



Estimulação ovariana na mulher com pobre resposta

Edson Borges Jr.



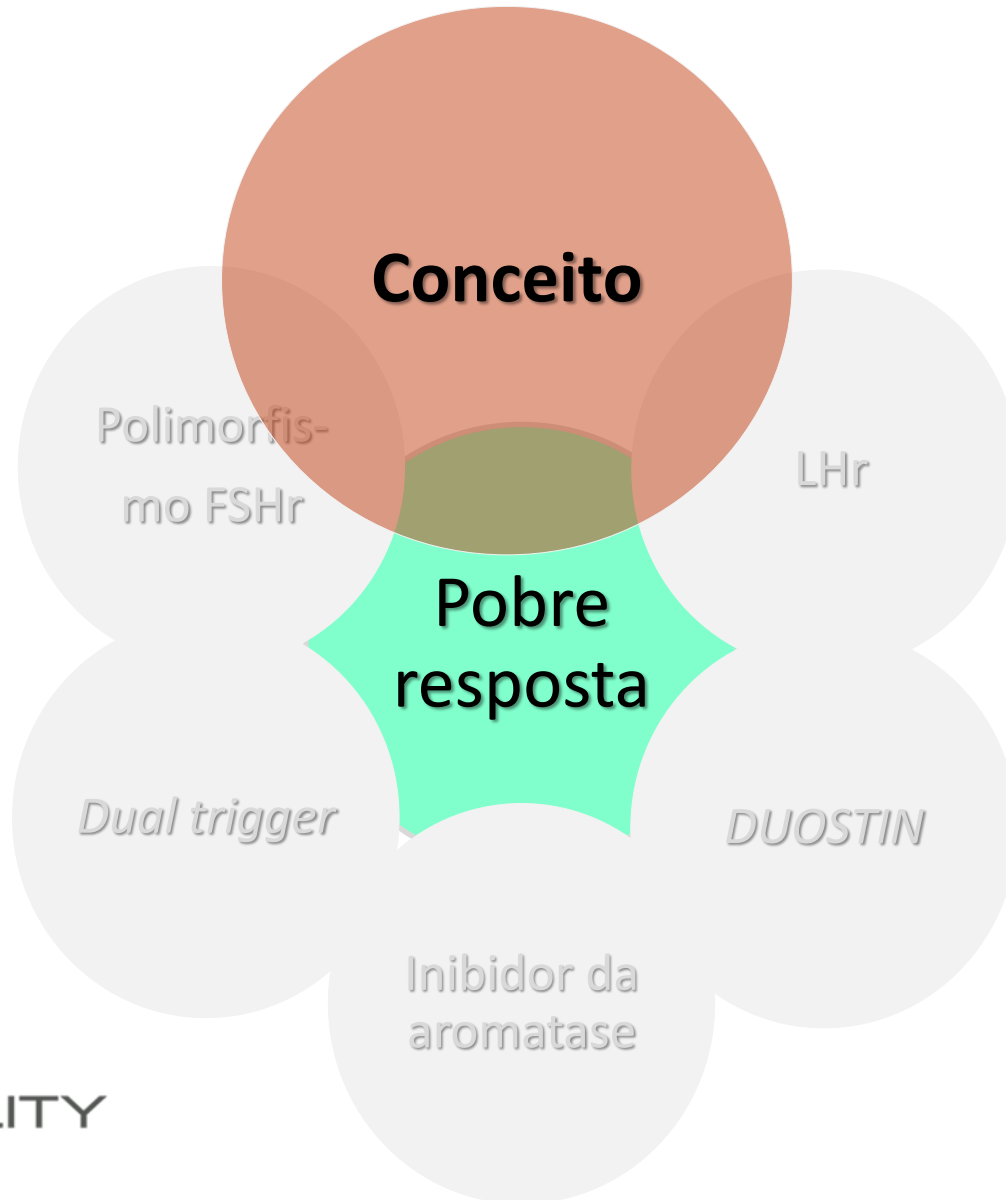
Declaro:

**Ausência de Conflito de
Interesse**

**Resolução do Conselho Federal de
Medicina nº 1.595/2.000**

AGENDA

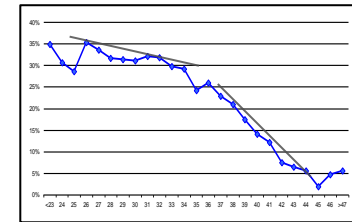
- ➔ Conceito
- ➔ Uso de LHr
- ➔ DUOSTIN – dupla estimulação
- ➔ Uso de inibidor da aromatase
- ➔ Dual trigger
- ➔ Polimorfismo FSHr



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***

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, *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

Age

Previous trials

AFC

FSH

Follicles, n

Oocytes retrieved, n

E2

Good quality embryos

FSH consumption

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 Marca², B.C.J.M. Fauser³, B. Tarlatzis⁴,
G. Nargund⁵, and L. Gianaroli¹ on behalf of the ESHRE working group
on Poor Ovarian Response Definition[‡]

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

Dois de três critérios:

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



FERTILITY

Estimulação ovariana: *pobre resposta*

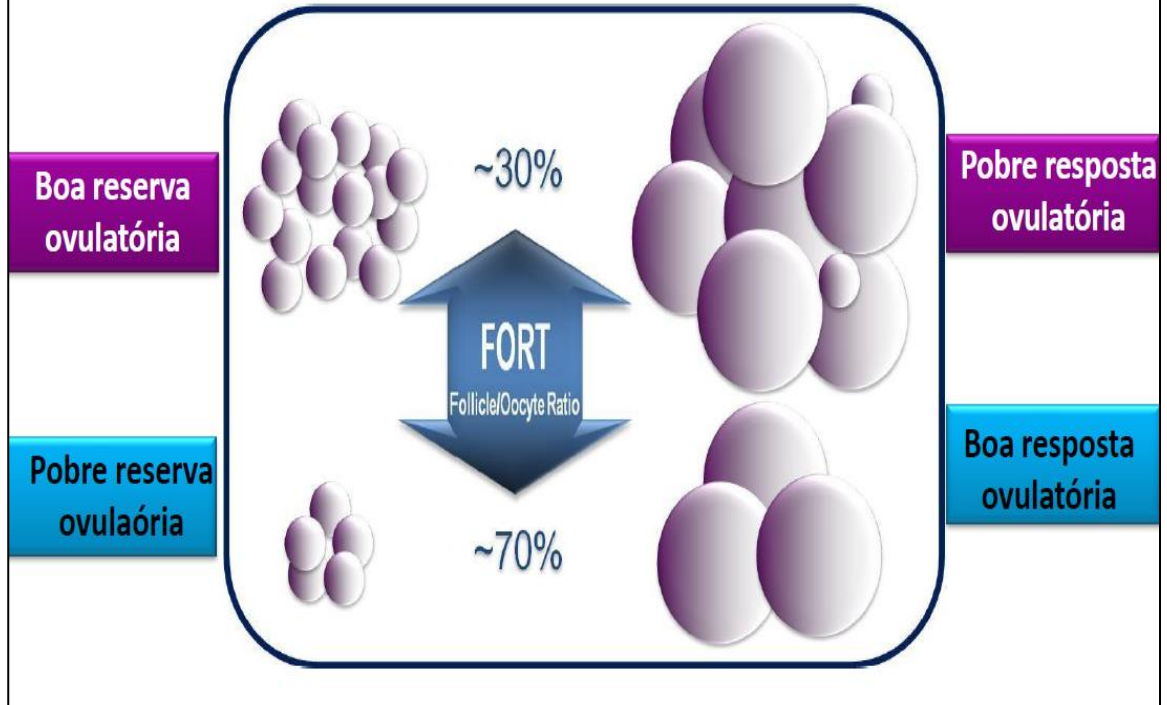
Human Reproduction, Vol.27, No.4 pp. 1064-1072, 2012
Advanced Access publication on January 24, 2012. doi:10.1093/humrep/der479

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^{1,2,3,6}

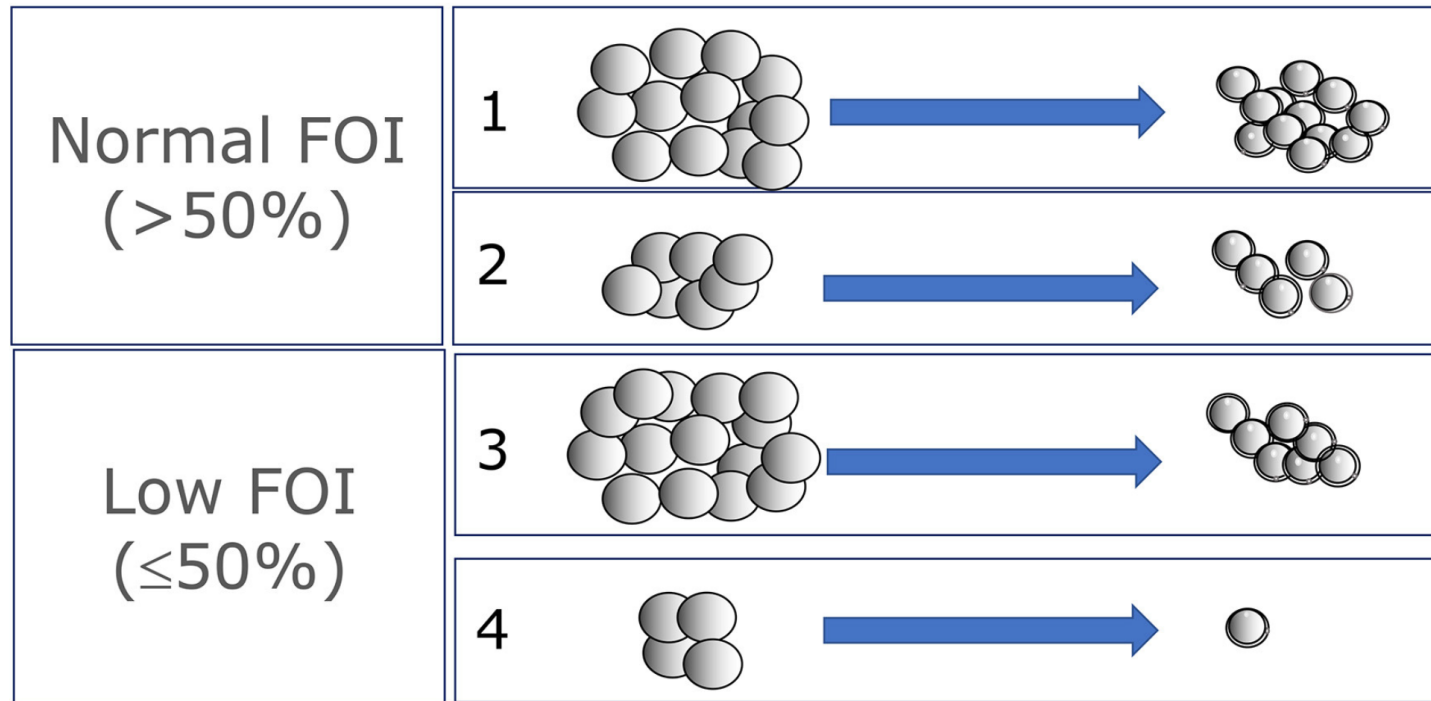
“Follicle output ratio”
“Taxa de produção folicular”



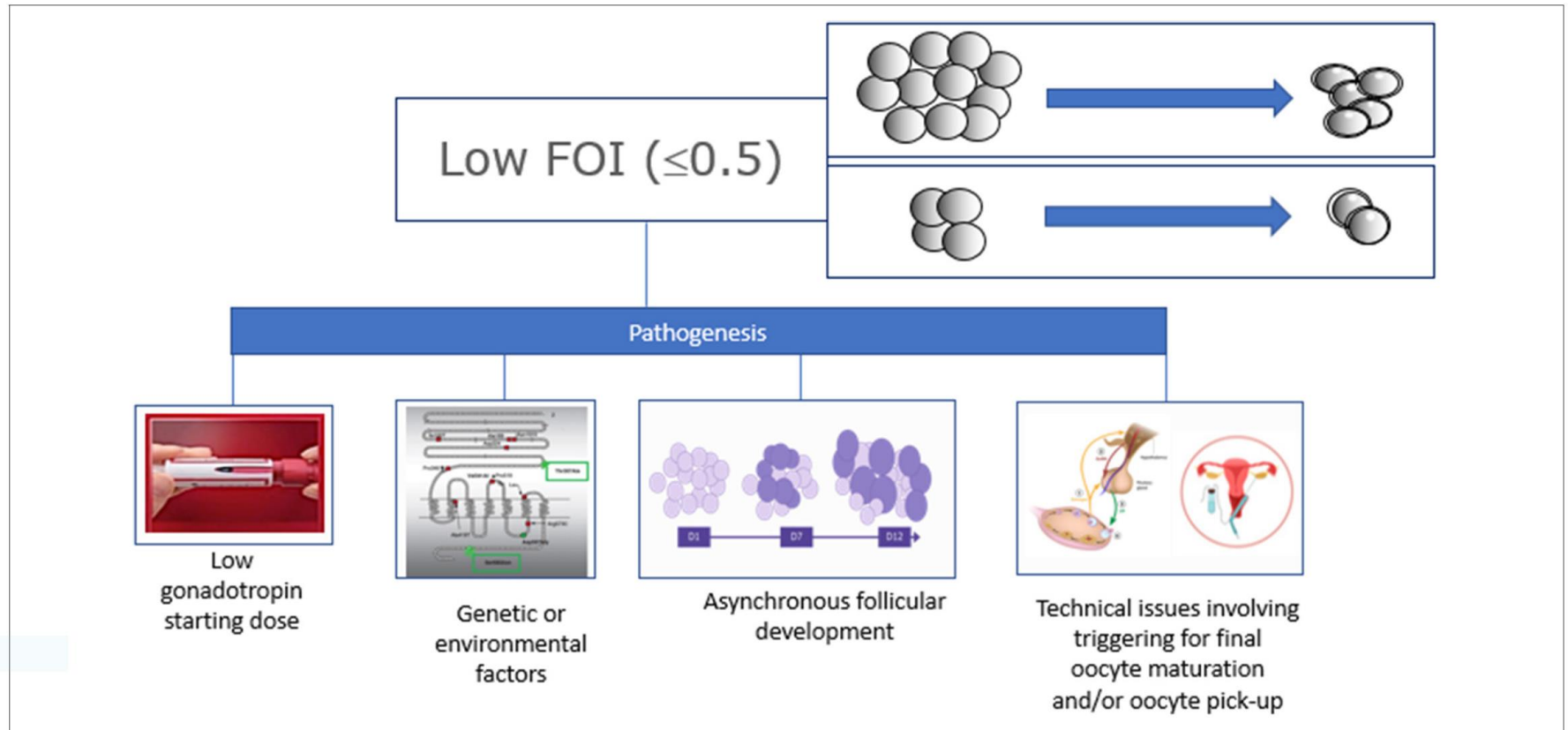
$$\text{FORT} = \frac{\text{número de folículos 16-22 mm X 100}}{\text{número de folículos 3-8 mm}}$$

Estimulação ovariana: *pobre resposta*

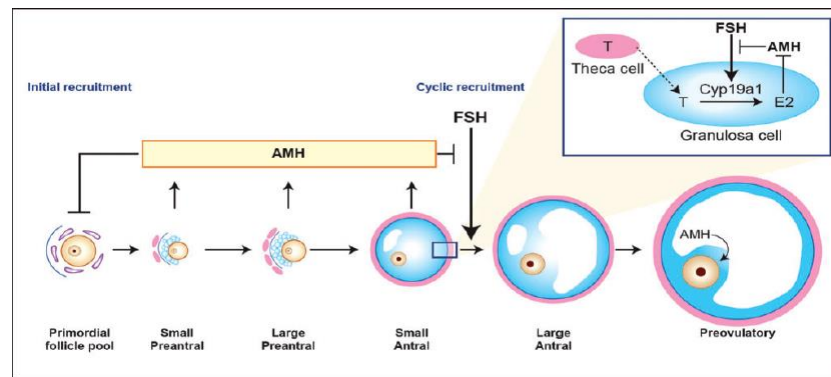
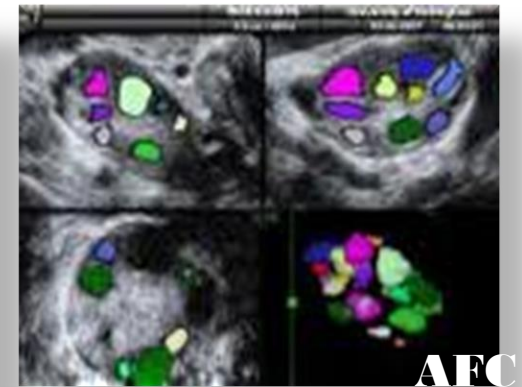
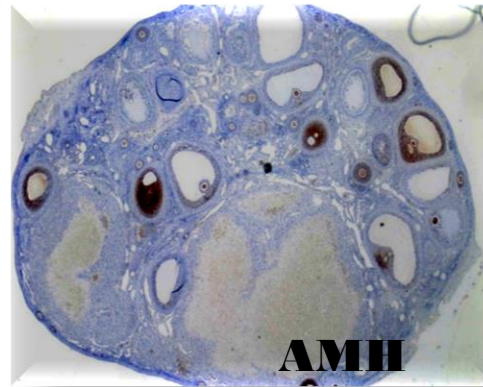
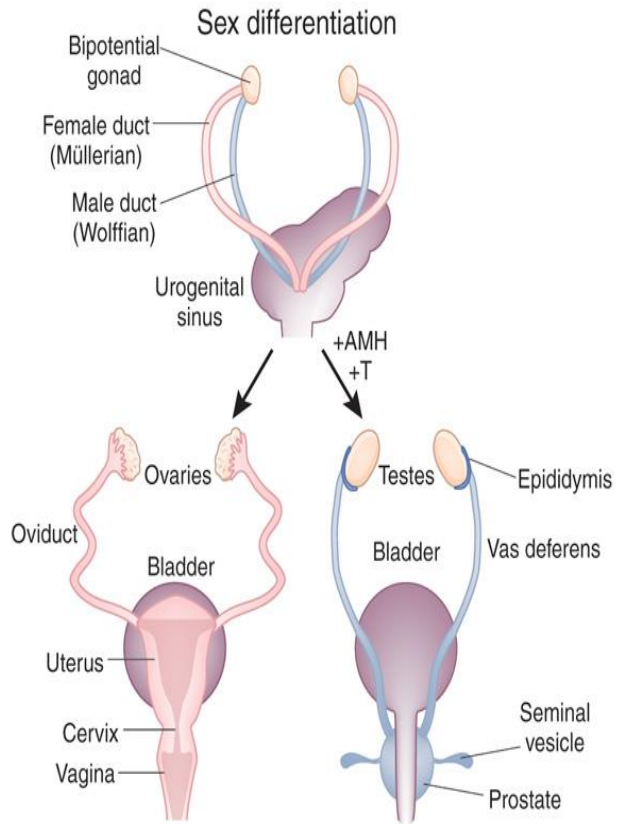
Follicle-to-Oocyte Index (FOI)* = Oocyte Number/Antral Follicle Countx100



Estimulação ovariana: *pobre resposta*

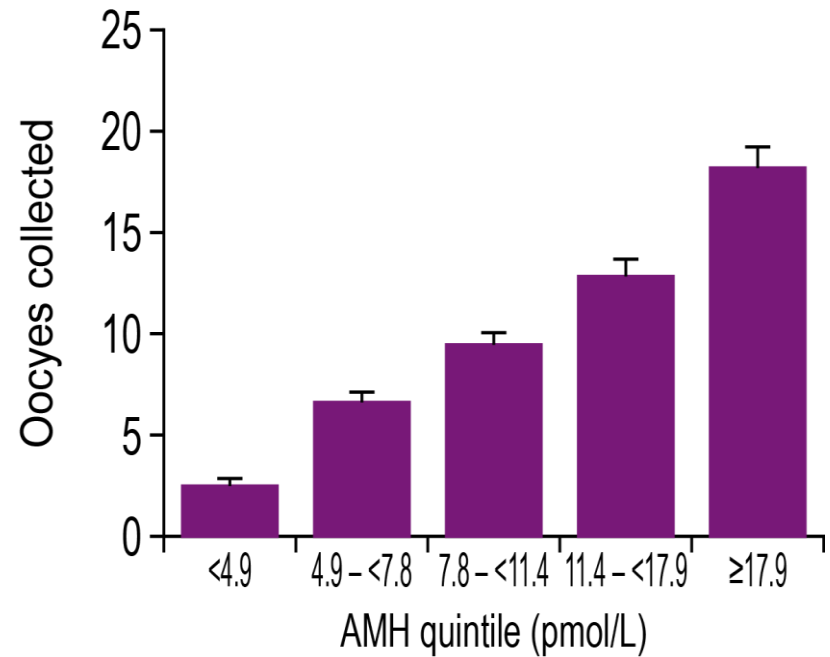
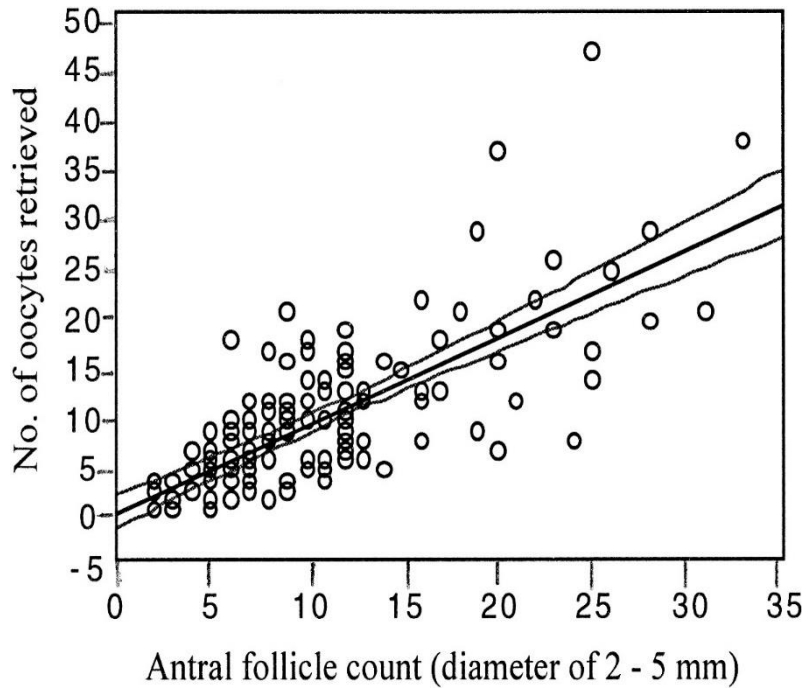


AMH and AFC: Best predictors of ovarian response



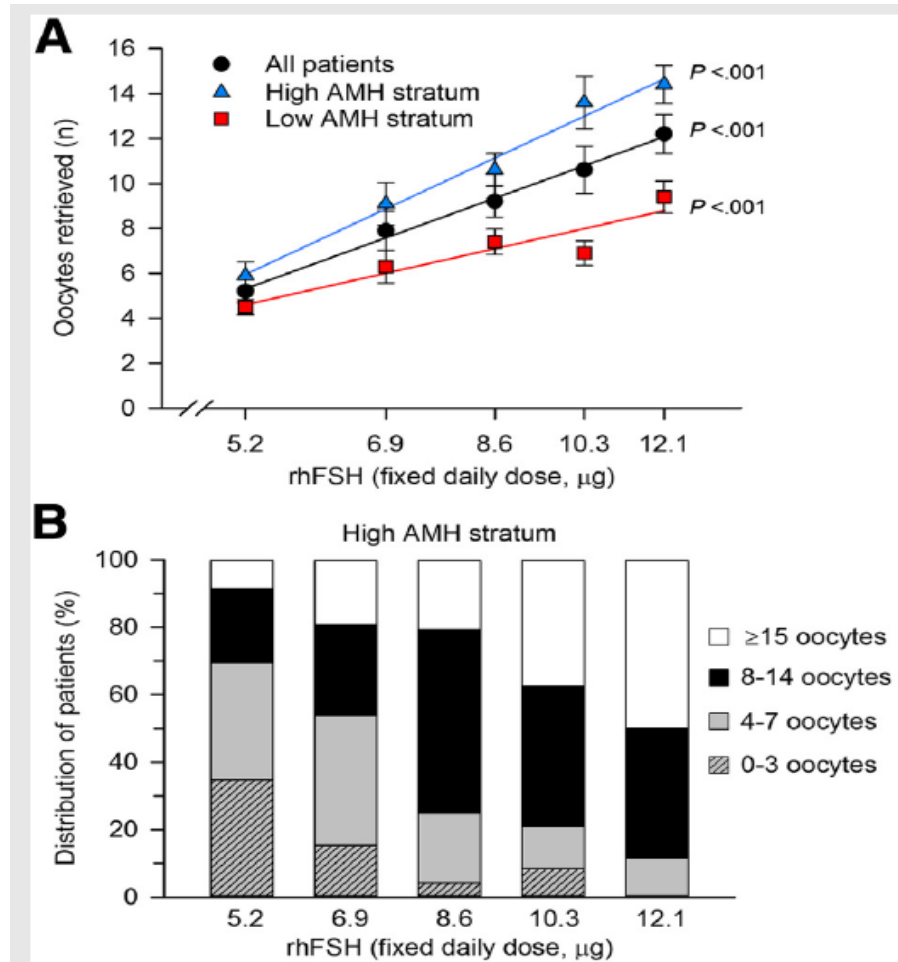
Katie Vicari

Both predict oocyte yield



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

AMH predict oocyte yield according rFSH dose



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

Estimulação ovariana: *pobre resposta*

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 \geq 5; AMH \geq 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 \geq 35 years with adequate ovarian reserve parameters (AFC \geq 5; AMH \geq 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 (\geq 35 years) with poor ovarian reserve pre-stimulation parameters

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



Estimulação ovariana: *pobre resposta*

Baixa reserva ovariana ≠ Hipo-sensibilidade

Má-respondedora (ESHRE, Bologna)

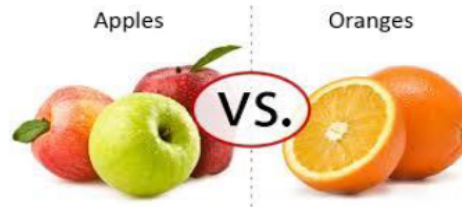
Dois de três critérios:

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

Hipo-respondedora

- Mulheres jovens, normogonadotróficas, com reserva ovariana adequada que apresentam resposta sub-ótima ou inesperada má resposta ao FSH exógeno.
- Mesmo apresentando resposta ovariana normal (p.ex., >5 oócitos) há necessidade de aumento na dose cumulativa de FSH (p.ex. $>2500-3000$ IU) e na duração do estímulo (hipossensibilidade ao FSH)

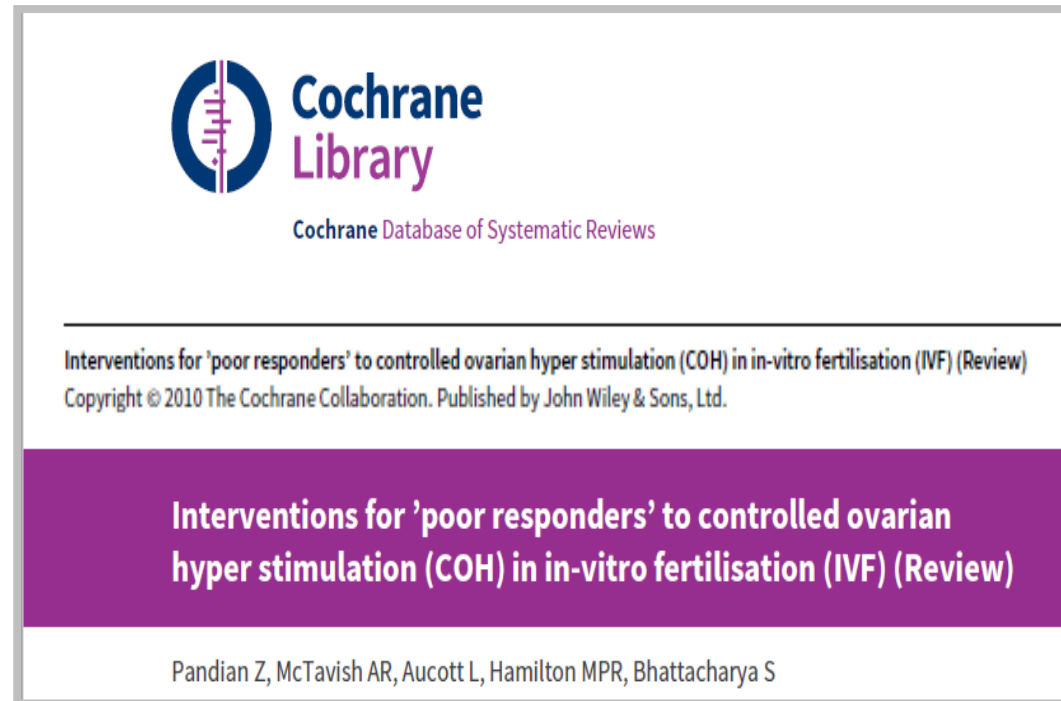
Ferraretti et al. Hum Reprod; 2011.



De Placido, et al. Hum Reprod 2001; Clin Endocrinol 2004; Hum Reprod 2005; Drugs 2008.
Ferraretti, et al. Fertil Steril 2004. Kailasam, et al. Hum Reprod 2004.
Alviggí, et al. RBMOnline 2006; RBMOnline 2009; Reprod Biol Endocrinol 2009; 2011.
Devroey, et al. Hum Reprod Update 2009 (EVAR) Workshop Group 2008.

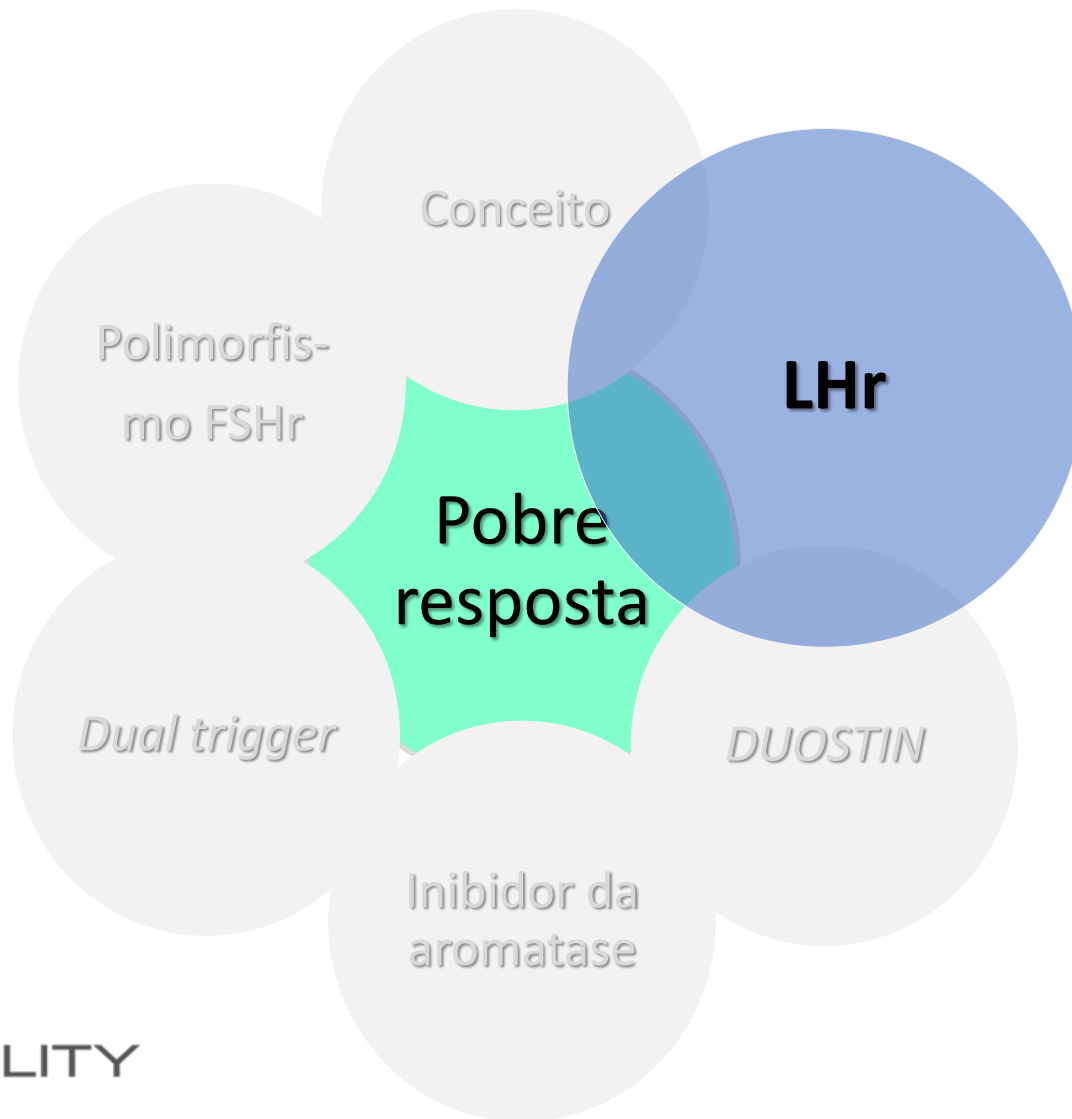


Estimulação ovariana: *pobre resposta*



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

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



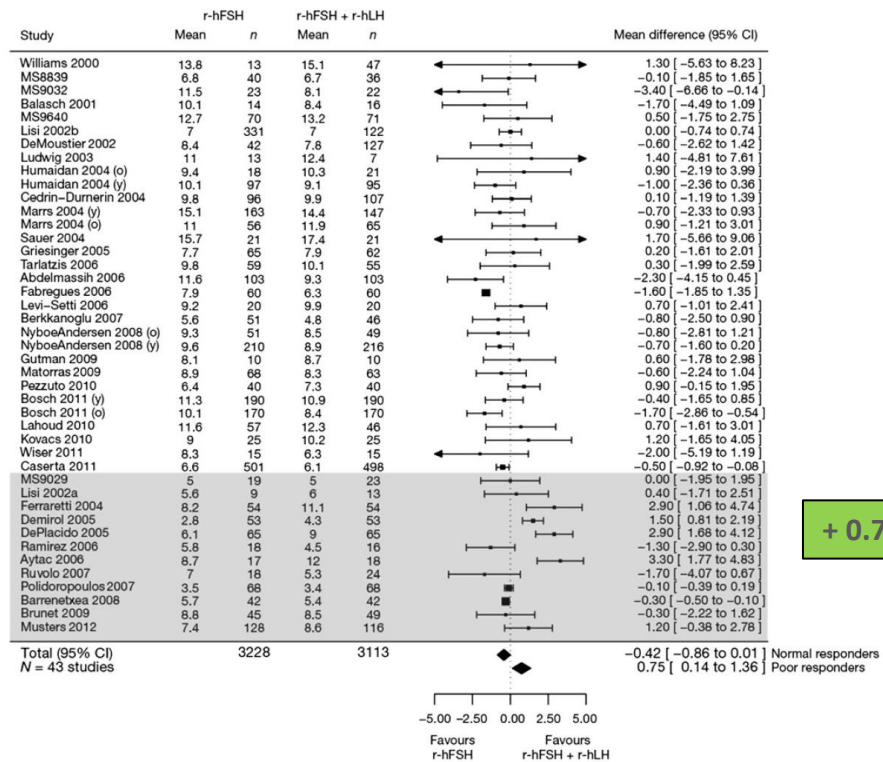
RESEARCH

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

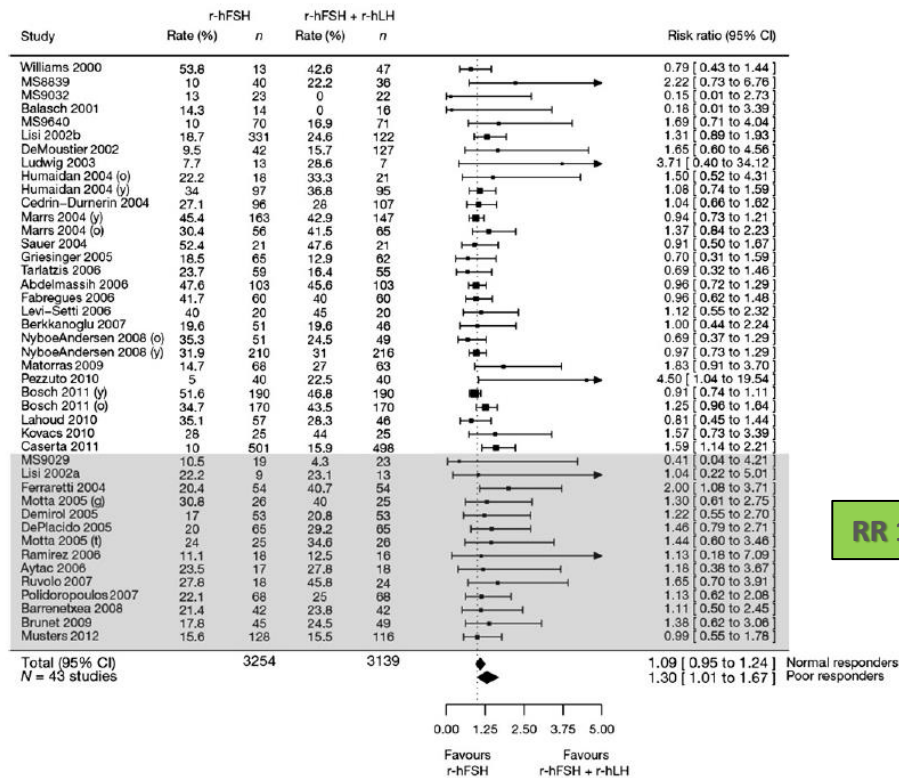
Philippe Lehert^{1,2*}, Efstratios M Kolibianakis³, Christos A Venetis³, Joan Schertz⁴, Helen Saunders^{5,6}, Pablo Arriagada^{5,6}, Samuel Copt^{5,7} and Basil Tarlatzis³

- 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



+ 0.75 ovocitos; IC 95% 0.14-1.36

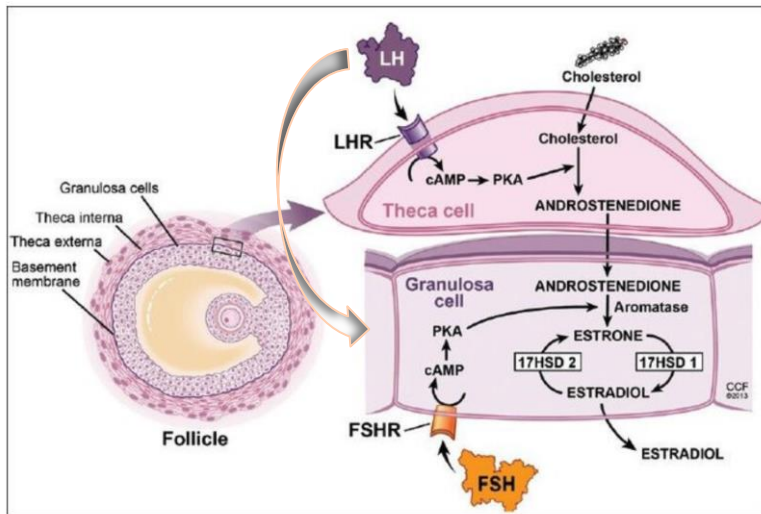
Figure 2 Forest plot of the number of oocytes retrieved in normal versus poor responders (intention-to-treat population). Studies are listed by first author's last name followed by the year of publication. Some studies were divided by subgroup designations: y, young/normal or o, advanced maternal age. 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.



RR 1.30; IC 95% 1.01–1.67

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.

LH receptors

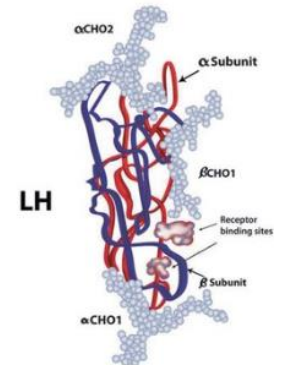


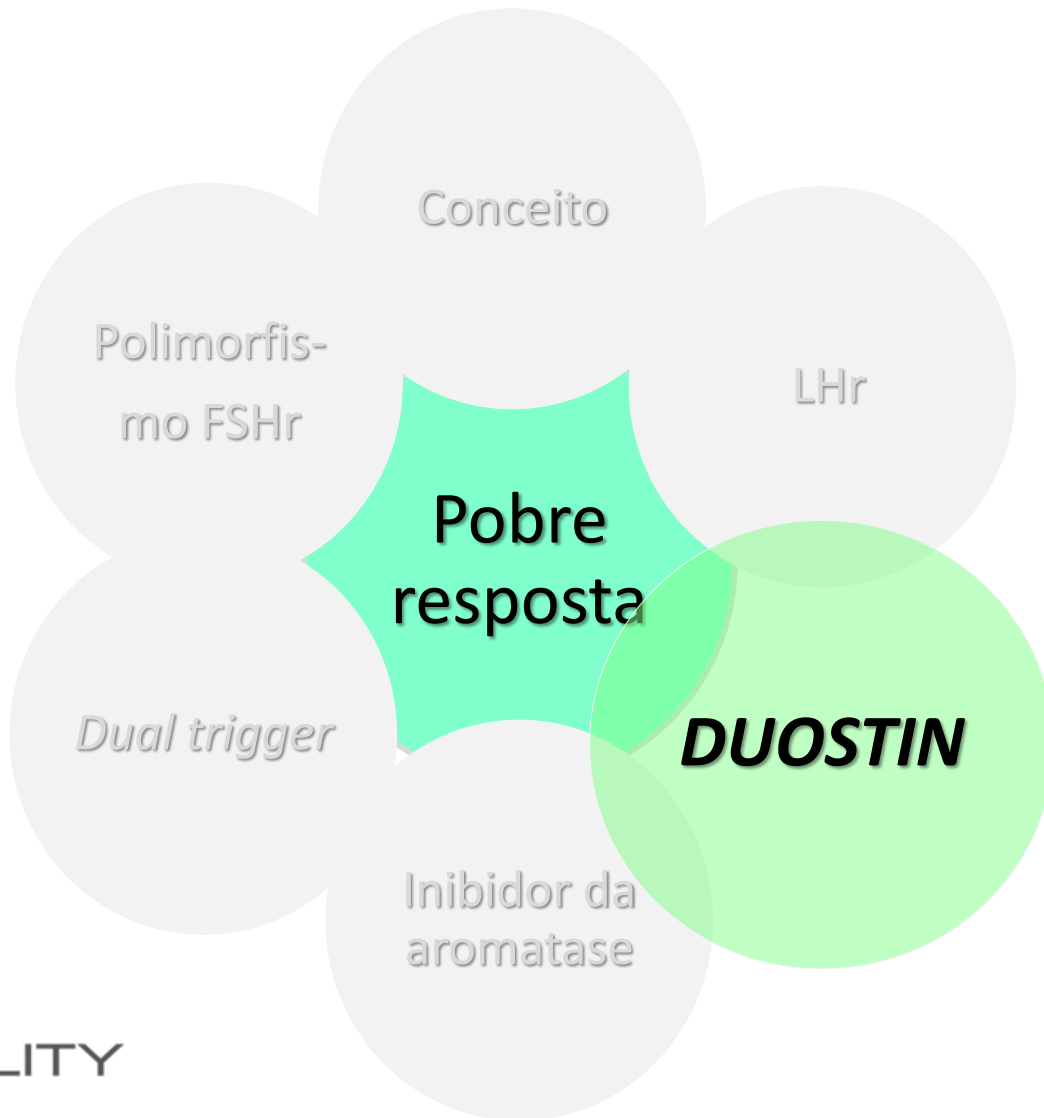
LH receptors are also expressed on GCs, especially after follicular selection, and their expression is 10 times higher in the GCs of preovulatory follicles than in antral follicles 3–10mm in diameter.

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

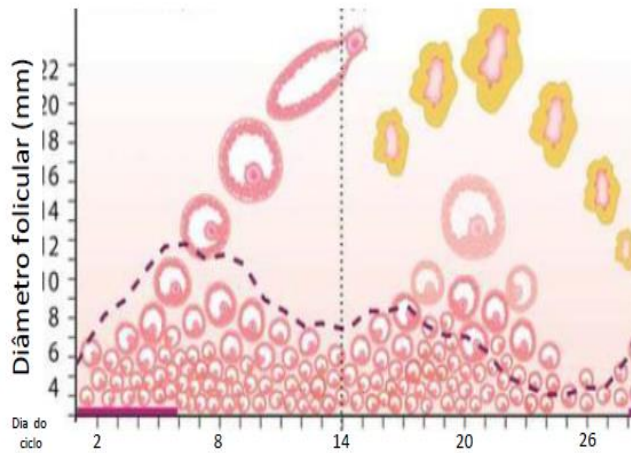
- The ovarian responses are affected by the timing of administration more than the total-dose of rLH;
- The optimal window to administer rLH appears to be the mid-to-late follicular phase,
- LH supplementation at GnRH-ant administration compensates for the severe drop in levels of endogenous LH due to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



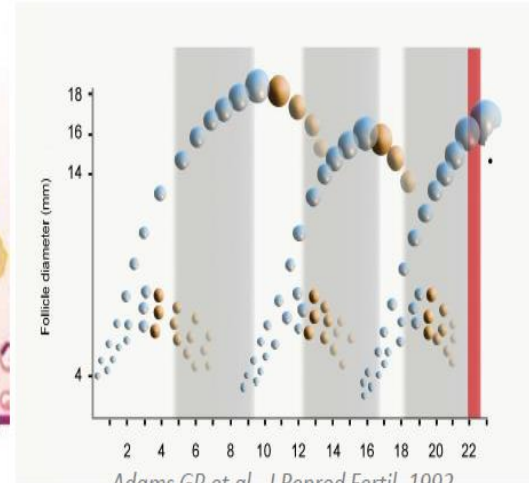


Estimulação ovariana: *pobre resposta*

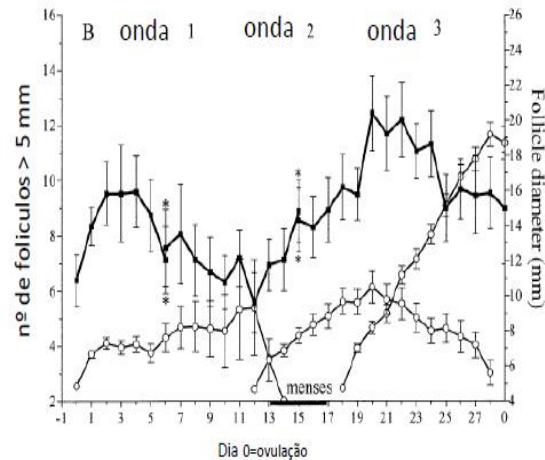
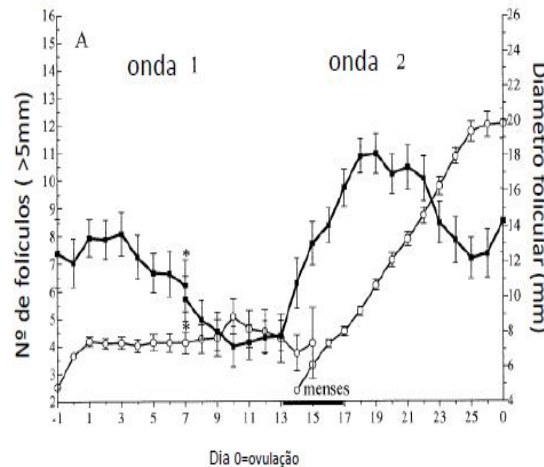
Dinâmica de recrutamento folicular



Baerwald et al Hum Reprod Update 2013



Adams GP et al., J Reprod Fertil, 1992



■ Nº de folículos > 5 mm ○ diâmetro dos maiores folículos

Baerwald et al, Fertil Steril 2003



FERTIL

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?

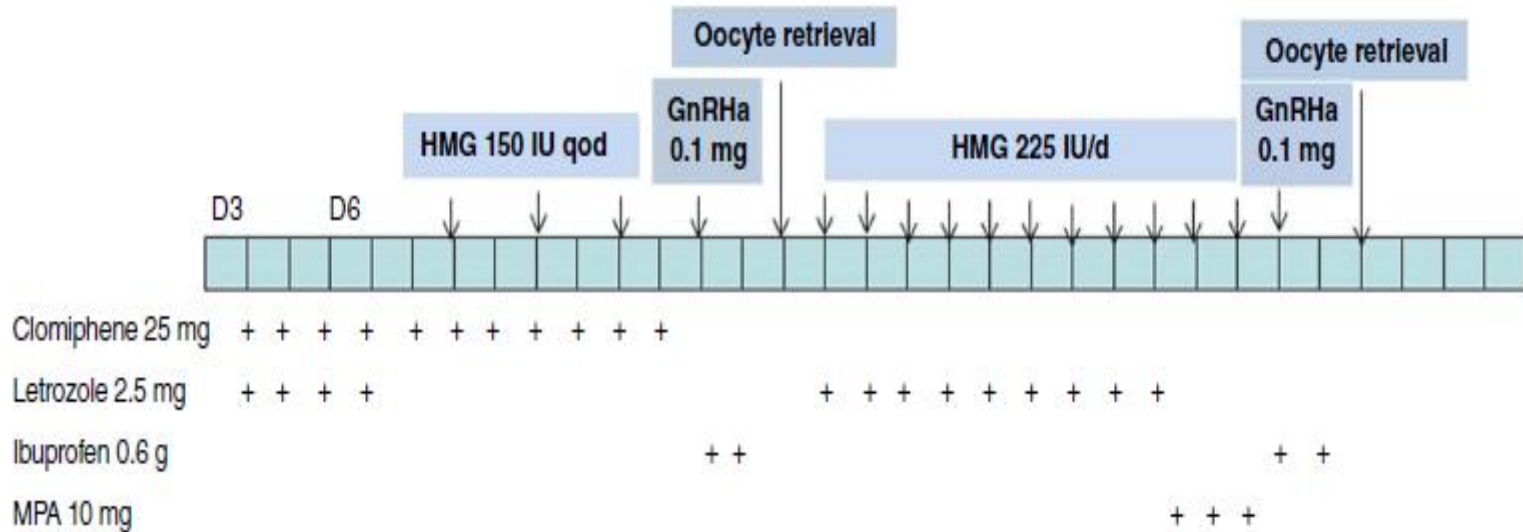
Estimulação ovariana: *pobre resposta*

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*

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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 retrieval | Embryos from second oocyte retrieval | 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)



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CONCLUSÃO:

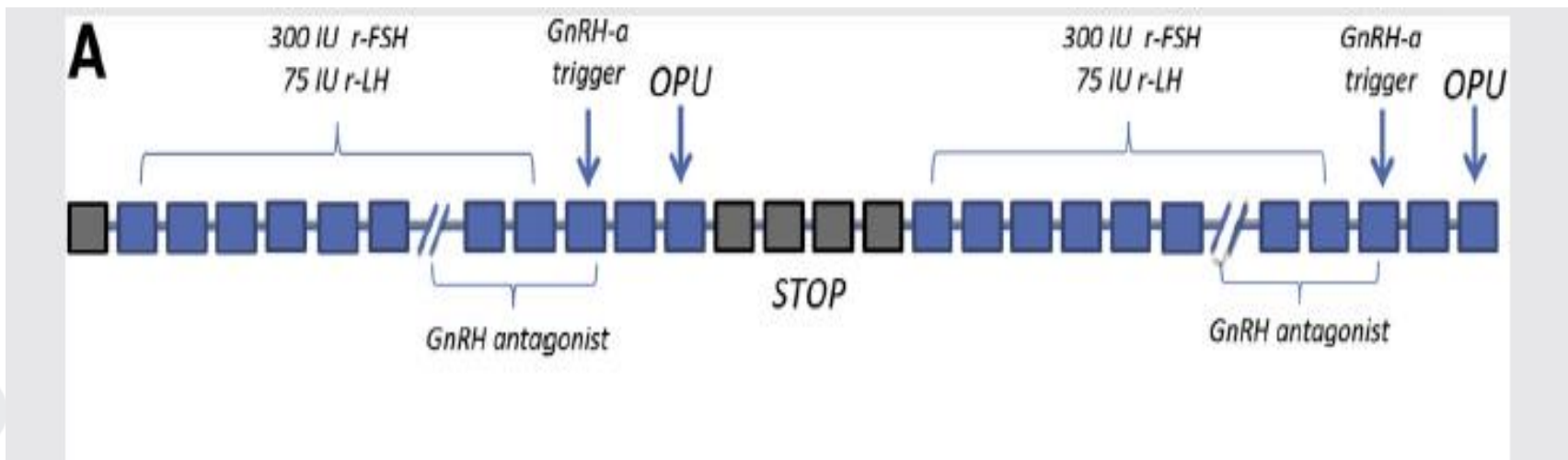
Protocolo a ser utilizado para pacientes com:

- ***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 Alviqai, M.D., Ph.D.^{d,e}
^f *Fertility and Sterility*® Vol. 105, No. 6, June 2016 0015-0282 and Laura Rienzi, M.Sc.^{a,b,c}



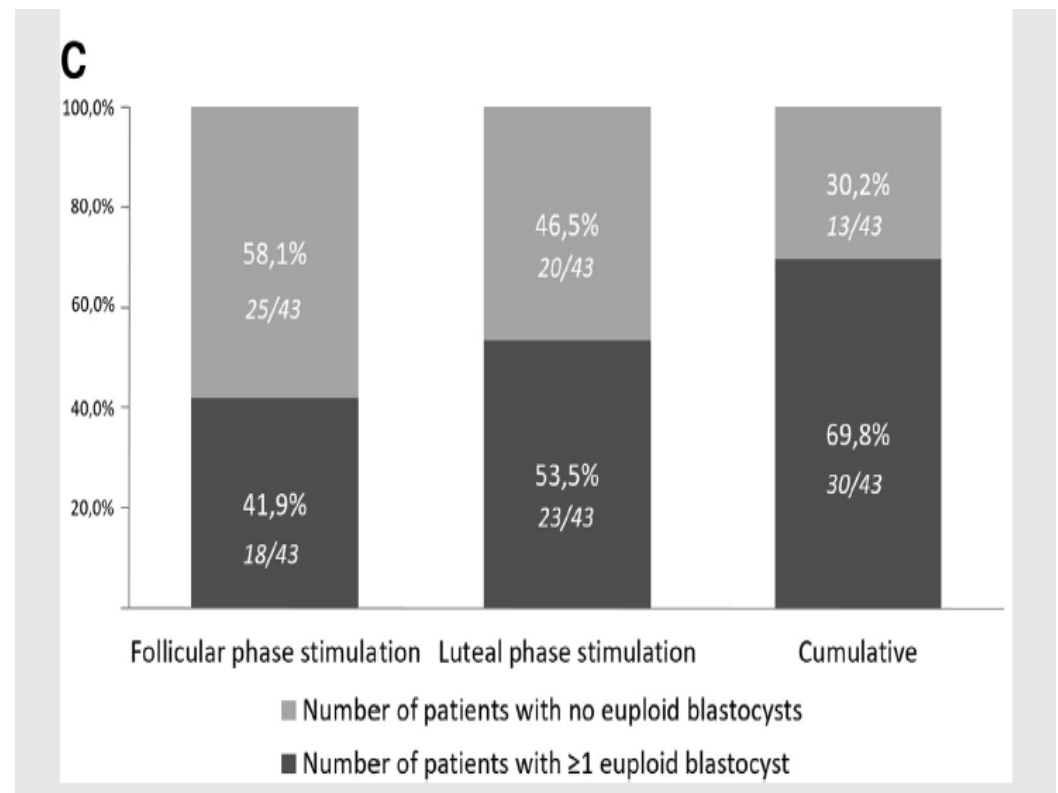
Estimulação ovariana: *pobre resposta*

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Fertility and Sterility® Vol. 105, No. 6, June 2016 0015-0282
Filippo Maria Ubaldi, M.D., M.Sc.,^{A,B,C} Antonio Capalbo, Ph.D.,^{A,B,C} Alberto Valarelli, M.D., Ph.D.,^{A,B}
Danilo Cimadomo, M.Sc.,^{A,B,D} Silvia Colamaria, M.D.,^{A,D} Carlo Aliviggi, M.D., Ph.D.,^{A,D}
Elisabetta Trabucco, M.D.,^{A,B} Roberta Venturella, M.D.,^{A,B} Gabor Vajta, Ph.D.,^{A,B} and Laura Rienzi, M.Sc.^{A,B,C}

Pacientes :

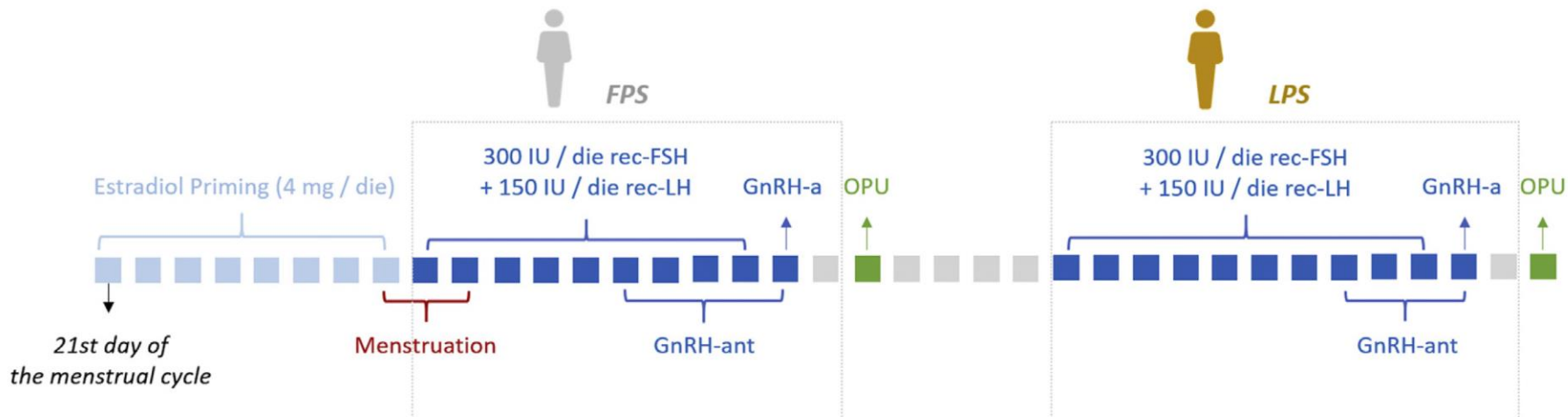
- HAM < 1,5 ng/mL
- Tratamentos prévios < 3 ovócitos
- < 6 folículos antrais ou < 5 ovócitos
- PGT-A





Estimulação ovariana: *pobre resposta*

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

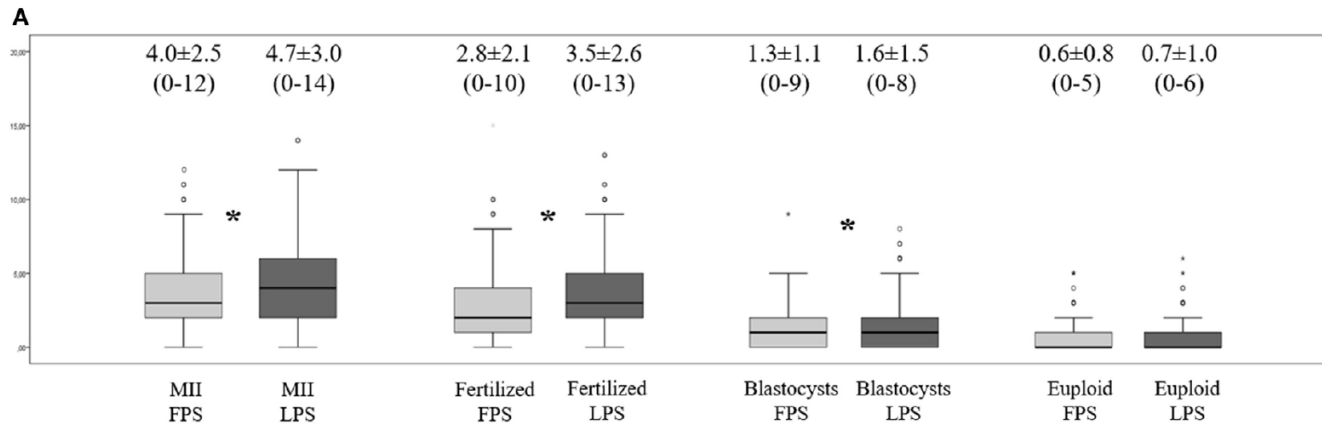


Main differences between the two ovarian stimulation strategies adopted (DuoStim and conventional) in patients fulfilling the Bologna criteria during the observational period.

| 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 1 st COS: 38 After 2 nd 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.



B

| | FPS | LPS |
|-----------------------------------|---------------|---------------|
| Mean fertilization rate per cycle | 69.4% ± 31.5% | 69.8% ± 31.2% |
| Mean blastocyst rate per cycle | 34.9% ± 31.4% | 32.6% ± 27.7% |
| Mean euploidy rate per cycle | 15.7% ± 24.1% | 13.0% ± 19.8% |

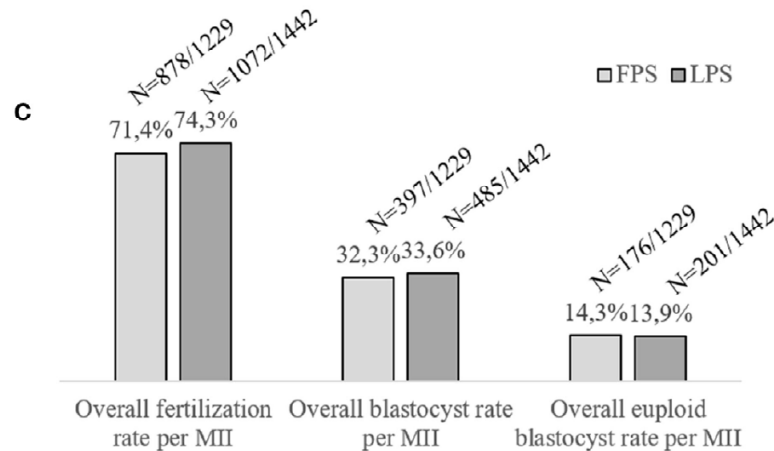


FIGURE 1 | Multicenter clinical experience at the G.EN.E.R.A. centers for reproductive medicine (Rome, Naples, Marostica, and Umbertide) with the application of a DuoStim approach. **(A)** Mean number of metaphase (MII) oocytes, fertilized embryos, blastocysts, and euploid blastocysts obtained per cycle 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.



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. Ragab¹, Amal Shohayeb¹, Waleed Saber¹, Sherif Ekladios², Eman A. Hussein¹, Akmal El-Mazny¹, Ayman Hany¹

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

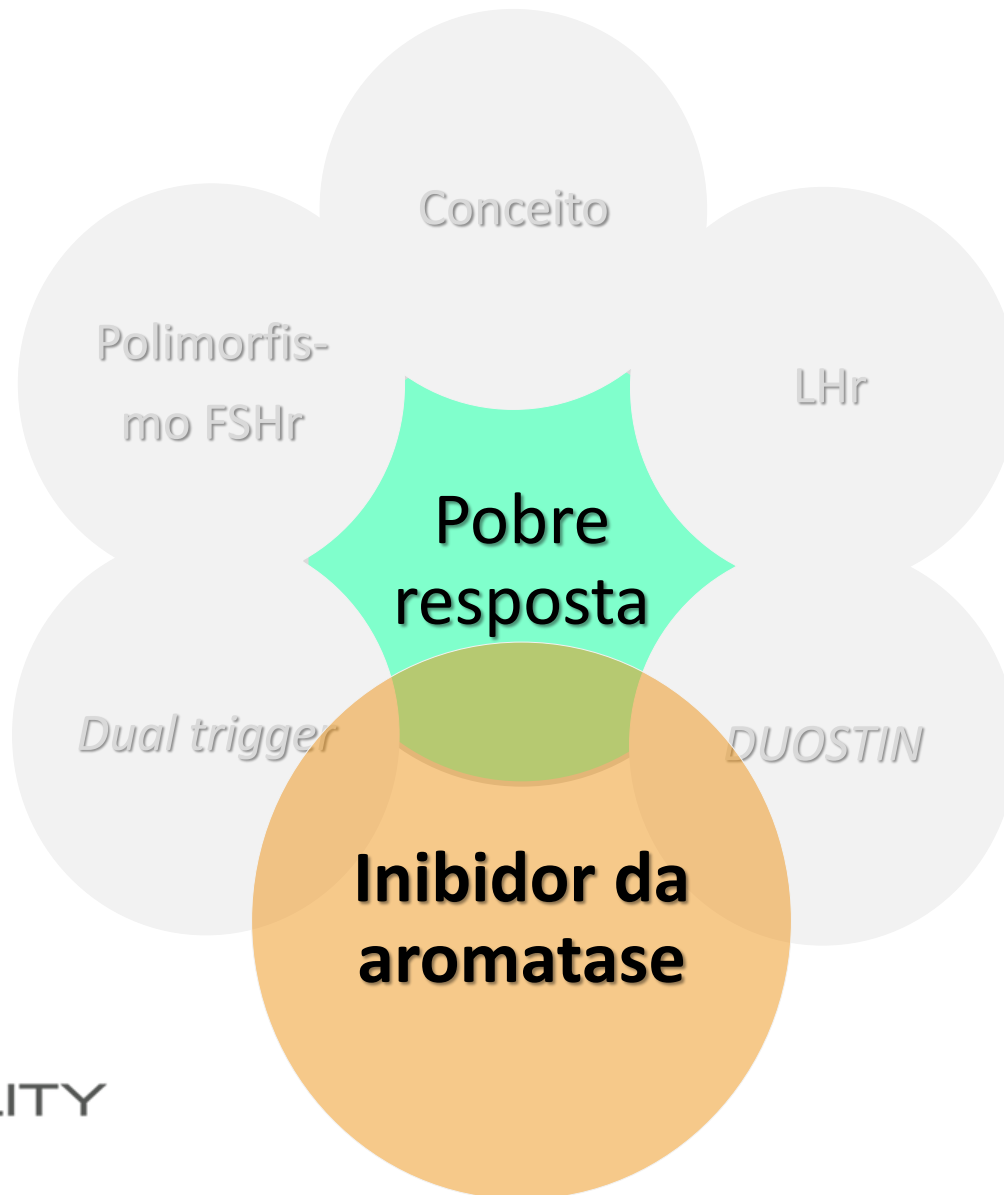
² Clinical Pathology Department, Kasr Alainy Hospital Cairo University, Cairo, Egypt

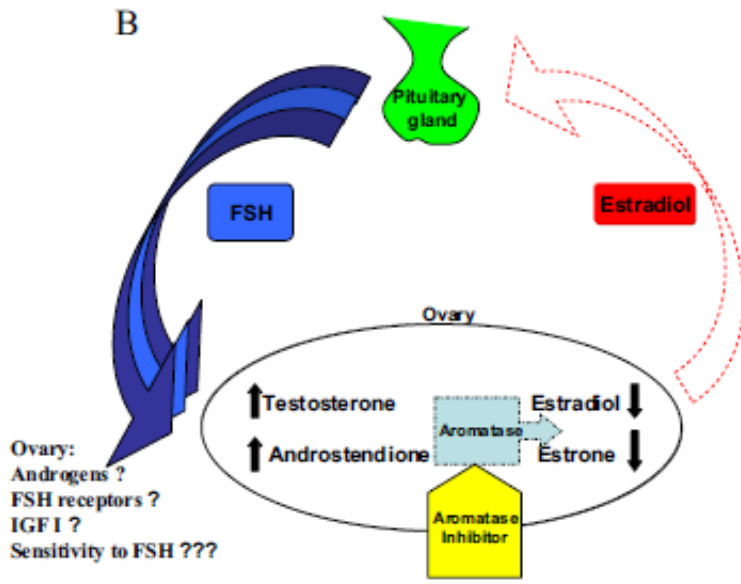
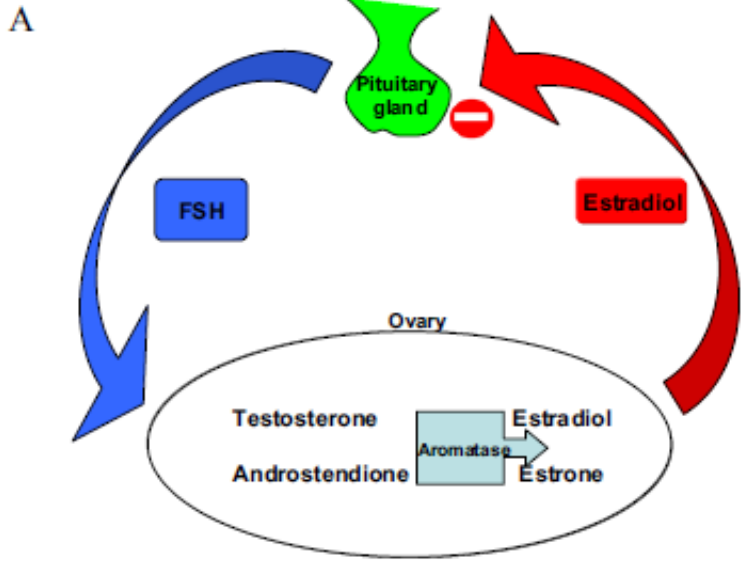
Randomized Controlled Trial > [Int J Gynaecol Obstet. 2021 Mar;152\(3\):395-400.](#)

TABLE 3. Outcome parameters

| | Single trigger (n=80) | Dual trigger (n=80) | <i>P</i> 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).





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

278 Holzer et al. **A new era in ovulation induction**

Vol. 85, No. 2, February 2006

Letrozole / Anastrozole Inibe a conversão de andrógenos em estrógenos

TT – E2

Androstenediona – estrona

OBS: (off label)

REVIEW

Open Access

Aromatase inhibitors in stimulated IVF cycles

Evangelos G Papanikolaou^{1*}, Nikolaos P Polyzos², Peter Humaidan³, George Pados⁴, Ernesto Bosch⁵, Herman Tournaye² and Basil Tarlatzis⁴

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%



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

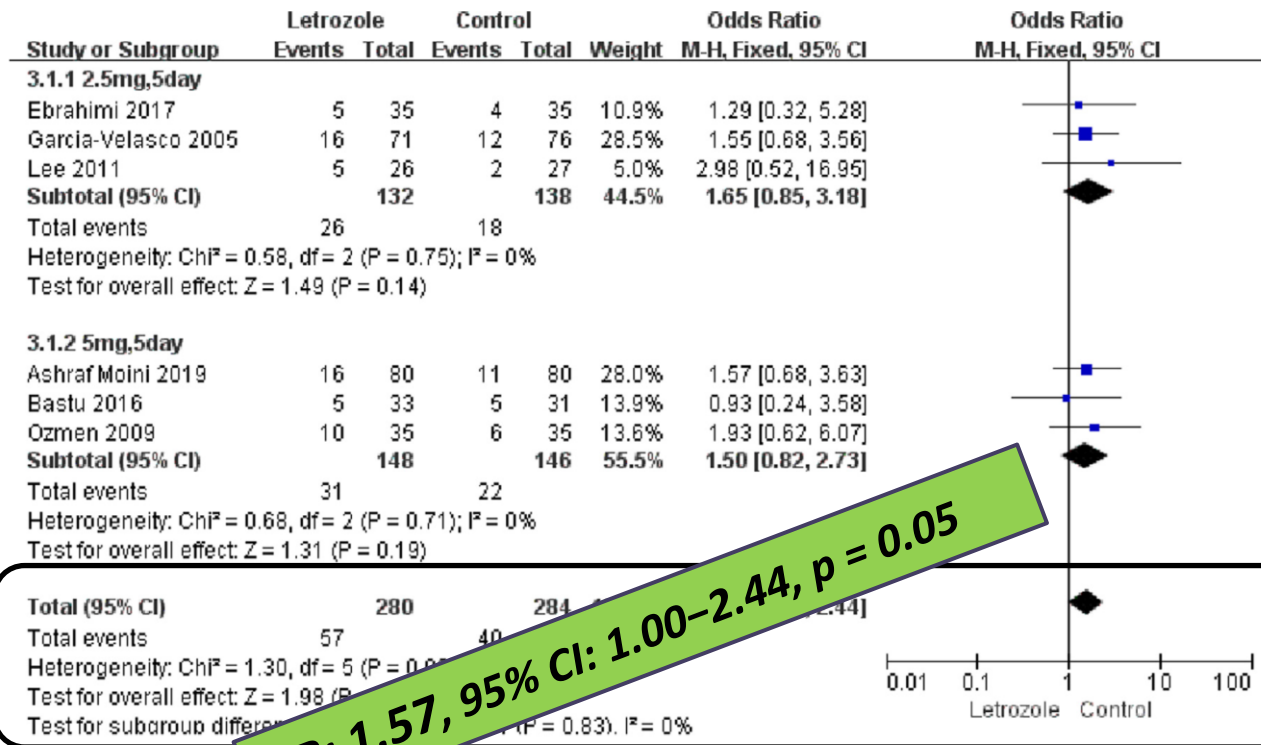
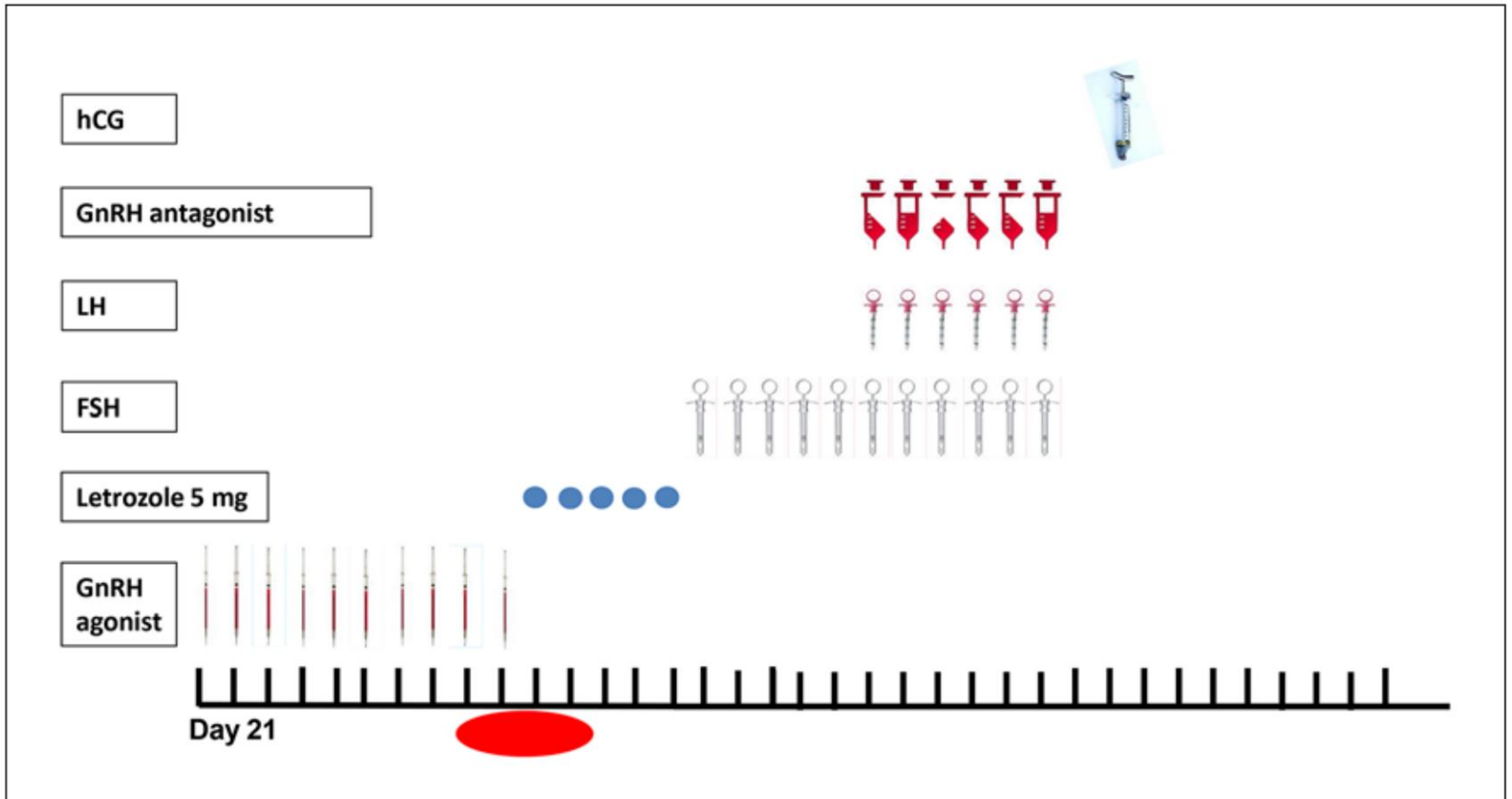


Fig. 3. Forest plot for clinical pregnancy rate (per cycle).



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

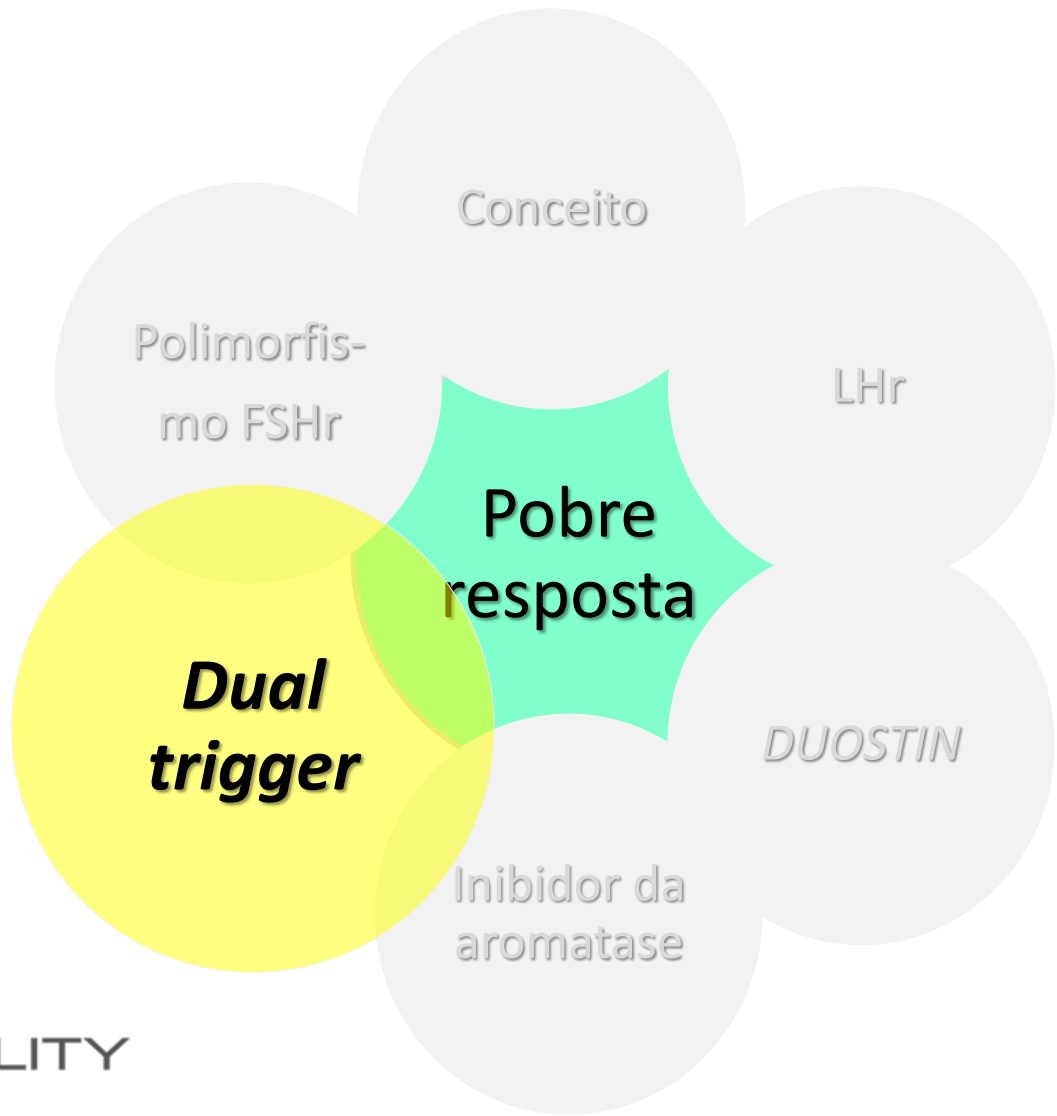
Raoul Orvieto^{a,b} Ravit Nahum^a Adva Aizer^a Jigal Haas^a
Michal Kirshenbaum^a



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



FERTILITY



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 Zhang¹, Yun Wang¹, Xiaoyan Mao¹, 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)

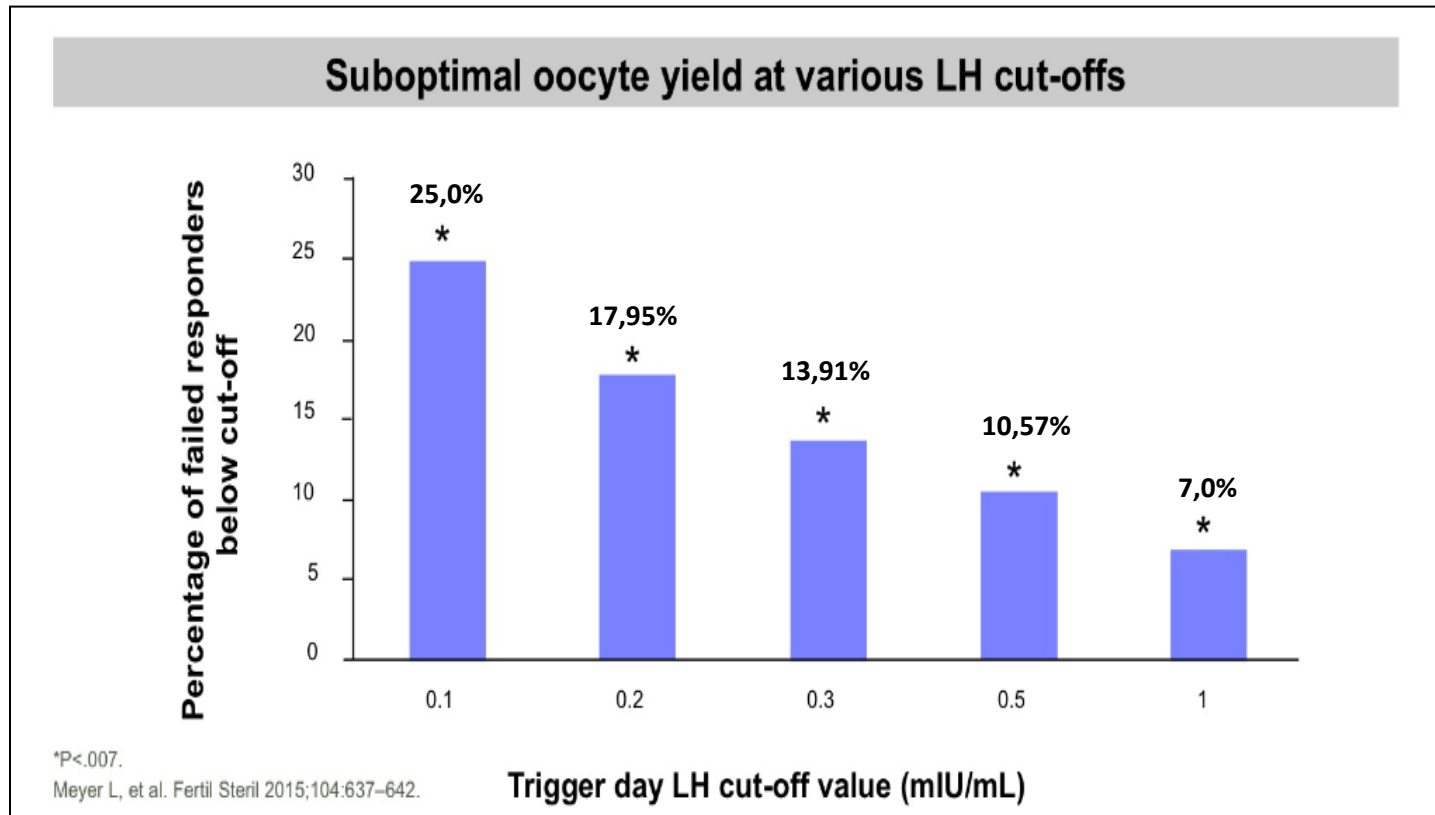
Dual trigger: pobre resposta

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 = 319) | P-value ^d | P-value ^e |
|---|--------------------------------------|--|--|--|----------------------|----------------------|
| No. of oocytes retrieved ^b | 2 (0-9) | 3 (0-11) | 2 (0-9) | 2 (0-9) | <0.001 | <0.001 |
| No. of mature oocytes ^b | 2 (0-8) | 3 (0-10) | 2 (0-9) | 2 (0-9) | <0.001 | <0.001 |
| No. of top-quality embryos ^b | 1 (0-5) | 1 (0-7) | 1 (0-6) | 1 (0-6) | NS | NS |
| No. of viable embryos ^b | 1 (0-4) | 1 (0-7) | 1 (0-6) | 1 (0-7) | NS | NS |
| ICSI rate, n (%) ^c | 118 (35.7) | 117 (30.3) | 118 (32.5) | 97 (31.1) | NS | NS |
| Oocyte retrieval rate, n/n (%) ^c | 638/784 (81.4) | 990/1123 (88.2) | 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).

Dual trigger: resposta inadequada



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



FERTILITY

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

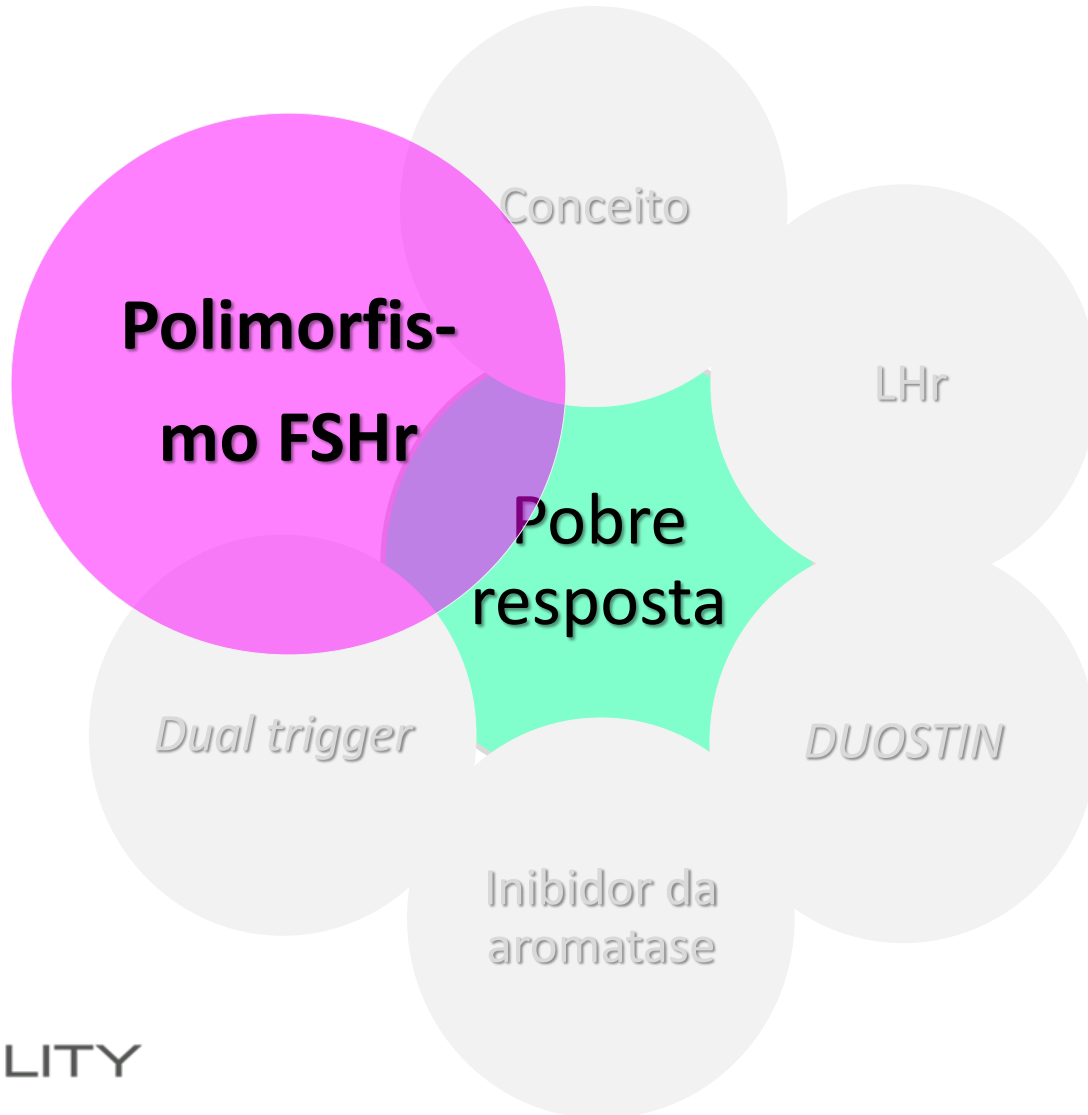
Jigal Haas, M.D., Libby Ophir, B.Sc., Eran Barzilay, M.D., Ph.D., Ronit Machtinger, M.D., Ph.D., Yuval Yung, Ph.D., Raoul Orvieto, M.D., and Ariel Hourvitz, M.D.

Conclusion(s):

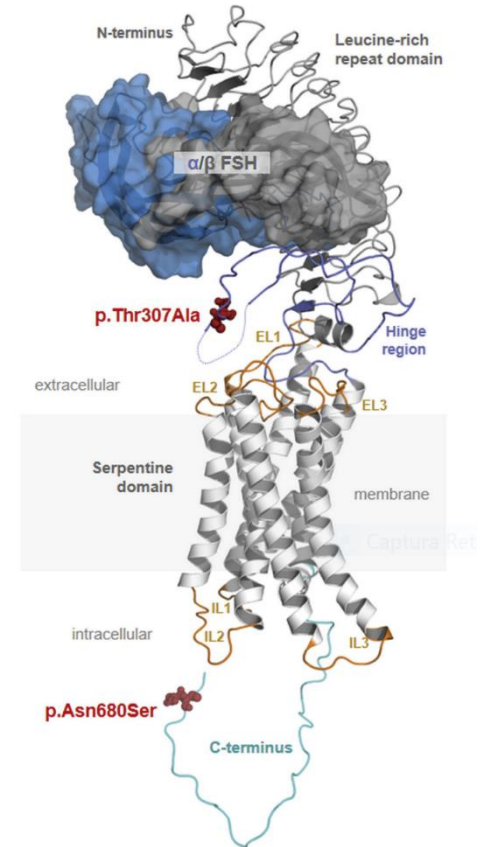
The messenger RNA (mRNA) expression of reproduction-related genes in granulosa cells (GCs) from patients receiving the double trigger may explain and ***suggested improved oocyte and embryo quality related to the double triggering group.***



FERTILITY



Polimorfismo FSH



FERTILITY

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. Uvebrant², A. Dejmek³, L. Kjaer¹, E. Henic⁴, M. Bungum⁴, L. Bungum⁵, C. Cilio², I. Leijonhufvud⁴, S. Skouby⁵, C. Yding Andersen⁶, and Y. Lundberg Giwercman¹

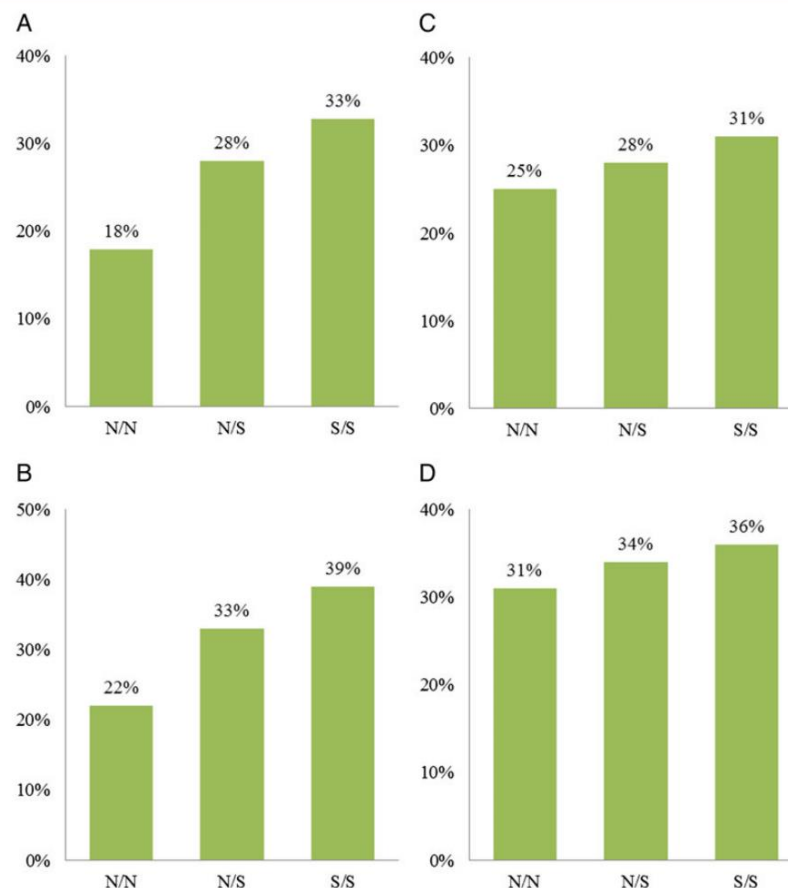


Figure 1 Pregnancy frequencies for the *LHCGR* N312S and *FSHR* N680S polymorphisms. **(A)** *LHCGR* N312S, all women in the study: N/N ($n = 67$), N/S ($n = 175$), S/S ($n = 131$); **(B)** *LHCGR* N312S, only women receiving embryo transfer: N/N ($n = 54$), N/S ($n = 147$), S/S ($n = 109$); **(C)**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

Até quando tratar?

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



Até quando o casal desejar e suportar!!!!

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.

Figure 2. Cum



JAMA. 2015;314(24)

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FERTILITY

Obrigado!

Dr. Edson Borges Jr.

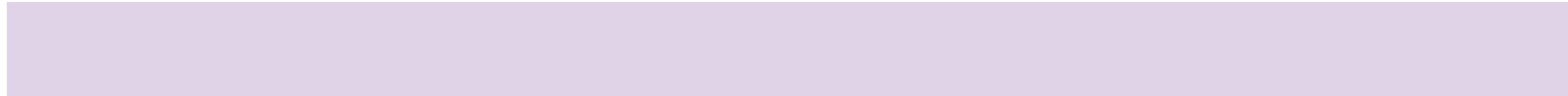
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