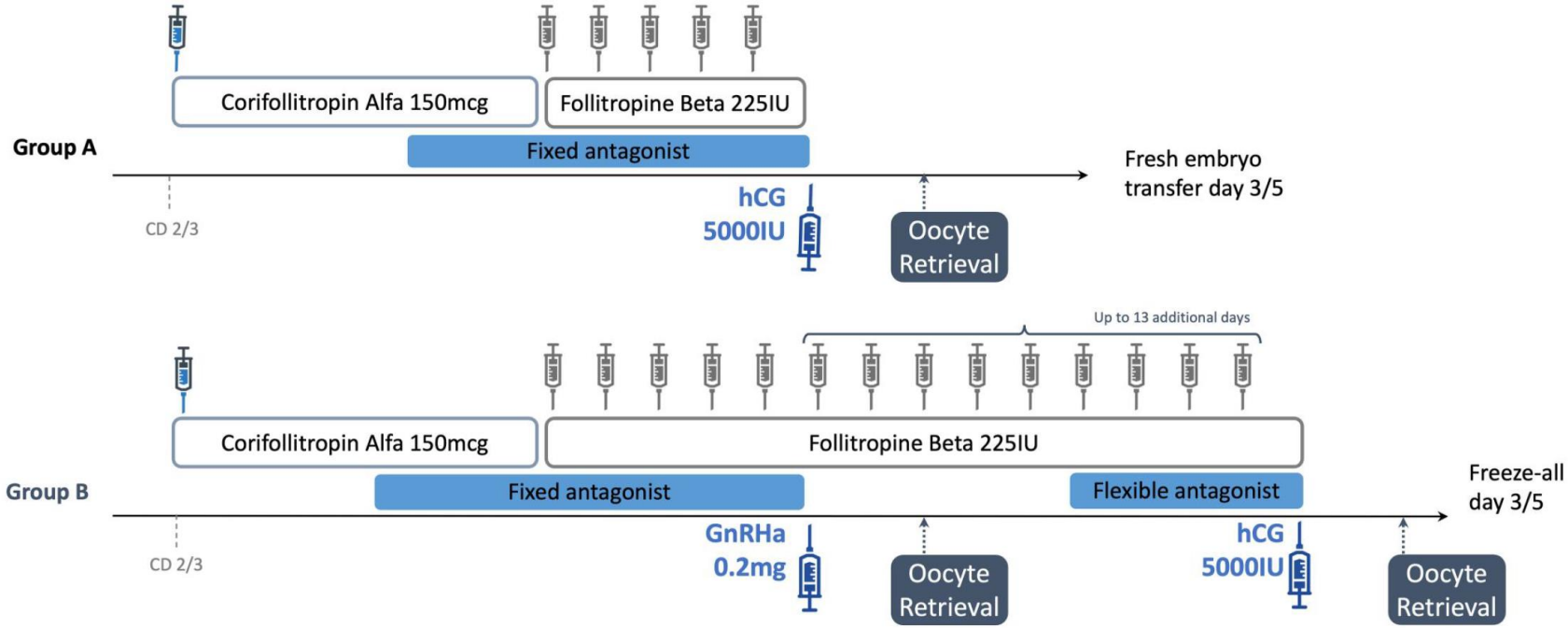


Figure 2. Study protocol. CD: cycle day; IU: international units.

SUMMARY ANSWER: There is no increase in the total number of MII oocytes when comparing one conventional OS to a continuous stimulation with double oocyte aspiration.

JIVFww

Braga D, Setti A, Morishima C, Iaconelli A, Borges E. Understanding the implications of follicular output rate (FORT) and follicle to oocyte index (FOI) on human embryo morphokinetics. *Journal of IVF-Worldwide*. 2024;2(1). doi:10.46989/001c.91041

Original Research Articles

Understanding the implications of follicular output rate (FORT) and follicle to oocyte index (FOI) on human embryo morphokinetics

Daniela Braga[1,2a], Amanda Setti[1,2], Christina Morishima[1,2], Assumpto Iaconelli[1,2], Edson Borges[1,2]

[1] Fertility Medical Group Av. Brigadeiro Luis Antonio, 4545 São Paulo – SP, Brazil. Zip: 01401-002, [2] Instituto Sapientiae – Centro de Estudos e Pesquisa em Reprodução Humana Assistida Rua Vieira Maciel, 62 São Paulo – SP, Brazil. Zip: 04503-040

Keywords: Time-lapse microscopy, morphokinetic assessment, Follicular Output Rate (FORT), Follicle-to-Oocyte index (FOI), ICSI

https://doi.org/10.46989/001c.91041

Journal of IVF-Worldwide

Vol. 2, Issue 1, 2024

Table 1. Comparison of demographic and cycle characteristics between low and high follicle-to-oocyte index (FOI) groups

		Low FOI	High FOI	P value
n		247	2,223	
Female age (years)		38.6 ± 3.4	38.3 ± 3.8	0.213
Male age (years)		39.5 ± 5.9	39.5 ± 5.7	0.683
Female BMI (kg/m^2)		24.9 ± 4.4	24.3 ± 3.8	0.081
Total dose of FSH	Follitropin alfa (IU)	2531.5 ± 1000.6	2574.9 ± 774.0	0.241
	Follitropin delta (mcg)	148.0 ± 32.3	152.0 ± 29.9	0.124
Oestradiol level (pg/mL)		1351.7 ± 1002.0	1546.4 ± 384	**0.001**
Follicles (n)		7.5 ± 6.3	16.4 ±10.4	**<0.001**
Retrieved oocytes (n)		3.9 ± 3.4	12.5 ± 8.4	**<0.001**
Mature oocyte (n)		3.0 ± 2.7	9.2 ± 6.8	**<0.001**

Note: Values are means ± standard error. unless otherwise noted. ICSI – intracytoplasmic sperm injection; BMI – body mass index; FSH – follicle stimulating hormone; hCG – human chorionic gonadotropin.

Table 2. Comparison of demographic and cycle's characteristics between low, medium, and high follicular output rate (FORT) groups

		Low FORT	Medium FOI	High FORT	P value
n		753	874	843	
Female age (years)		36.9 ± 3.3	37.1 ± 3.4	37.2 ± 2.9	0.651
Male age (years)		39.0 ± 4.7	39.3 ± 3.9	39.4 ± 5.6	0.615
Female BMI (kg/m^2)		24.1 ± 3.3	24.5 ± 3.4	24.6 ± 4.1	0.162
Total dose of FSH	Follitropin alfa (IU)	2539.7 ± 785.6	2558.5 ± 958.0	2545.6 ± 789.9	0.953
	Follitropin delta (mcg)	151.0 ± 32.3	149.0 ± 35.4	151.5 ± 29.8	0.457
Oestradiol level (pg/mL)		1495.9 ± 547.6^a	1545.2 ± 475.7^b	1639.2 ± 547.9^c	0.001
Follicles (n)		7.3 ± 5.9^a	12.3^b ± 5.6	14.1 ± 9.3^c	<0.001
Retrieved oocytes (n)		4.1 ± 3.6 ^{a}	10.1 ± 7.9 ^{b}	11.1 ^{c} ± 9.1	<0.001
Mature oocyte (n)		3.4 ± 2.5 ^{a}	7.9 ± 6.3 ^{b}	8.9 ^{c} ± 5.1	<0.001

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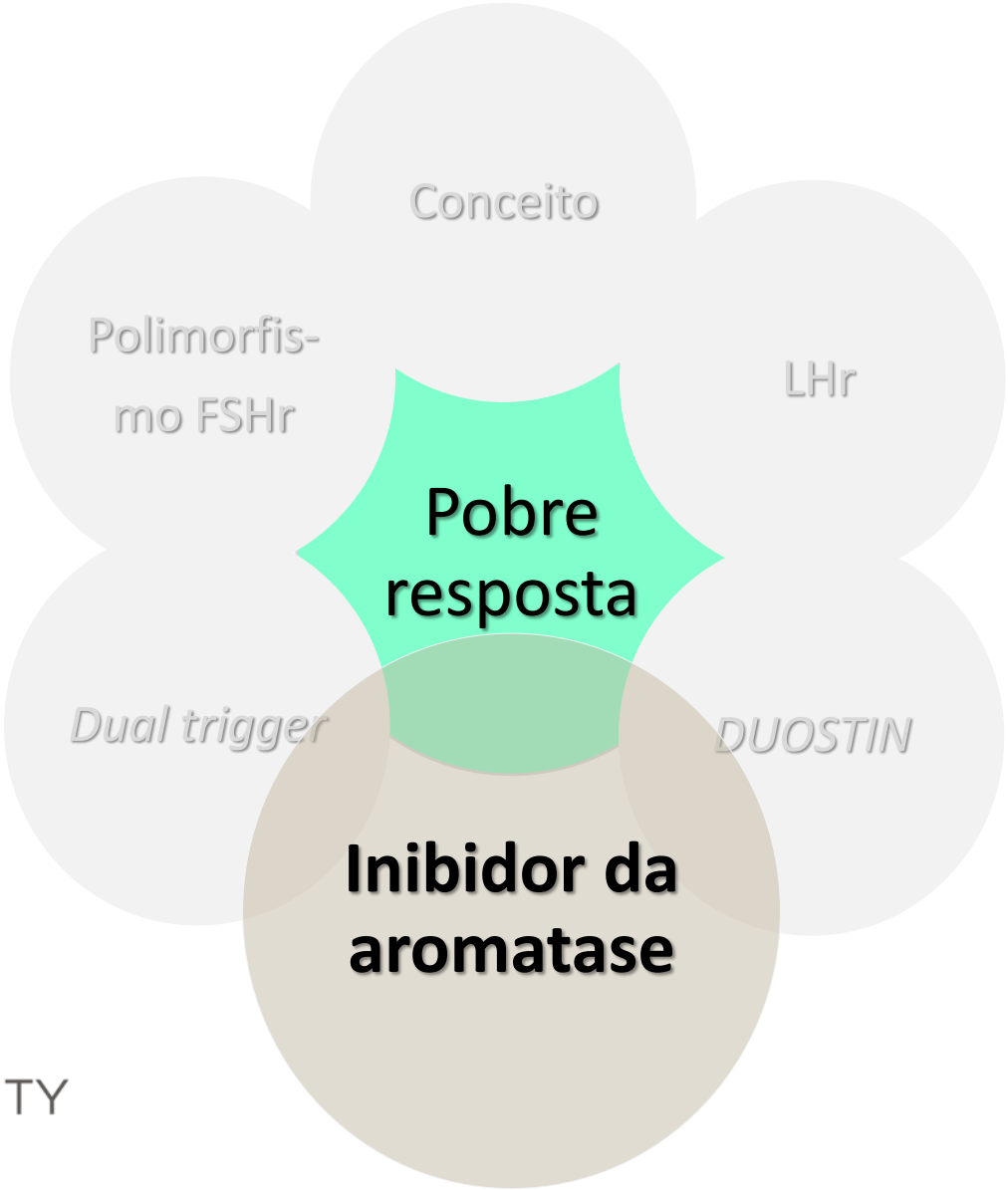
Table 4. Comparison of known implantation diagnosis (KID) score D5 and intracytoplasmic sperm injection (ICSI) outcomes between the low and high follicle-to-oocyte (FOI) index groups.

Variable	Low FOI	High FOI	p value	B/OR	95% IC
Cycles	247	2.223			
Embryos	894	7532			
Kid score	5.1 ± 0.09	5.60 ± 0.03	**< 0.001**	-0.490*	-0.691 - -0.288
Fertilization rate (%)	70.0 ± 1.39	71.71 ± 0.72	0.299	-1.61*	-1.4 – 4.7
Blastocyst rate (%)	53.6 ± 0.92	44.85 ± 1.87	**< 0.001**	-8.8*	-12.9 - -4.7
Implantation rate (%)	24.8 ± 0.32	26.08 ± 0.53	**0.037**	-0.051	-0.099 – -0.004
Pregnancy rate (%)	32.4± 4.9 (80/247)	34.9 ± 3.22 (778/2.223)	0.573	1.157**	0.692 – 1.93
Miscarriage rate (%)	13.7 ± 3.6 (11/80)	16.2 ± 3.2 (130/800)	0.451	1.145**	0.847 – 1.547
Livebirth (%)	27.5 ± 2.1 (68/247)	30.2 ± 2.4 (672/2.223)	0.547	1.547**	0.475 – 1.654

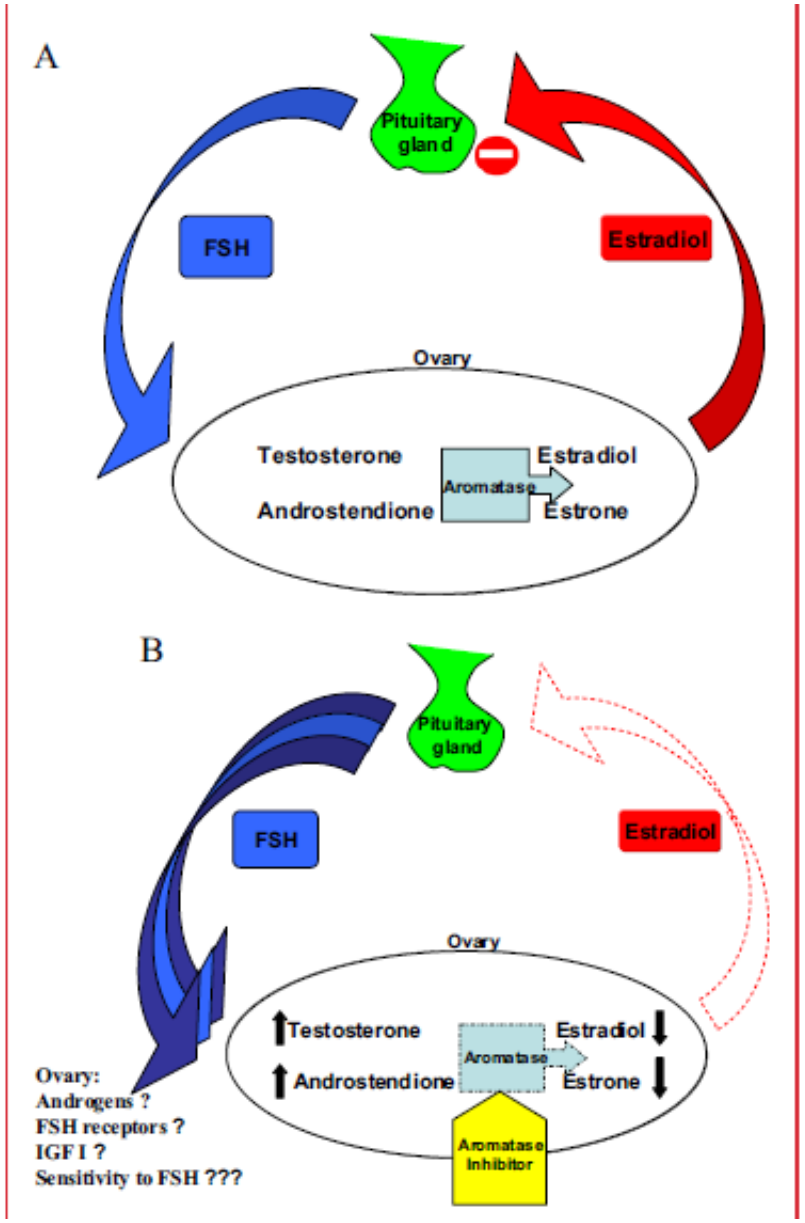
Table 6. Comparison of known implantation diagnosis (KID) score D5 and intracytoplasmic sperm injection (ICSI) outcomes between the low and high follicle-to-oocyte (FOI) index groups.

Variable	Low FORT	Medium FORT	High FORT	p value
Cycles	753	874	843	
Embryos	2,556	2,970	2,970	
Kid score	5.4 ± 0.5[a]	5.5 ± 0.5 [a,b]	5.6 ± 0.6 [b]	**0.021**
Fertilization rate (%)	63.7 ± 1.1	71.4 ± 1.1	73.3 ± 1.1	0.299
Blastocyst formation rate (%)	49.2 ± 1.4[a]	50.8 ± 1.4[a]	55.5 ± 1.4[b]	**< 0.001**
Implantation rate (%)	23.6 ± 0.4[a]	24.5 ± 0.4a	27.1 ± 0.5b	**< 0.001**
Pregnancy rate (%)	30.9 ± 4.4 (233/753)	35.9 ± 4.9 (314/874)	36.9 (311/843)	0.538
Miscarriage rate (%)	16.3 ± 3.45 (38/233)	16.2 ± 4.1 (51/314)	16.7 ± 3.9 (52/311)	0.457
Livebirth (%)	27.2 ± 2.1 (205/753)	30.2 ± 2.1 (264/874)	32.1 ± 2.2 (271/843)	0.345

FERTGROUP | FER



FERTGROUP | FERTILITY



MODERN TRENDS

Edward E. Wallach, M.D.
Associate Editor

A new era in ovulation induction

Hananel Holzer, M.D.,[a] *Robert Casper, M.D.,*[b] *and Togas Tulandi, M.D., M.H.C.M.*[a]

[a] Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec; and [b] University of Toronto, Toronto, Ontario, Canada

Letrozole / Anastrazole Inibe a conversão de andrógenos em estrógenos

TT – E2

Androstenediona – estrona

OBS: (off label)

Papanikolaou *et al. Reproductive Biology and Endocrinology* 2011, **9**:85
http://www.rbej.com/content/9/1/85

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

REVIEW Open Access

Aromatase inhibitors in stimulated IVF cycles

Evangelos G Papanikolaou[1*], Nikolaos P Polyzos[2], Peter Humaidan[3], George Pados[4], Ernesto Bosch[5], Herman Tournaye[2] and Basil Tarlatzis[4]

Table 1 Available randomized trials regarding the use of letrozole during the follicular phase in IVF/ICSI cycles

	Pituitary downregulation protocol/groups	Ovarian stimulation	Patients (N)	Clinical pregnancy rate (%)	Implantation rate (%)	Fertilization rate (%)	No oocytes (mean)	Total FSH dose (mean)
Normoresponders								
Verpoest 2006 [9]	Antagonist	rFSH +letrozole	10	50	31.25	63.3	13.8	1575
	Antagonist	rFSH	10	20	12.5	77.4	9.6	1650
Poor responders								
Goswami 2004 [10]	-	rFSH +letrozole	13	23	NA	NA	1.6	150
	Agonist	rFSH	25	24	NA	NA	2.1	2865
Garcia-Velasco 2005 [4]	Antagonist	rFSH+ HMG + letrozole	71	22.4	25	68.2	6.1	3627
	Antagonist	rFSH+ HMG	76	15.2	9.4	63.3	4.3	3804
Ozmen 2009 [11]	Antagonist	rFSH +letrozole	35	28.6	NA	92.4	4.9	2980
	Antagonist	rFSH	35	17.1	NA	97.2	4.8	3850
Davar 2010 [12]	Antagonist	rFSH/HMG + letrozole	45	4.4	3.8	67.3	2.8	3158
	Agonist	rFSH or HMG	49	12.3	7.7	70.7	4.4	3458

N, number; NA, not data available

~25% ~18%

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J Gynecol Obstet Hum Reprod 50 (2021) 102139

Contents lists available at ScienceDirect

Journal of Gynecology Obstetrics and Human Reproduction

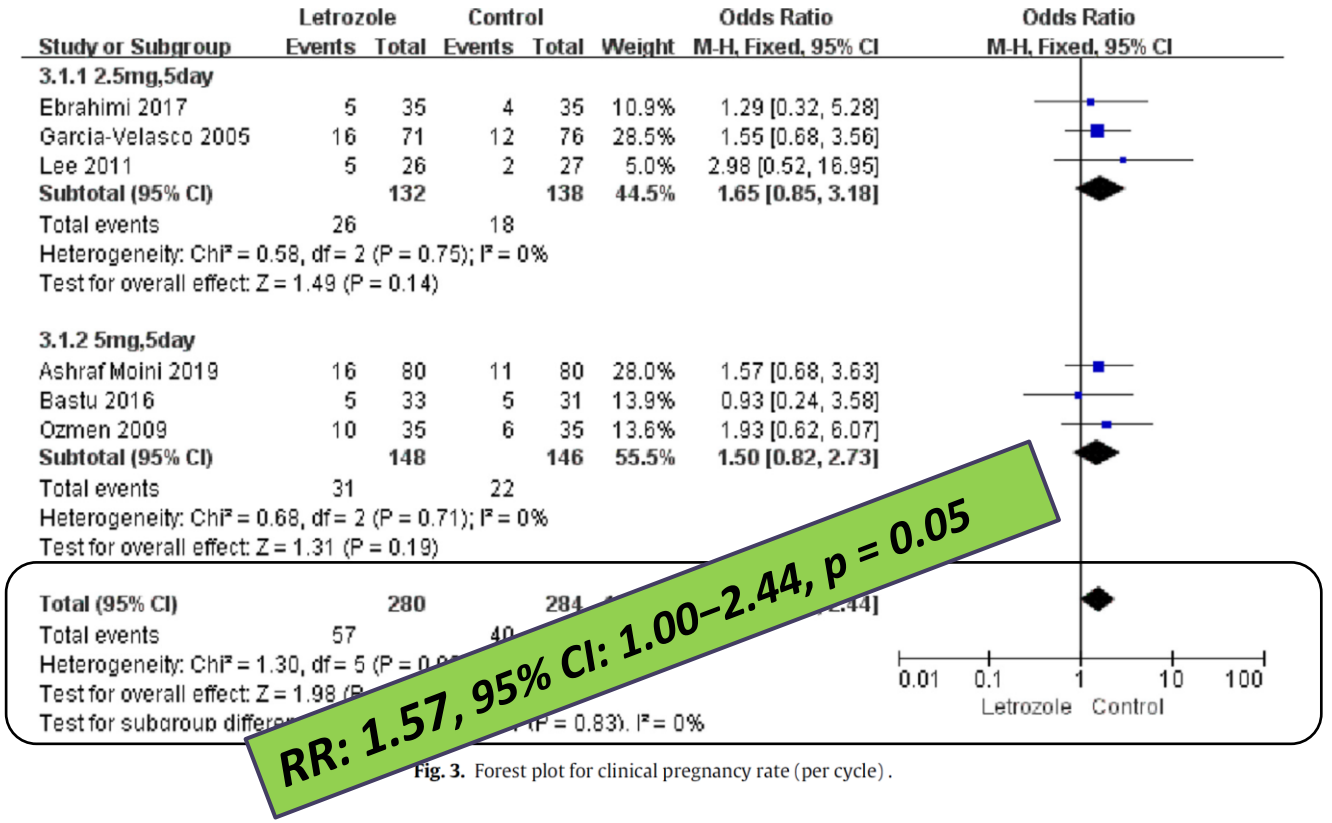
journal homepage: www.elsevier.com

Review

Effects of using letrozole in combination with the GnRH antagonist protocol for patients with poor ovarian response: A meta-analysis

Ying Qin

Reproductive Medicine Center, Guangzhou Women and Children's Medical Center, No. 9 Jinsui Road, Guangzhou, Guangdong, 510120, China



RR: 1.57, 95% CI: 1.00–2.44, p = 0.05

Fig. 3. Forest plot for clinical pregnancy rate (per cycle) .

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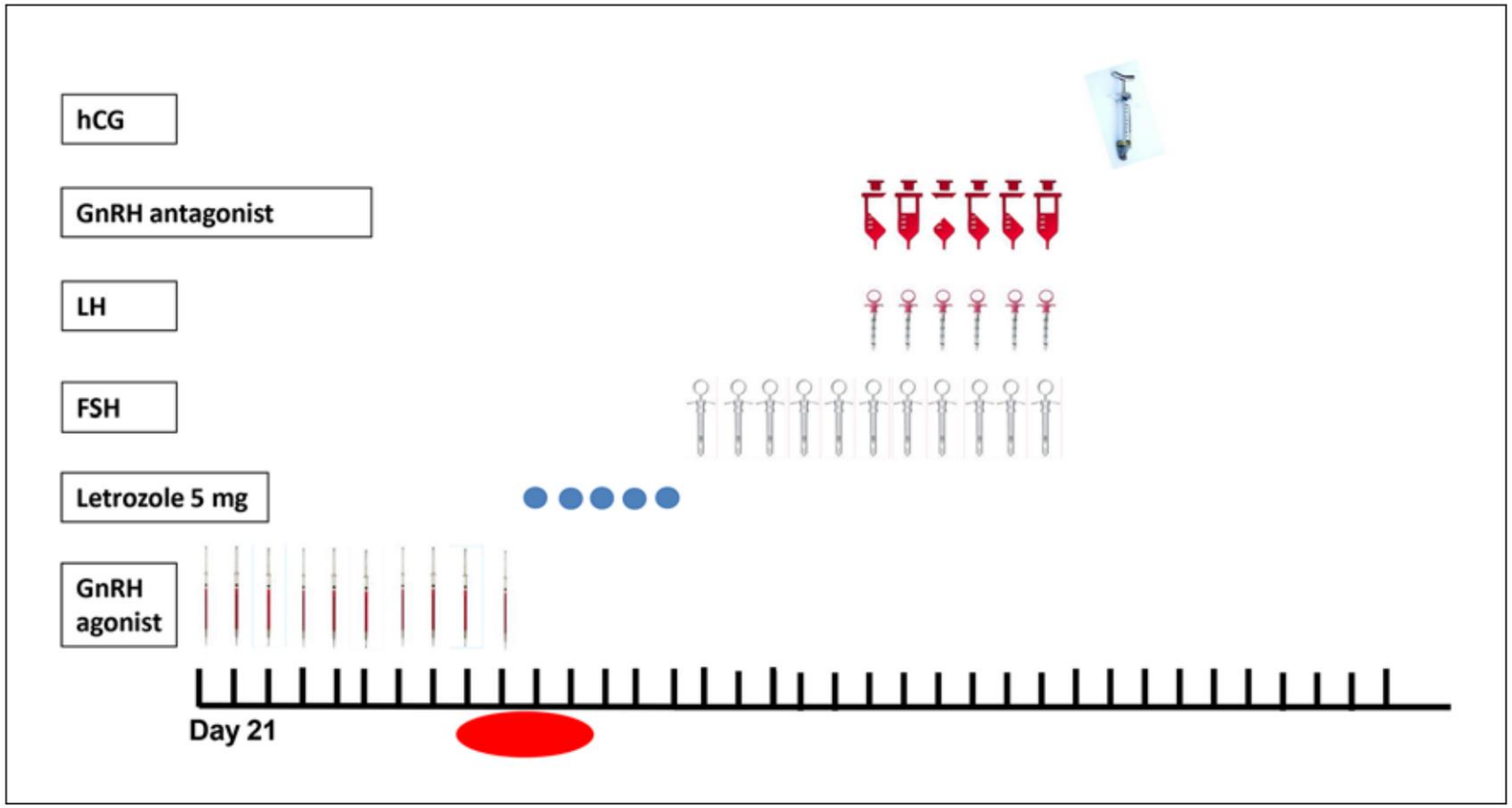
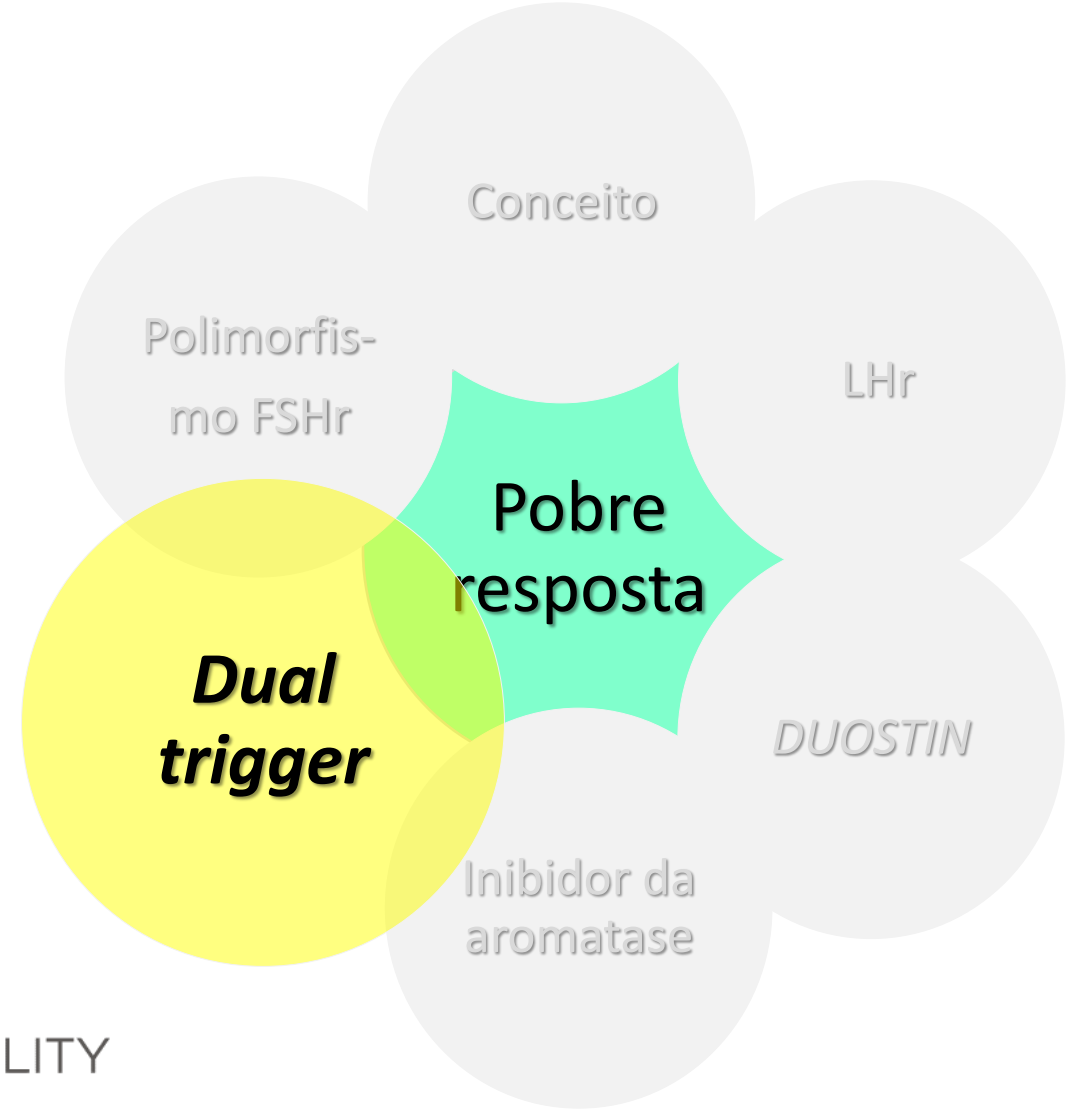
A Novel Stimulation Protocol for Poor-Responder Patients: Combining the Stop GnRH-ag Protocol with Letrozole Priming and Multiple-Dose GnRH-ant: A Proof of Concept

Raoul Orvieto[a, b] Ravit Nahum[a] Adva Aizer[a] Jigal Haas[a]
Michal Kirshenbaum[a]



Gynecol Obstet Invest 2021;86:149–154
DOI: 10.1159/000513669



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Dual trigger: *pobre resposta*

Article REPRODUCTIVE BIOMEDICINE ONLINE 35 (2017) 701–707

Dual trigger of final oocyte maturation in poor ovarian responders undergoing IVF/ICSI cycles

*Jie Zhang [1], Yun Wang [1], Xiaoyan Mao [1], Qiuju Chen, Qingqing Hong, Renfei Cai, Shaozhen Zhang, Yanping Kuang **

- 1350 patients undergoing 1389 ICSI cycles. Poor responders: Bologna criteria
- Patients triggered with 5000 IU hCG alone (328 cycles) were compared with those undergoing dual triggering with 5000 IU hCG + 0.1 mg gonadotrophin-releasing hormone agonist (GnRHa) (386 cycles).
- And patients triggered with 10,000 IU hCG (363 cycles) were compared with those undergoing dual triggering with 10,000 IU hCG plus 0.1 mg GnRHa (312 cycles)

Dual trigger: *pobre resposta*

Table 2 – Cycle outcomes and endocrine profiles of each group.

	Group A: 5000 IU HCG (n = 328)	Group B: 0.1 mg GnRHa + 5000 IU HCG (n = 386)	Group C: 10,000 IU HCG (n = 363)	Group D: 0.1 mg GnRHa + 10,000 IU HCG (n = 31[illegible])	P-value[d]	P-value[e]
No. of oocytes retrieved[b]	2 (0–9)	3 (0–11)	2 (0–[illegible])		<0.001	<0.001
No. of mature oocytes[b]	2 (0–8)	3 (0–10)			<0.001	<0.001
No. of top-quality embryos[b]	1 (0–5)	1 (0–7)		1 (0–6)	NS	NS
No. of viable embryos[b]	1 (0–[illegible])		1 (0–6)	1 (0–7)	NS	NS
ICSI rate, n (%)[c]			118 (32.5)	97 (31.1)	NS	NS
Oocyte retrieval rate, n/n (%)[c]		[illegible]/1623 (68.9)	886/1532 (57.8)	936/1372 (68.2)	<0.001	<0.001
Mature oocyte rate, n/n (%)[c]	638/784 (81.4)	990/1119 (88.5)	717/886 (80.9)	820/936 (87.6)	<0.001	<0.001

Dual trigger: Higher number of oocytes collected, number of mature oocytes (P < 0.001), oocyte retrieval rate and percentage of mature oocytes(P < 0.001).

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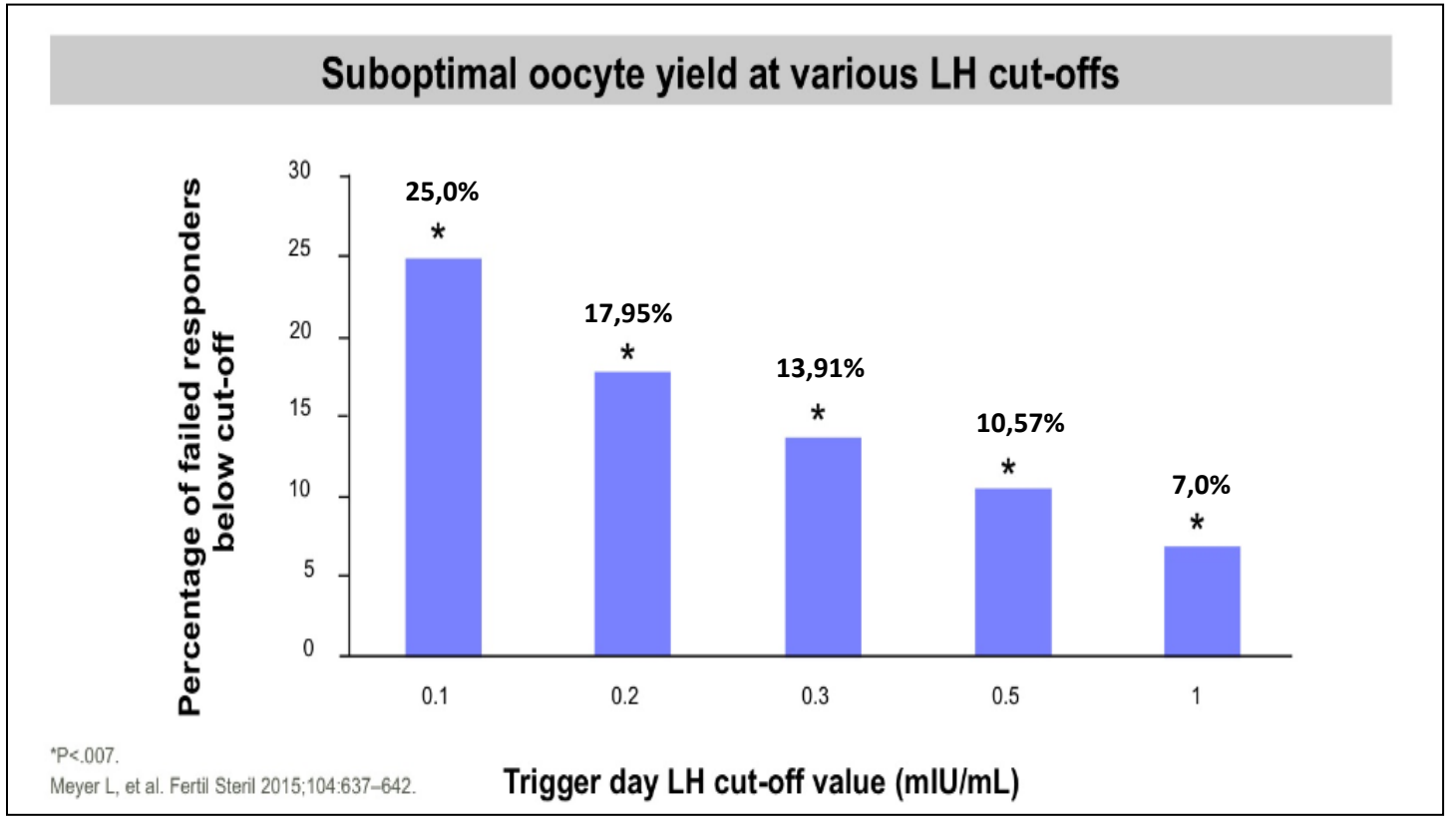
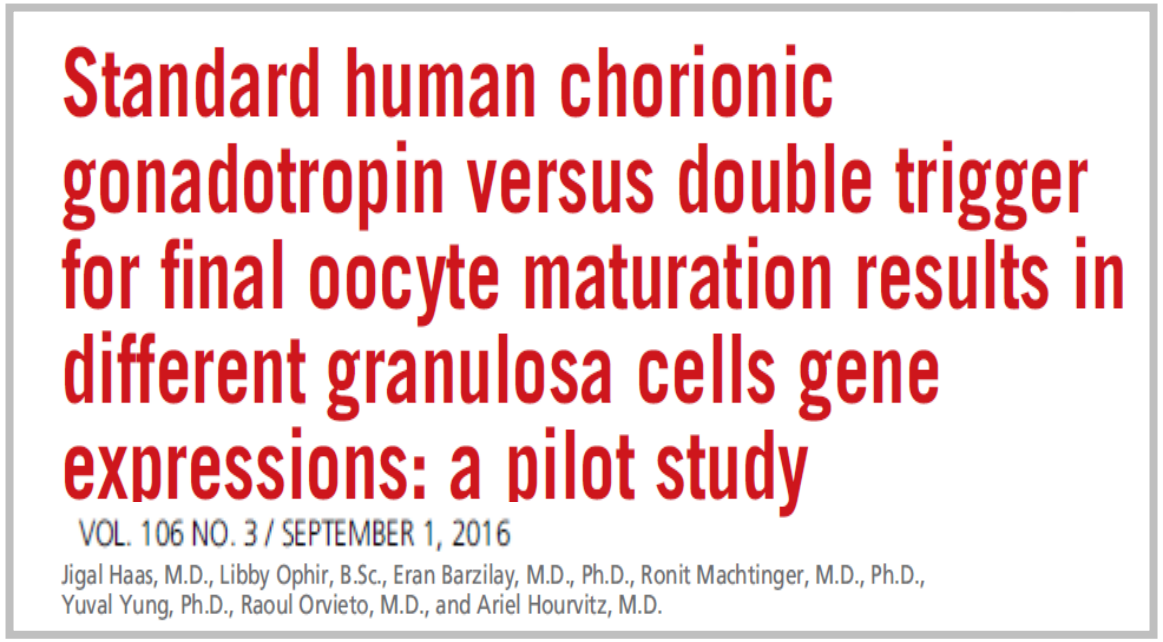
Dual trigger: *resposta inadequada*



Limiting GnRH-agonist trigger alone to patients with a trigger day LH ≥ 0.5 would have reduced the rate of suboptimal response.

Dual trigger



Standard human chorionic gonadotropin versus double trigger for final oocyte maturation results in different granulosa cells gene expressions: a pilot study

VOL. 106 NO. 3 / SEPTEMBER 1, 2016

Jigal Haas, M.D., Libby Ophir, B.Sc., Eran Barzilay, M.D., Ph.D., Ronit Machtinger, M.D., Ph.D., Yuval Yung, Ph.D., Raoul Orvieto, M.D., and Ariel Hourvitz, M.D.

Conclusion(s):

The messenger RNA (mRNA) expression of reproduction-related genes in granulosa cells (GCs) from patients receiving the double trigger may explain and ***suggested improved oocyte and embryo quality related to the double triggering group.***

CLINICAL ARTICLE

Comparative study between single versus dual trigger for poor responders in GnRH-antagonist ICSI cycles: A randomized controlled study

Ahmed M. Maged[1,*], Mohamed A. Ragab[1], Amal Shohayeb[1], Waleed Saber[1], Sherif Ekladious[2], Eman A. Hussein[1], Akmal El-Mazny[1], Ayman Hany[1]

[1] Obstetrics and Gynecology Department, Kasr Alainy Hospital Cairo University, Cairo, Egypt

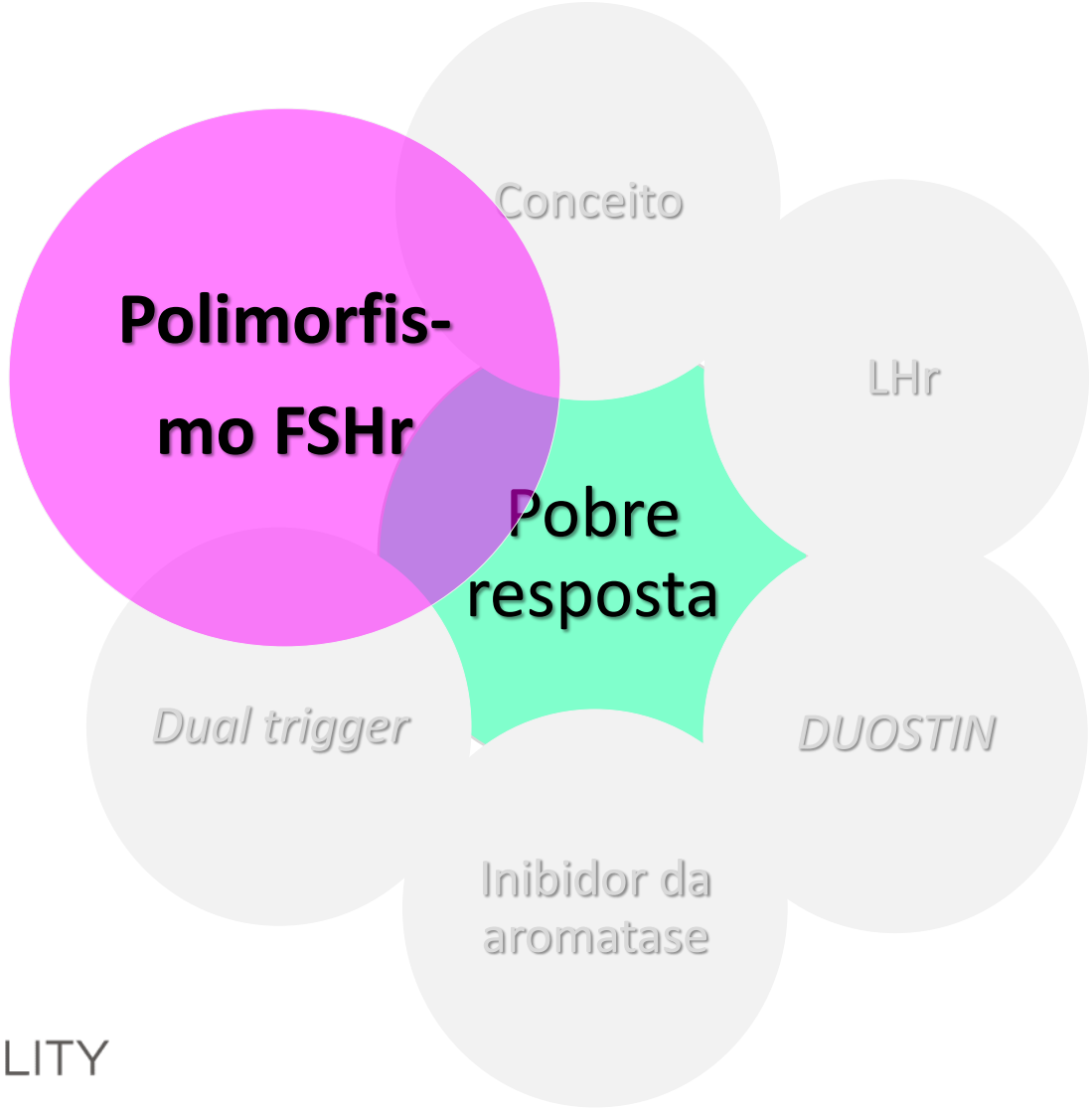
[2] Clinical Pathology Department, Kasr Alainy Hospital Cairo University, Cairo, Egypt

Randomized Controlled Trial › Int J Gynaecol Obstet. 2021 Mar;152(3):395-400.

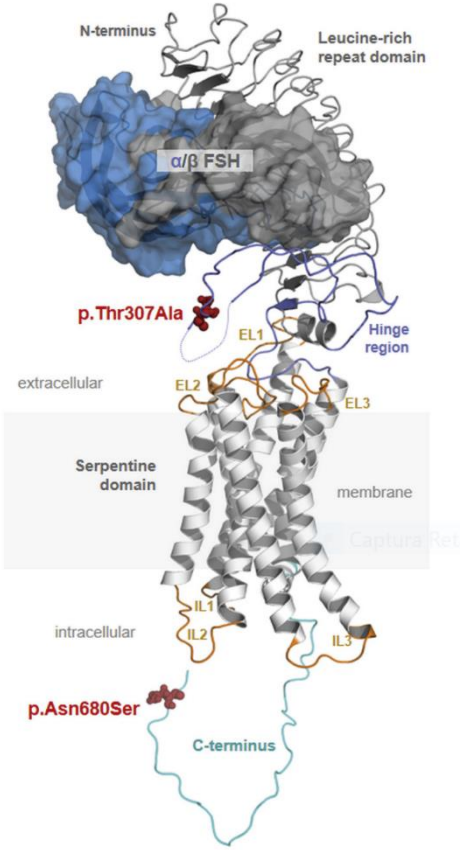
TABLE 3. Outcome parameters

	Single trigger (n=80)	Dual trigger (n=80)	*P* value
Chemical pregnancy rate	9/80 (11.3%)	20/80 (25.0%)	0.039
Clinical pregnancy rate	7/80 (8.8%)	18/80 (22.5%)	0.028
Implantation rate	7/76 (9.2%)	13/148 (8.8%)	>0.99

All results are presented as number (percentage).


Polimorfis-
mo FSHr
Pobre
resposta
Conceito
LHr
Dual trigger
DUOSTIN
Inibidor da
aromatase

Polimorfismo FSH



Human Reproduction, Vol.31, No.3 pp. 672–683, 2016
Advanced Access publication on January 14, 2016 doi:10.1093/humrep/dev342

human reproduction ORIGINAL ARTICLE *Reproductive genetics*

Combined assessment of polymorphisms in the *LHCGR* and *FSHR* genes predict chance of pregnancy after *in vitro* fertilization

I. Lindgren[1,†*], M. Bååth[1,†], K. Uvebrant[2], A. Dejmek[3], L. Kjaer[1], E. Henic[4], M. Bungum[4], L. Bungum[5], C. Cilio[2], I. Leijonhufvud[4], S. Skouby[5], C. Yding Andersen[6], and Y. Lundberg Giwercman[1]

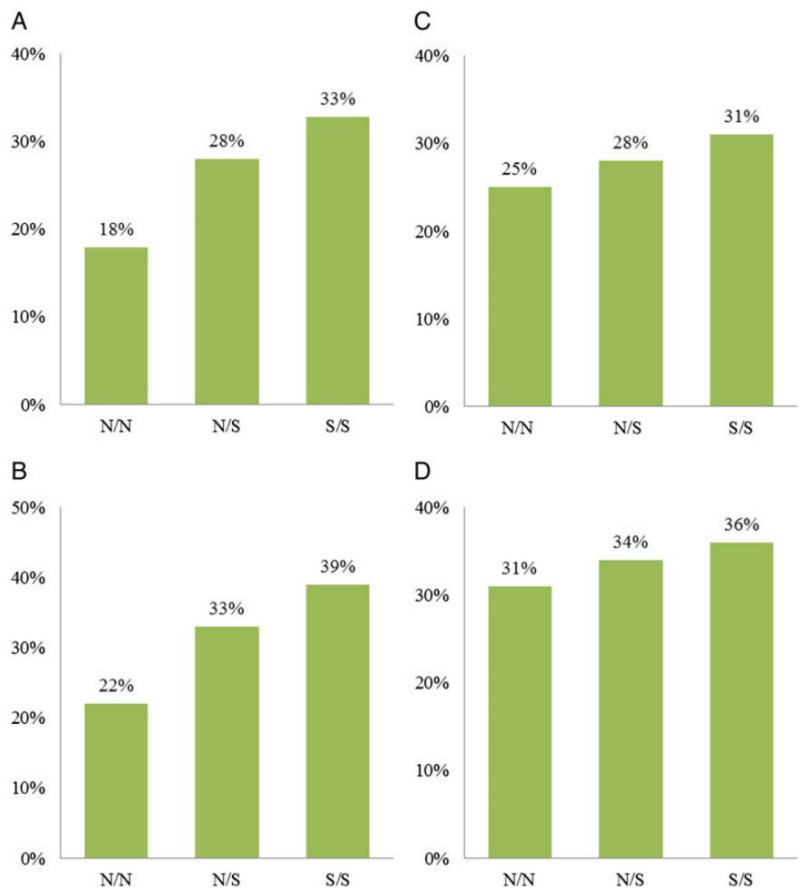


Figure 1 Pregnancy frequencies for the *LHCGR* N312S and *FSHR* N680S polymorphisms. (**A**) *LHCGR* N312S, all women in the study: N/N ($n = 67$), N/S ($n = 175$), S/S ($n = 131$); (**B**) *LHCGR* N312S, only women receiving embryo transfer: N/N ($n = 54$), N/S ($n = 147$), S/S ($n = 109$); (**C**) *FSHR* N680S, all women: N/N ($n = 102$), N/S ($n = 206$), S/S ($n = 65$); (**D**) *FSHR* N680S, embryo transfer: N/N ($n = 84$), N/S ($n = 171$), S/S ($n = 55$).

Estimulação ovariana: *pobre resposta*

E quando a resposta é muito pobre / sem resposta?

- Aumento das Gns não aumenta o recrutamento folicular
- Terapias complementares ?? – sem comprovação
- Paciente quer continuar tratamento
- Doação de ovócitos: alternativa descartada

AUMENTAR O NÚMERO DE OVÓCITOS / EMBRIÕES

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JBRA Assisted Reproduction 2022;**00**(0):00-00
doi: 10.5935/1518-0557.20220030

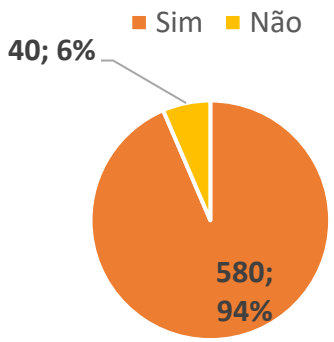
Editorial

Ethics and IVF add-ons: We need to talk about it

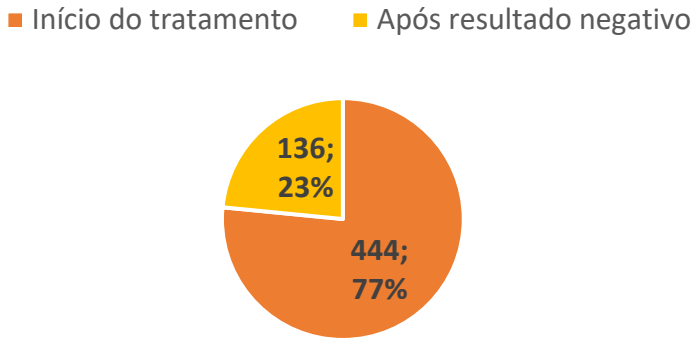
Daniela Paes de Almeida Ferreira Braga[1,2], Amanda Souza Setti[1,2], Edson Borges Jr.[1,2]

[1]Fertility Medical Group, Av. Brigadeiro Luis Antonio, 4545, São Paulo – SP, Brazil. Zip: 01401-002
[2]Sapientiae Institute – Centro de Estudos e Pesquisa em Reprodução Humana Assistida, Rua Vieira Maciel, 62, São Paulo – SP, Brazil. Zip: 04503-040

Intenção de se submeter aos add-ons (n=620)



Quando se submeteriam aos add-ons (n=580)



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JBRA Assisted Reproduction 2022;**00**(0):00-00
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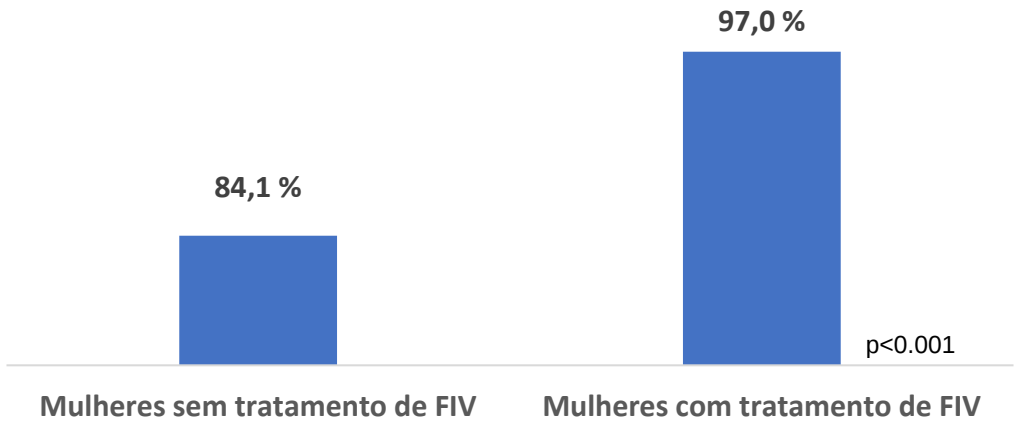
Intenção de se submeter aos add-ons



Add-ons

- São bem aceitos pela maioria das pacientes inférteis, especialmente, aquelas que já iniciaram o tratamento de fertilização *in vitro*

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JBRA Assisted Reproduction 2023;**27**(4):727-738
doi: 10.5935/1518-0557.20230047

SBRA Pages

Delphi consensus on add-ons and social midia in Assisted Reproductive Technology

Alvaro Ceschin[1], Álvaro Petracco[2], Edson Borges Jr[3,4], Emerson Barchi Cordts[5], Hitomi Miura Nakagawa[6], Maria do Carmo Borges de Souza[7], **Maria Madalena Pessoa Caldas**[8], Newton Eduardo Busso[9], Paulo Gallo de Sá[10], Pedro Augusto Araújo Monteleone[11], Rui Alberto Ferriani[12]

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OXFORD human reproduction

Human Reproduction, 2023, **38(8)**, 1590–1600
https://doi.org/10.1093/humrep/dead121
Advance Access Publication Date: June 20, 2023
Meta-Analysis

Reproductive epidemiology

How common is natural conception in women who have had a livebirth via assisted reproductive technology? Systematic review and meta-analysis

Annette Thwaites, Jennifer Hall, Geraldine Barrett, and Judith Stephenson *
Sexual and Reproductive Health, Institute of Women's Health, University College London, London, UK

- Eleven studies including 5.180 women were selected for this review
- The pooled estimate for the proportion of women having natural conception pregnancies after ART livebirth *was 0.20 (95% CI, 0.17–0.22*).

OXFORD human reproduction

Human Reproduction, 2023, **38(8)**, 1590–1600
https://doi.org/10.1093/humrep/dead121
Advance Access Publication Date: June 20, 2023
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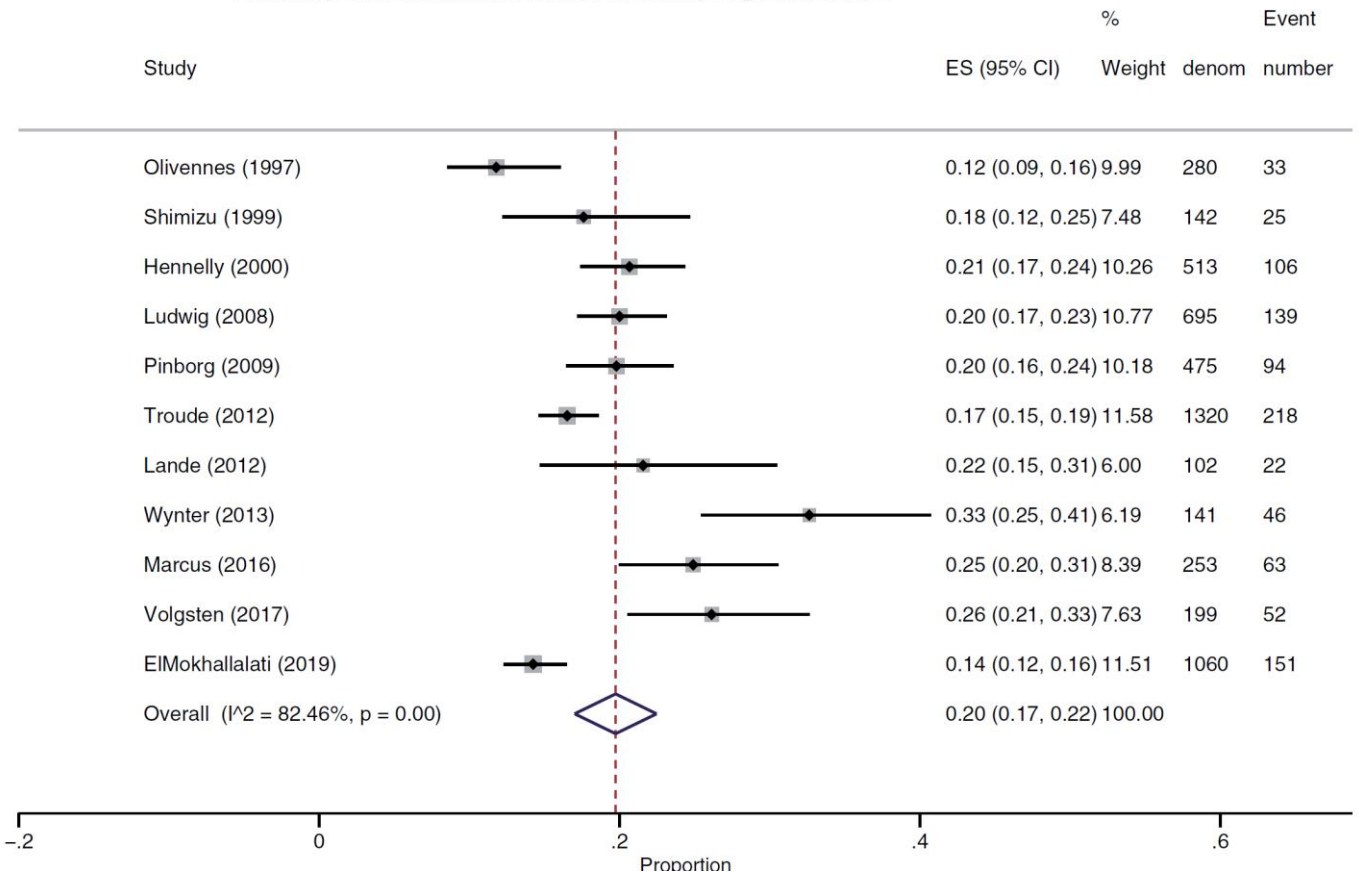
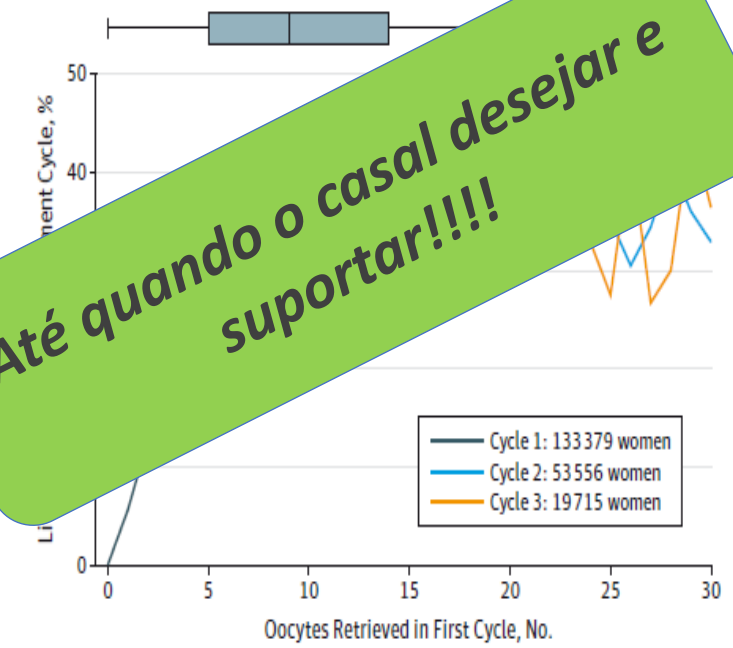


Até quando tratar?

Figure 4. Live-Birth Rate Within Each Single In Vitro Fertilization Treatment Cycle by Oocyte Retrieval in First Cycle



The live-birth rate within each individual first, second, and third treatment cycle (ie, for each curve, the rate on the y-axis is the rate for just that 1 treatment cycle) according to the number of oocytes retrieved in the first treatment cycle. Analyses are for 134 903 women younger than 40 years using their own oocytes. Box and whiskers indicate the central 95% of the distribution of oocytes retrieved in the first cycle, as well as the median and lower and upper quartiles.

Até quando o casal desejar e suportar!!!!

Figure 2. Cum

JAMA. 2015;314(24

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Obrigado!

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