FERTILITY TALKS

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

Seeking the strategy against treatment failure

Edson Borges Jr.

FERTILITY MEDICAL GROUP

MERCK

Sucesso na FIV - ICSI

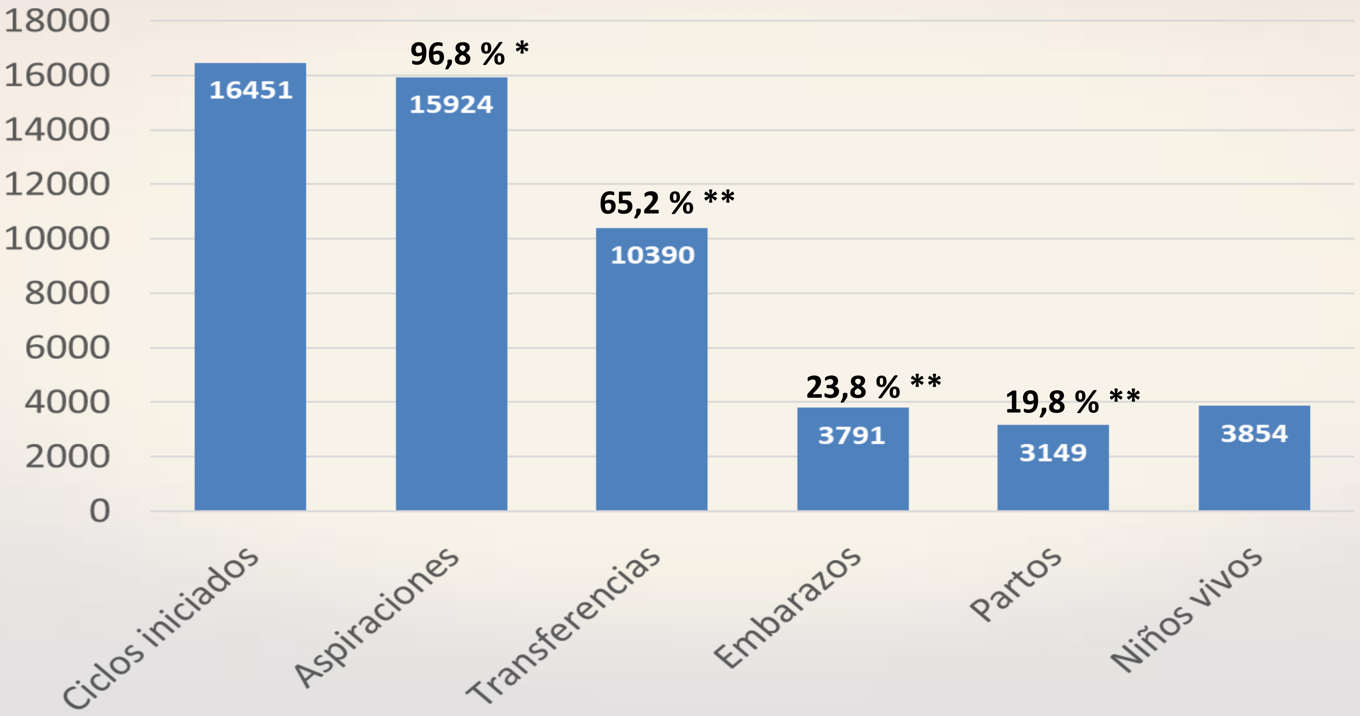
Como definir ?

- Obtenção de óvulos maduros?
- Fecundação?
- Embriões de boa qualidade?
- Implantação?
- Gestação?
- Nascimento?
- ***Bebê e mãe saudáveis após tratamento***!

Resultados globales de FIV/ICSI en Brasil el 2014

FERTILITY TALKS

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



* aspiraciones/ciclos iniciados
** xxx/aspiraciones

Red Latinoamericana de Reproducción Asistida

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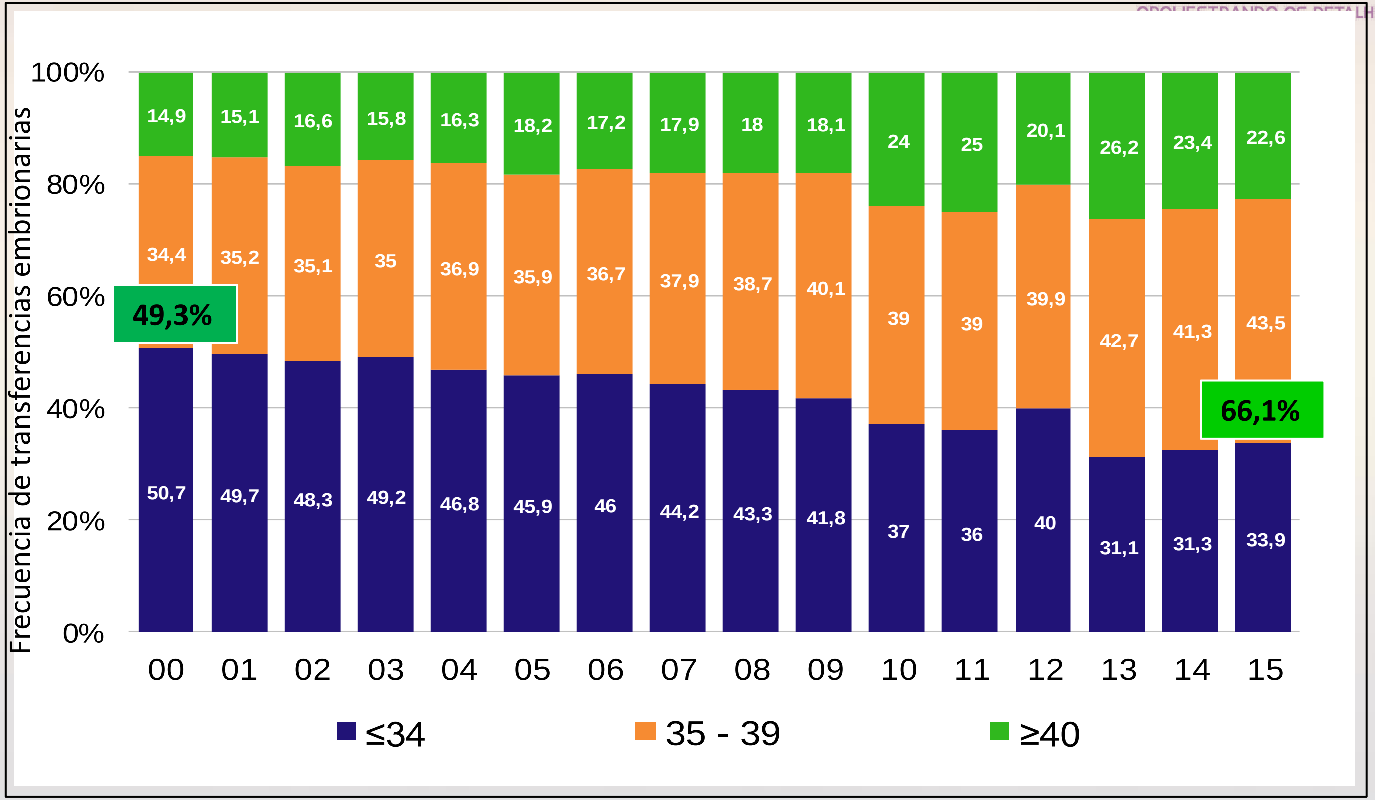
Frecuencia de transferencias embrionaria (FIV/ICSI) de acuerdo a la edad de la mujer - RLA 2000 - 2015

FERTILITY TALKS

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



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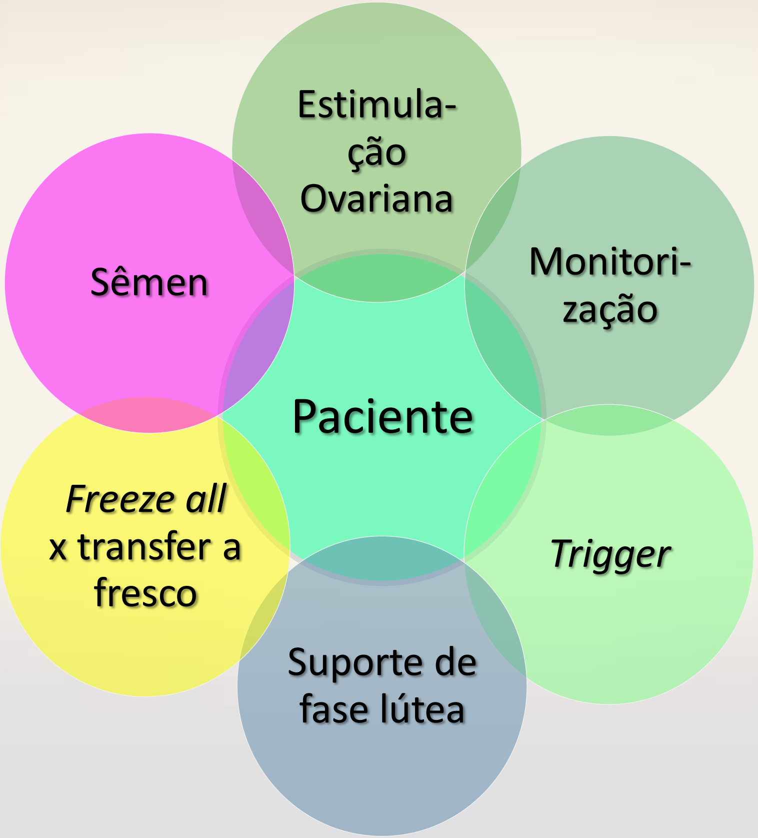
Sucesso na FIV - ICSI

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Estimula-ção Ovariana

Sêmen

Monitori-zação

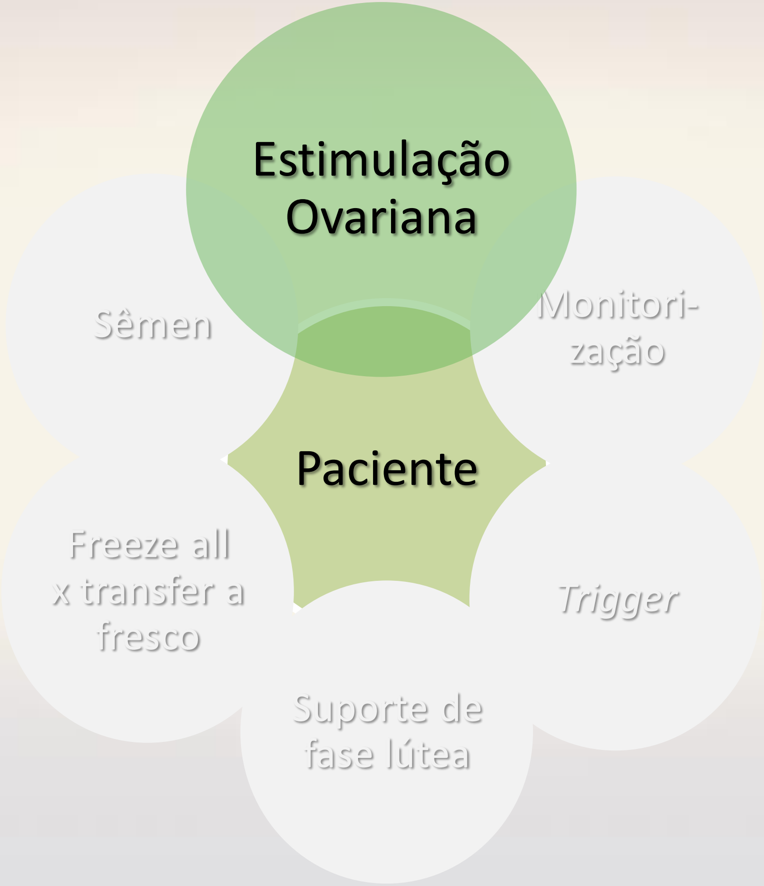
Paciente

Freeze all x transfer a fresco

Trigger

Suporte de fase lútea

Sucesso na FIV / ICSI



Estimulação Ovariana

Sêmen

Monitori-zação

Paciente

Freeze all x transfer a fresco

Trigger

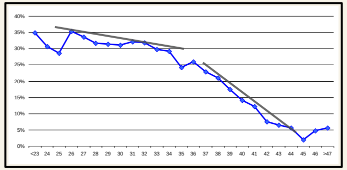
Suporte de fase lútea

MERCK

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

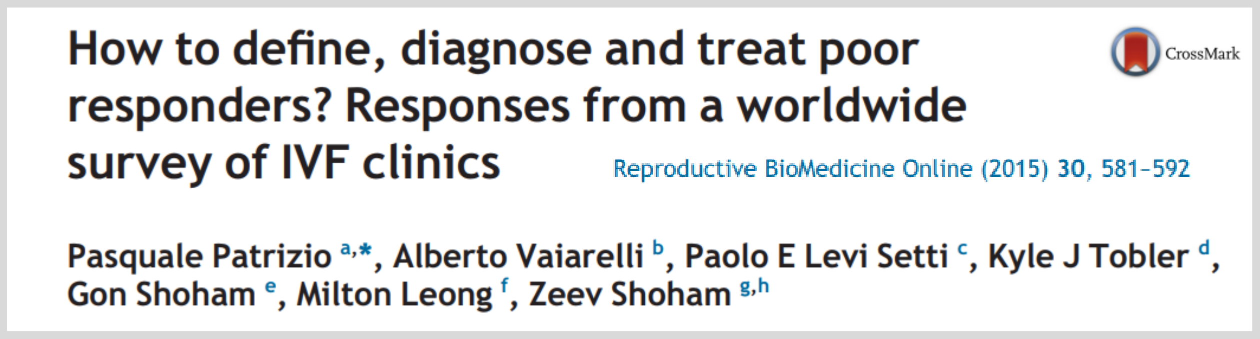


- 10-24% dos ciclos de FIV
- Causas prováveis: cromossômicas adquiridas, alterações genéticas, iatrogênicas

Porém:
SEM CAUSA APARENTE na maioria das vezes

Estimulação ovariana: *pobre resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



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]

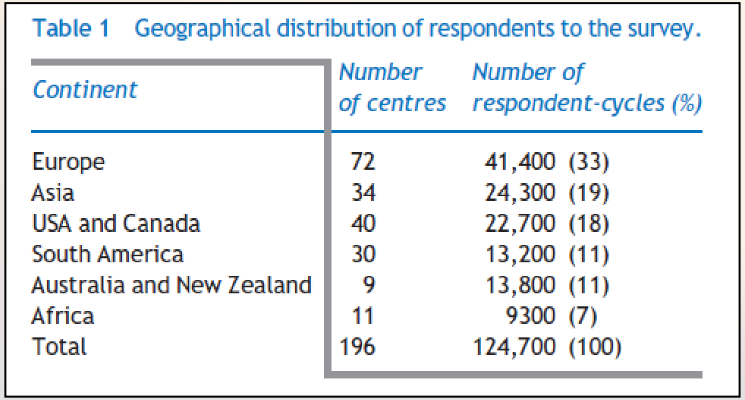


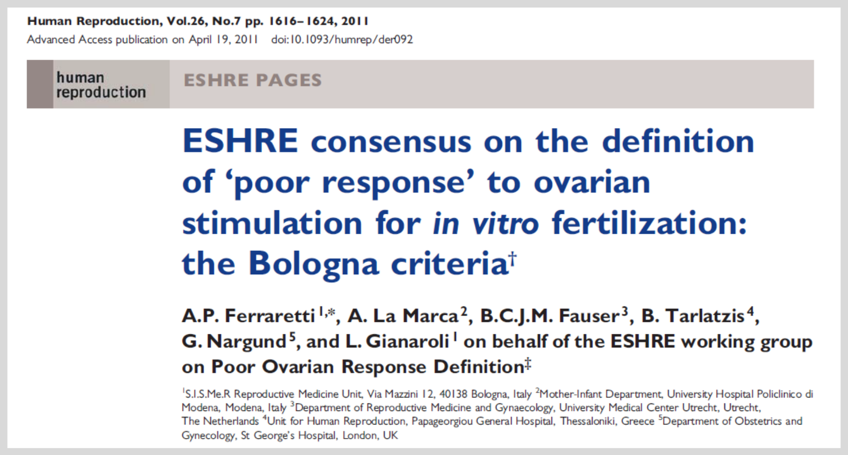
Table 1 Geographical distribution of respondents to the survey.

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*



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‡

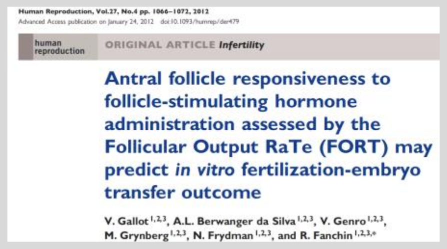
[1]S.I.S.Me.R Reproductive Medicine Unit, Via Mazzini 12, 40138 Bologna, Italy [2]Mother-Infant Department, University Hospital Policlinico di Modena, Modena, Italy [3]Department of Reproductive Medicine and Gynaecology, University Medical Center Utrecht, Utrecht, The Netherlands [4]Unit for Human Reproduction, 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)

- 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 oocitos) há necessidade de aumento na dose cumulativa de FSH (p.ex. >2500-3000 IU) e na duração do estímulo (hipossensibilidade ao FSH)

Estimulação ovariana: *pobre resposta*

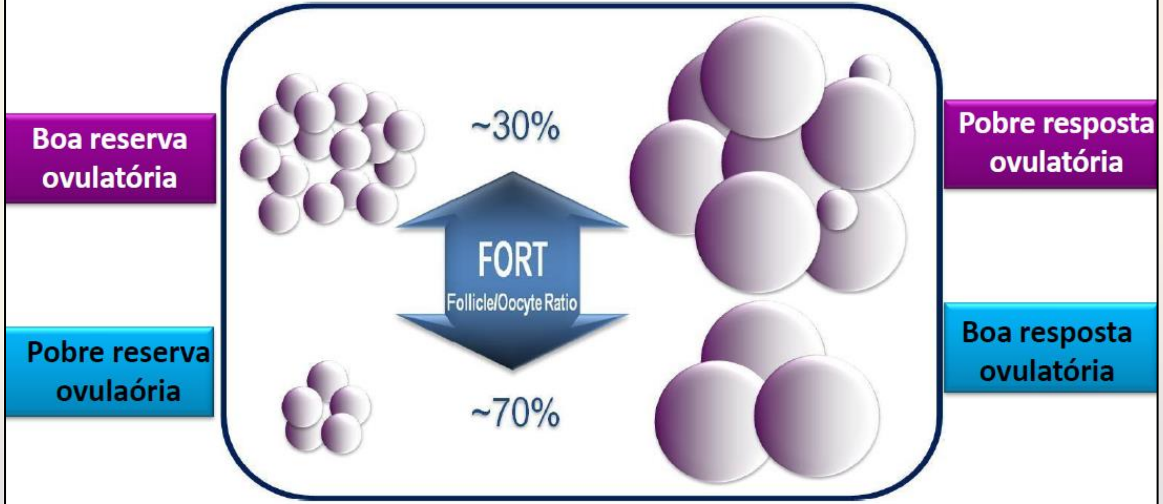


Human Reproduction, Vol.27, No.4 pp. 1066–1072, 2012
Advanced Access publication on January 24, 2012 doi:10.1093/humrep/der479

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,*}



"Follicle output ratio"

"Taxa de produção folicular"

Boa reserva ovulatória
Pobre reserva ovulaória
~30%
FORT
Follicle/Oocyte Ratio
~70%
Pobre resposta ovulatória
Boa resposta ovulatória

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

Estimulação ovariana: *pobre resposta*

E quando a resposta é muito pobre / sem resposta?

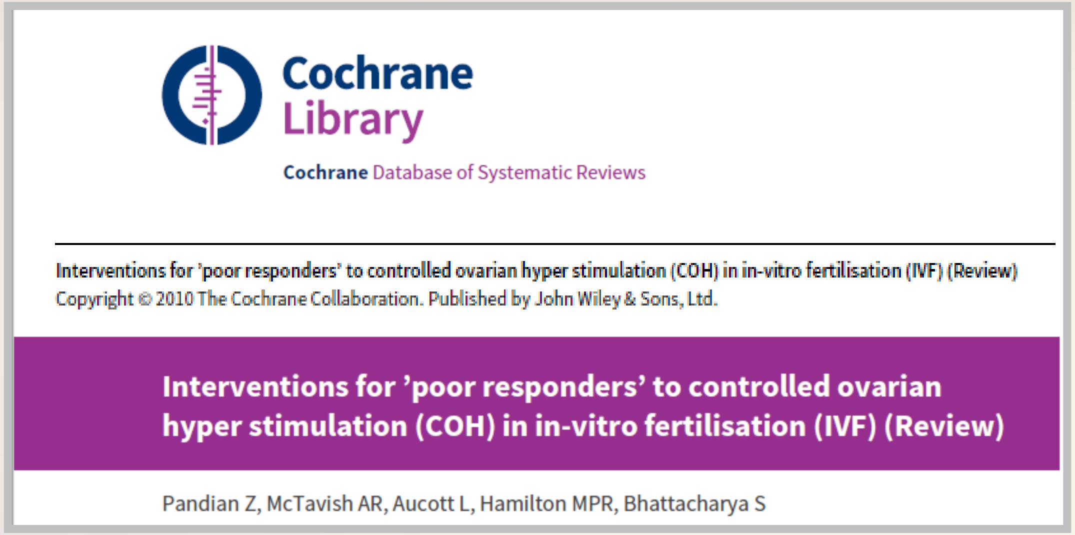
- Aumento das Gns não aumenta o recrutamento folicular
- Terapias complementares ?? – sem comprovação
- Paciente quer continuar tratamento
- Doação de ovócitos: alternativa descartada

WELCOME
TO THE REAL WORLD

AUMENTAR O NÚMERO DE OVÓCITOS / EMBRIÕES

Estimulação ovariana: *pobre resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF) (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF) (Review)

Pandian Z, McTavish AR, Aucott L, Hamilton MPR, Bhattacharya S

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

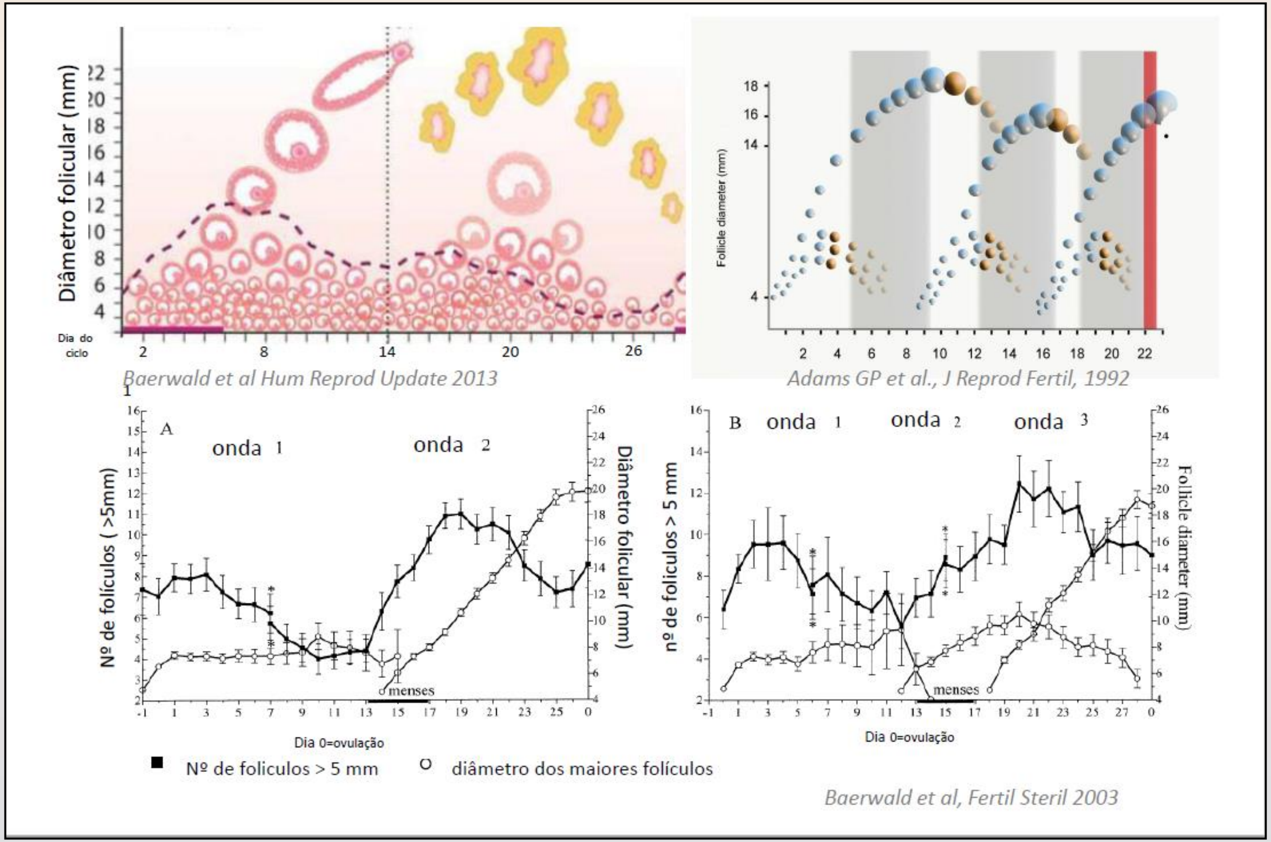
- ***pituitary down regulation,***
- ***ovarian stimulation or***
- ***adjuvant therapy***

Estimulação ovariana: *pobre resposta*

FERTILITY TALKS

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

Dinâmica de recrutamento folicular



Baerwald et al Hum Reprod Update 2013

Adams GP et al., J Reprod Fertil, 1992

Baerwald et al, Fertil Steril 2003

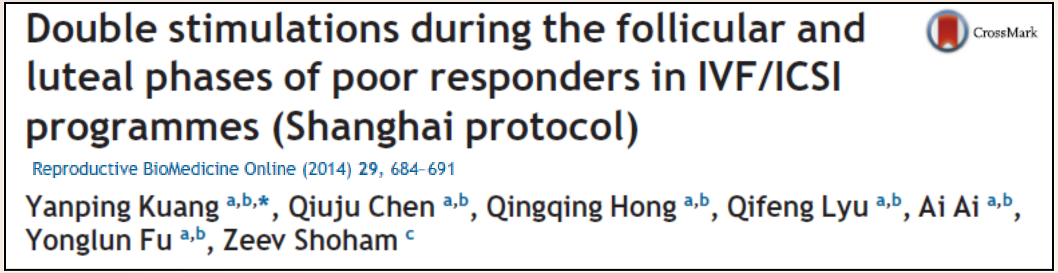
MERCK

Estimulação ovariana: *pobre resposta*

Dupla estimulação

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

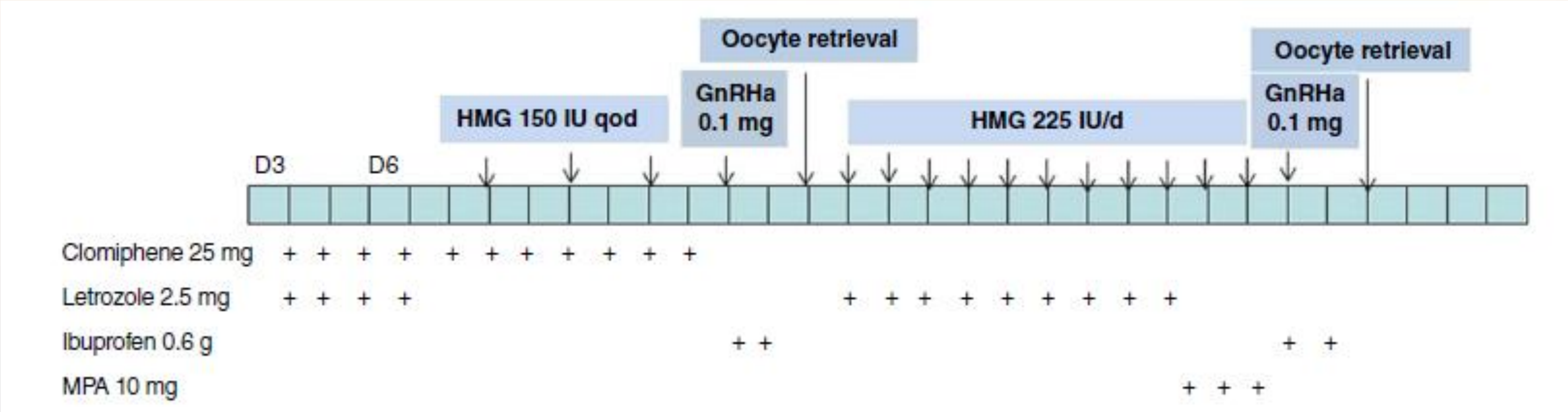
Estimulação ovariana: *pobre resposta*



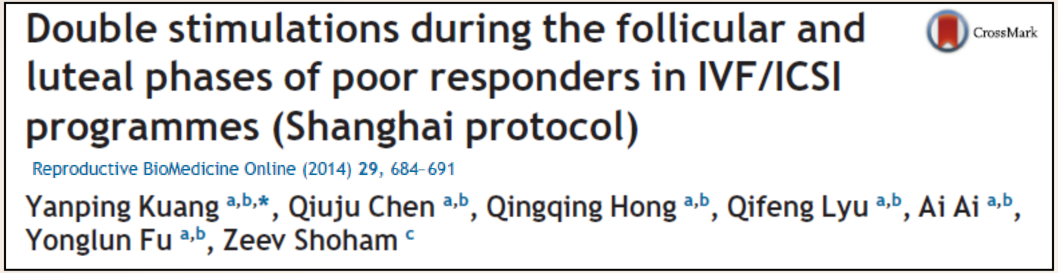
Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol)

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]


Oocyte retrieval
GnRHa 0.1 mg
HMG 150 IU qod
HMG 225 IU/d
Oocyte retrieval
GnRHa 0.1 mg
D3
D6
Clomiphene 25 mg
Letrozole 2.5 mg
Ibuprofen 0.6 g
MPA 10 mg

Estimulação ovariana: *pobre resposta*



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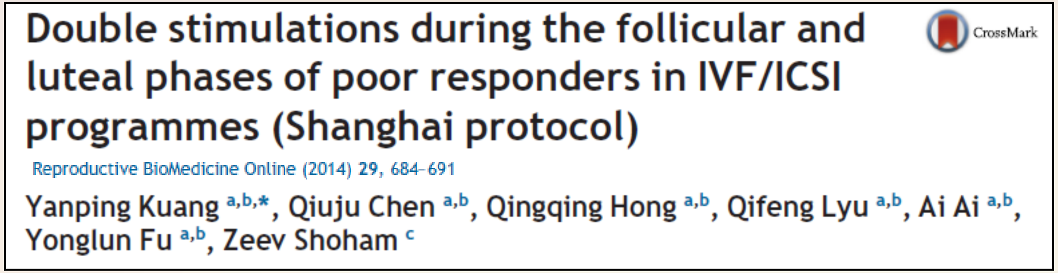
CONCEITOS:

- ***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

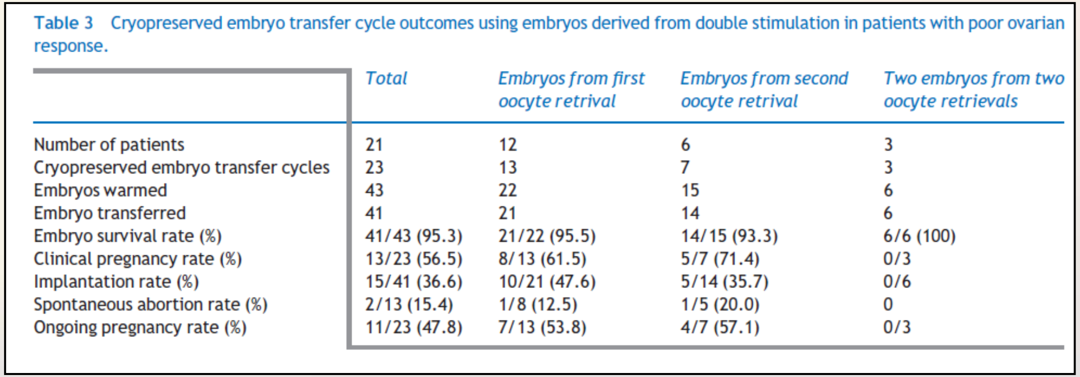
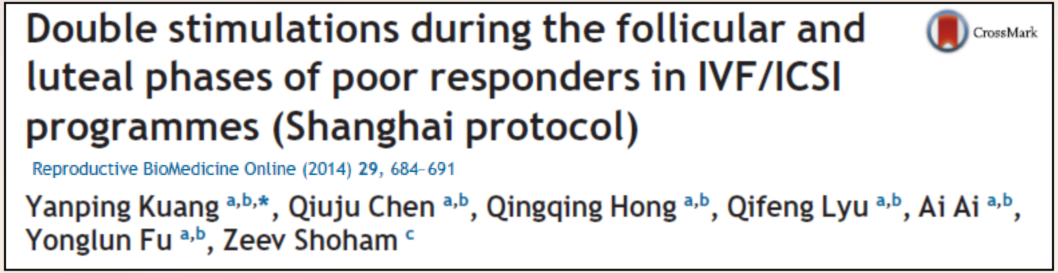


Table 3 Cryopreserved embryo transfer cycle outcomes using embryos derived from double stimulation in patients with poor ovarian response.

	Total	*Embryos from first oocyte 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*



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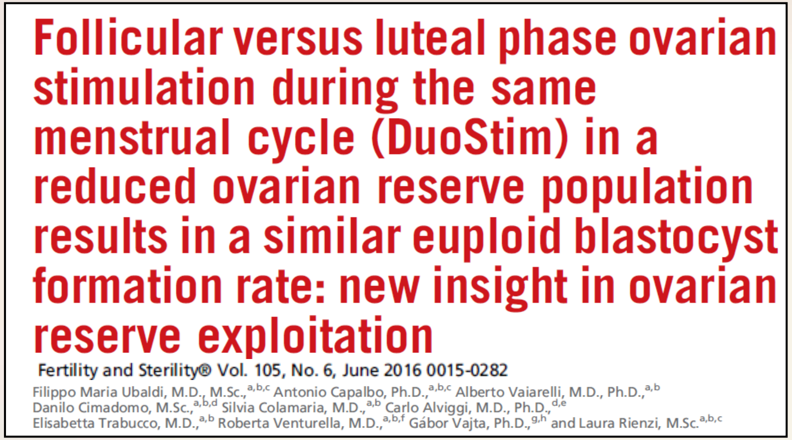
CONCLUSÃO:

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*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



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

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]
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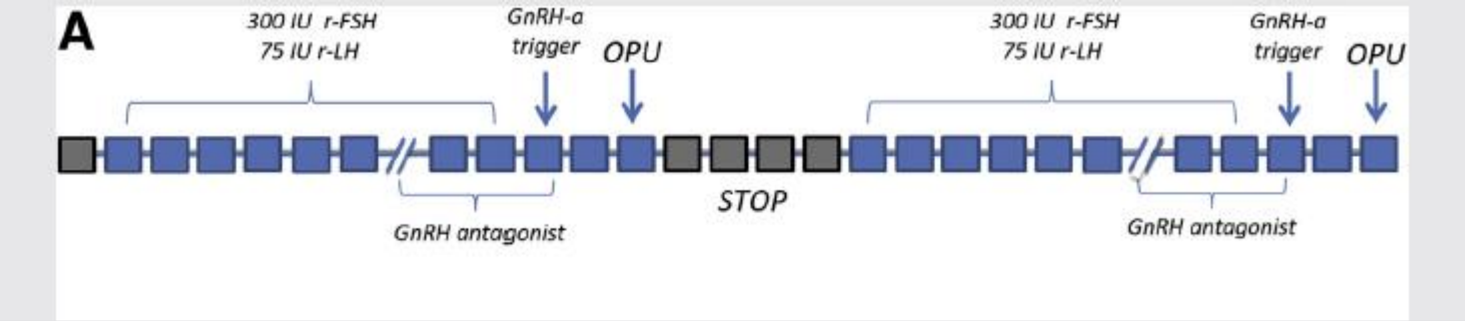
A
300 IU r-FSH
75 IU r-LH
GnRH-a
trigger
OPU
300 IU r-FSH
75 IU r-LH
GnRH-a
trigger
OPU
STOP
GnRH antagonist
GnRH antagonist

Estimulação ovariana: *pobre resposta*

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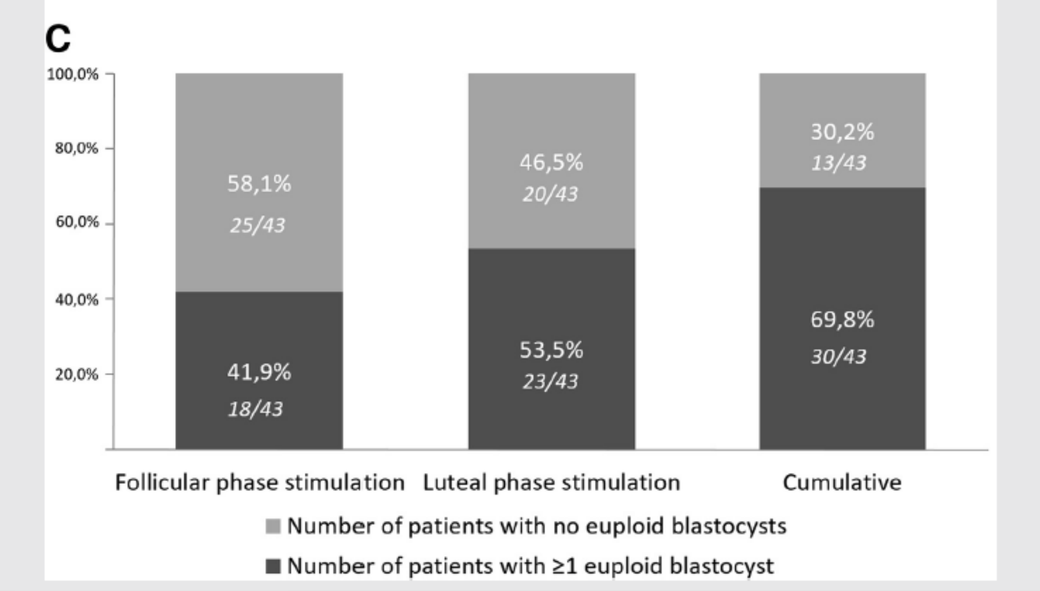
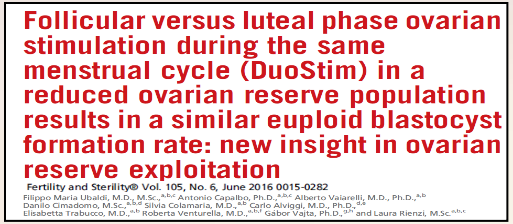
Pacientes :

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



Estimulação ovariana: *pobre resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



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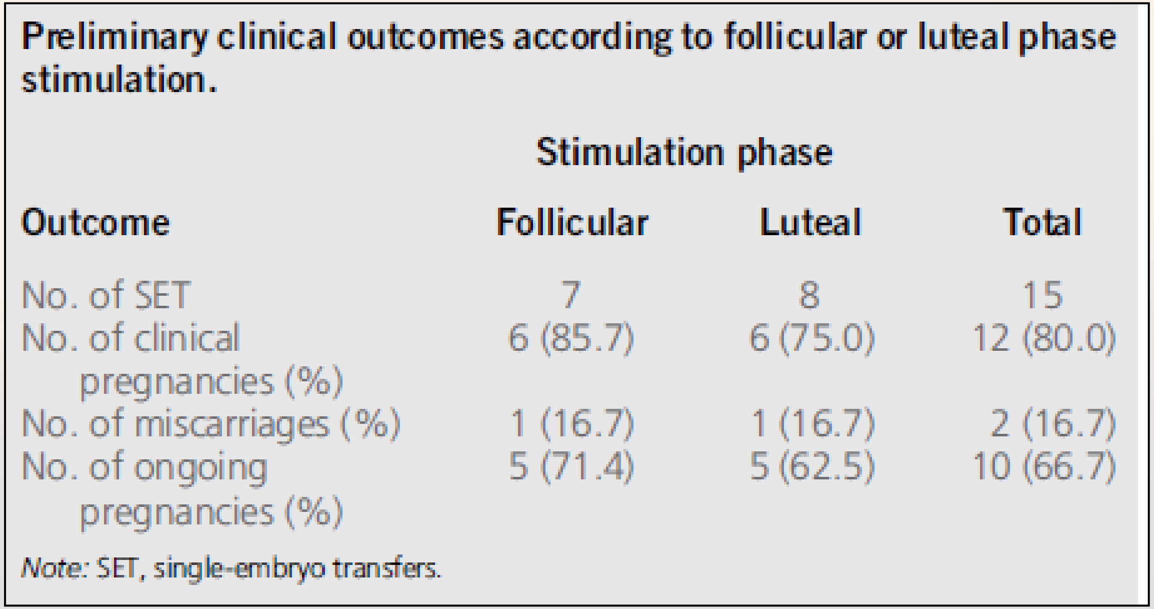


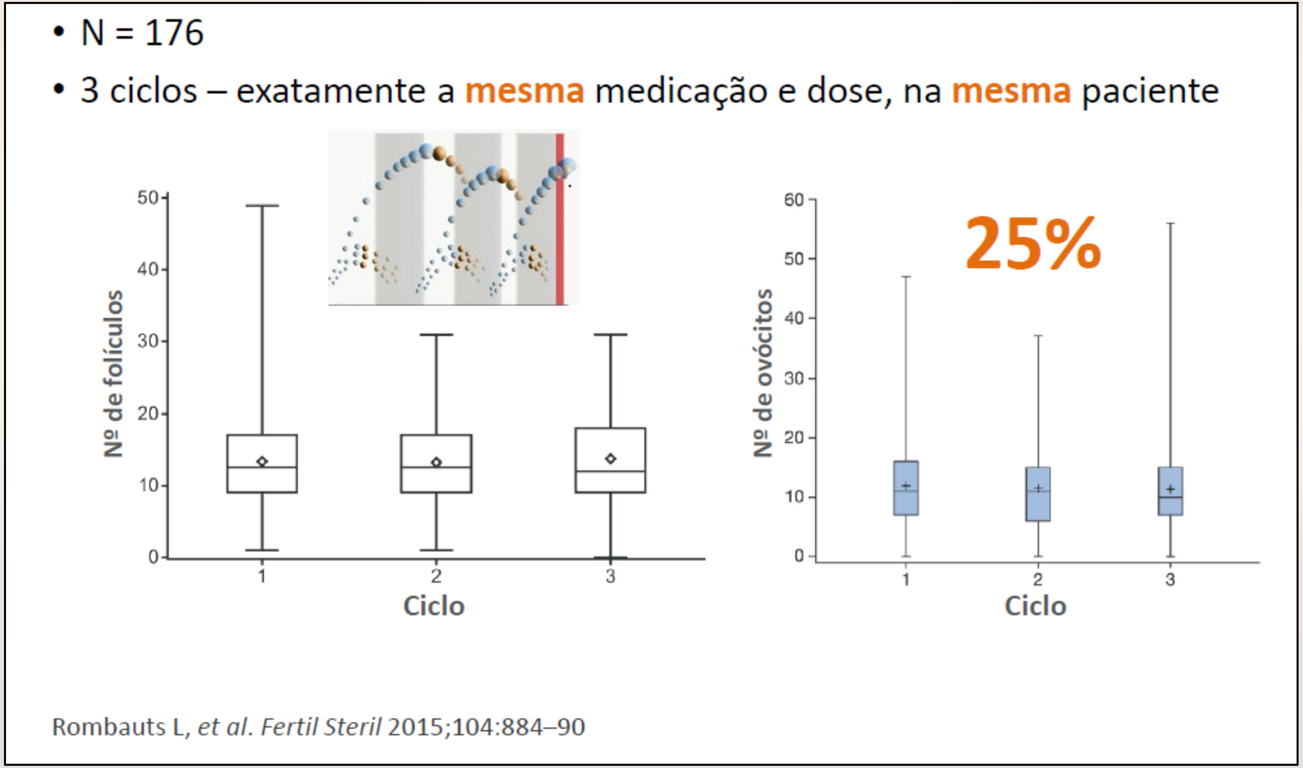
Preliminary clinical outcomes according to follicular or luteal phase stimulation.

	Stimulation phase		
Outcome	**Follicular**	**Luteal**	**Total**
No. of SET	7	8	15
No. of clinical pregnancies (%)	6 (85.7)	6 (75.0)	12 (80.0)
No. of miscarriages (%)	1 (16.7)	1 (16.7)	2 (16.7)
No. of ongoing pregnancies (%)	5 (71.4)	5 (62.5)	10 (66.7)

Note: SET, single-embryo transfers.

Estimulação ovariana: *pobre resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



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

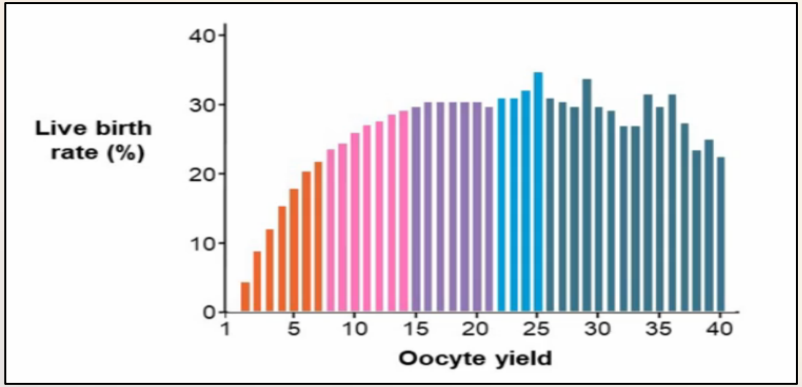
25%

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

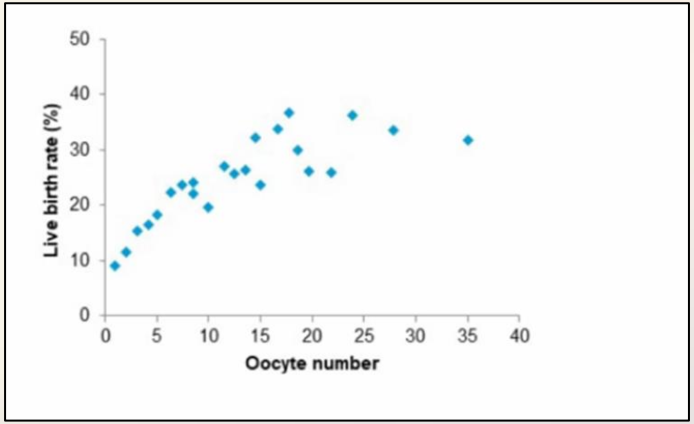
Estimulação ovariana: *hiper-resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

Estímulos com > 15 ovócitos: resultados mantidos



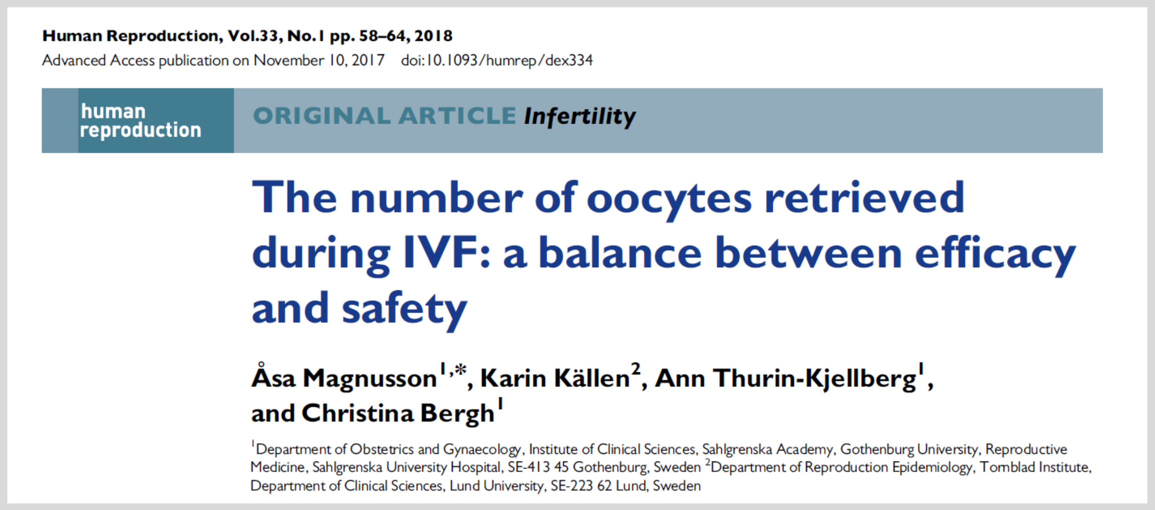
Sunkara SK, et al. Hum Rep 2011; 26:1768-1774



Brigg R, Hum Rep 2015; 30:81-87

Estimulação ovariana: *hiper-resposta*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Human Reproduction, Vol.33, No.1 pp. 58–64, 2018
Advanced Access publication on November 10, 2017 doi:10.1093/humrep/dex334

human reproduction ORIGINAL ARTICLE *Infertility*

The number of oocytes retrieved during IVF: a balance between efficacy and safety

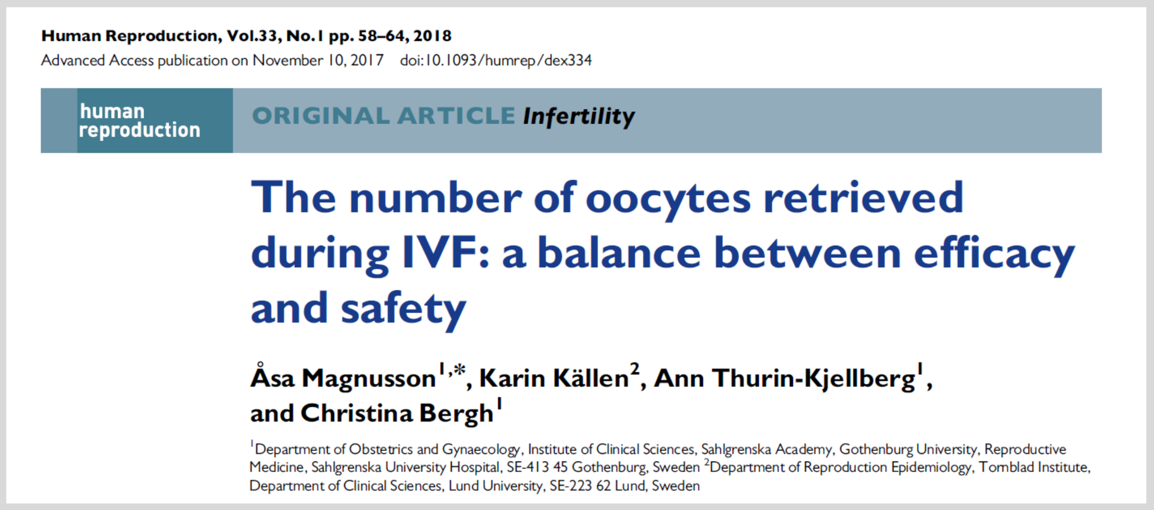
Åsa Magnusson[1,*], Karin Källen[2], Ann Thurin-Kjellberg[1], and Christina Bergh[1]

[1] Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden [2] Department of Reproduction Epidemiology, Tornblad Institute, Department of Clinical Sciences, Lund University, SE-223 62 Lund, Sweden

STUDY DESIGN, SIZE, DURATION:

- Retrospective population-based registry study (The National Quality Registry of Assisted Reproduction, Q-IVF)
- 39.387 women / 77.956 fresh IVF cycles in the period 2007–2013
- 36.270 consecutive transfers of frozen/thawed embryos in the period 2007–2014

Estimulação ovariana: *hiper-resposta*



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The number of oocytes retrieved during IVF: a balance between efficacy and safety

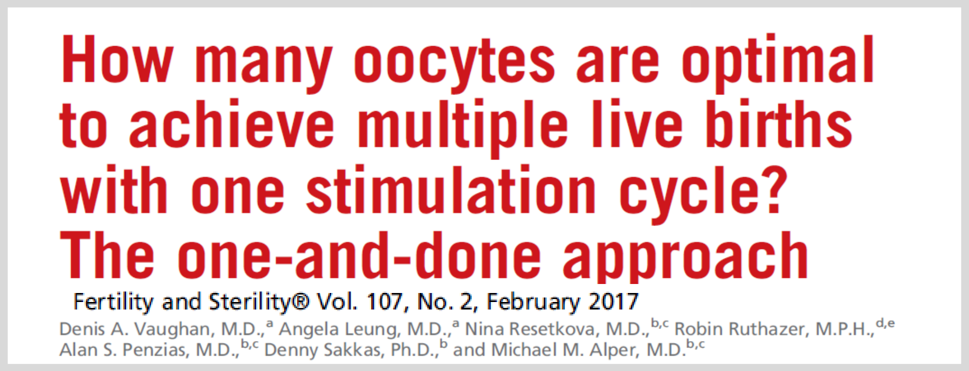
Åsa Magnusson[1,*], Karin Källen[2], Ann Thurin-Kjellberg[1], and Christina Bergh[1]

[1]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden [2]Department of Reproduction Epidemiology, Tornblad Institute, Department of Clinical Sciences, Lund University, SE-223 62 Lund, Sweden

SUMMARY ANSWER:

- Cumulative delivery rate per aspiration ***increases up to 20 oocytes*** retrieved and then evens out
- The incidence of severe OHSS increases more rapidly from ***around 18 oocytes***
- Thromboembolic events, although rare, occurs in particular if ***15 or more oocytes*** are retrieved.

Estimulação ovariana: *hiper-resposta*



How many oocytes are optimal to achieve multiple live births with one stimulation cycle? The one-and-done approach

Fertility and Sterility® Vol. 107, No. 2, February 2017

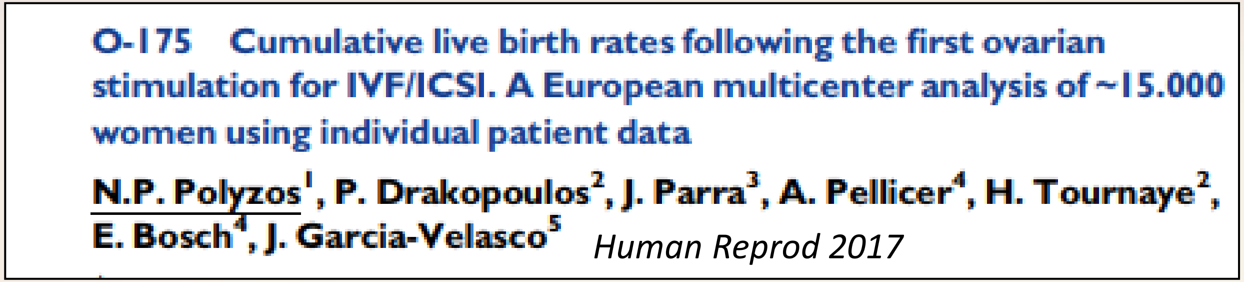
Denis A. Vaughan, M.D.,[a] Angela Leung, M.D.,[a] Nina Resetkova, M.D.,[b,c] Robin Ruthazer, M.P.H.,[d,e]
Alan S. Penzias, M.D.,[b,c] Denny Sakkas, Ph.D.,[b] and Michael M. Alper, M.D.[b,c]

Conclusion(s):

- One fresh cycle with high oocyte yield is an optimal way to plan IVF treatment.

- With modern cryopreservation methods, ***the concept of "one-and-done"*** could safely achieve $\geq$2 live births with just one stimulation cycle in almost a quarter of patients.

Estimulação ovariana: *hiper-resposta*



O-175 Cumulative live birth rates following the first ovarian stimulation for IVF/ICSI. A European multicenter analysis of ~15.000 women using individual patient data

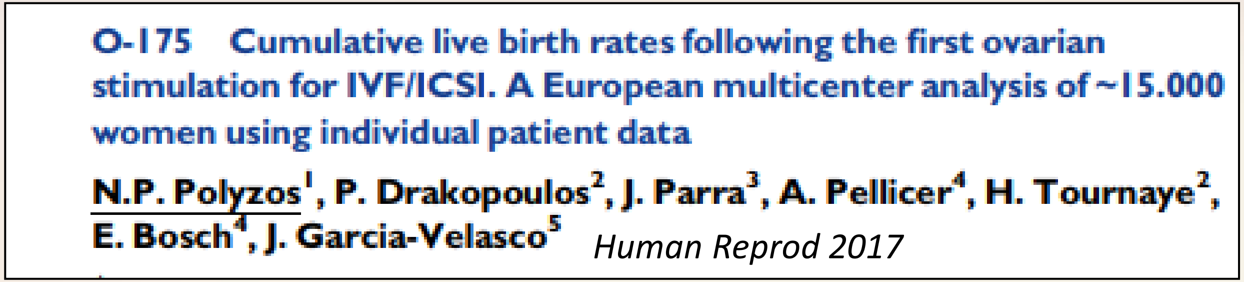
N.P. Polyzos[1], P. Drakopoulos[2], J. Parra[3], A. Pellicer[4], H. Tournaye[2], E. Bosch[4], J. Garcia-Velasco[5]

Human Reprod 2017

Study design, size, duration:

- This is the largest multi-center analysis using individual patient data, conducted in ***15 tertiary referral Hospitals in Europe.***
- The study included ***women undergoing their first ovarian stimulation cycle for IVF/ICSI in an antagonist protocol*** from 2009 to 2014.
- All patients were followed up for at least 2 years until using all their fresh and frozen embryos

Estimulação ovariana: *hiper-resposta*



O-175 Cumulative live birth rates following the first ovarian stimulation for IVF/ICSI. A European multicenter analysis of ~15.000 women using individual patient data

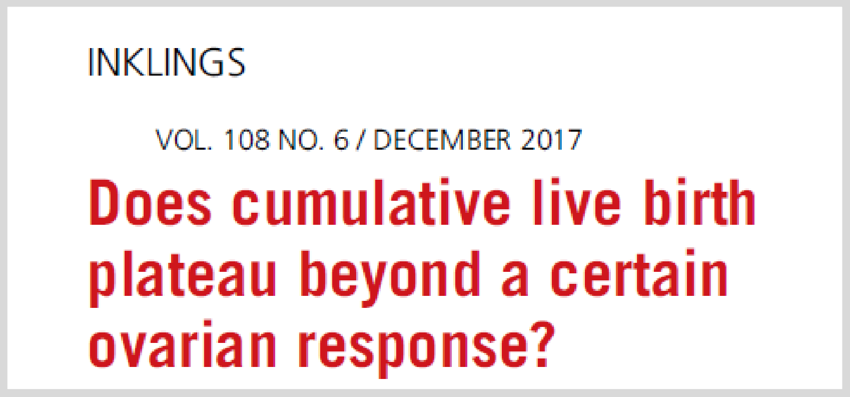
N.P. Polyzos[1], P. Drakopoulos[2], J. Parra[3], A. Pellicer[4], H. Tournaye[2], E. Bosch[4], J. Garcia-Velasco[5]

Human Reprod 2017

Main results and the role of chance:

- Cumulative live birth rates ***steadily increased*** with the number of oocytes, reaching even 70% when ≥25 oocytes were retrieved.
- No plateau in cumulative live birth rates was observed but a moderate increase of 5.1% in average was detected beyond 27 oocytes.

Estimulação ovariana: *hiper-resposta*



INKLINGS

VOL. 108 NO. 6 / DECEMBER 2017

Does cumulative live birth plateau beyond a certain ovarian response?

Razões das diferenças de resultados:

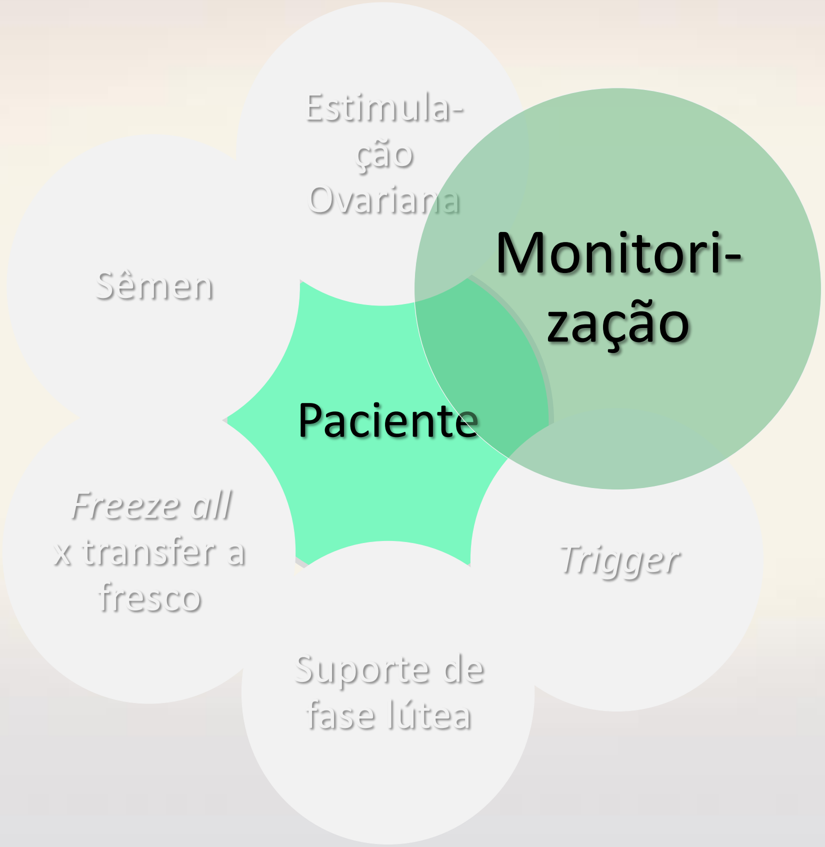
- Vários tipos e resultados de programas de criopreservação
- Dados mais antigos

Vantagens:

- Maior número ovócitos recuperados = maior número de blastocistos euplóides *(Labarta E et al. Biomed Res Int, 2017)*

Sucesso na FIV / ICSI

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Estimulação Ovariana

Monitorização

Sêmen

Paciente

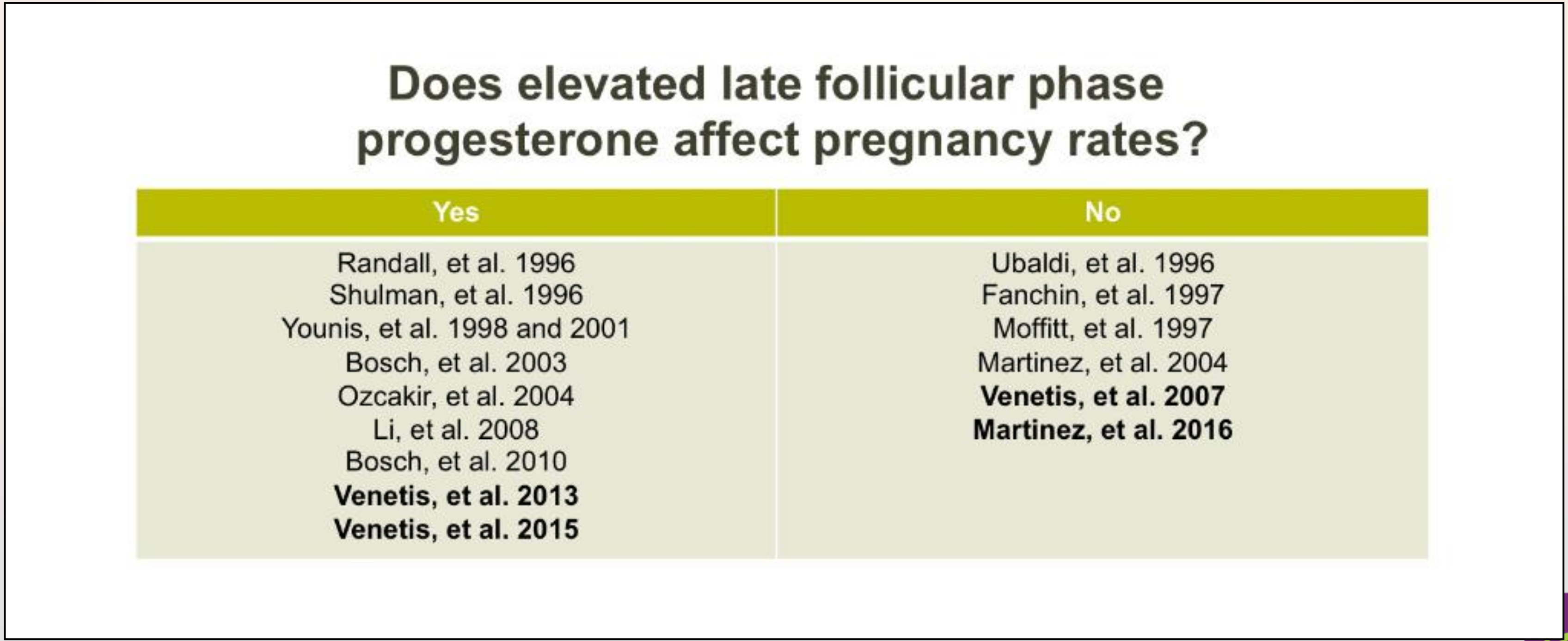
Freeze all x transfer a fresco

Trigger

Suporte de fase lútea

Monitorização

Progesterona: controvérsia?



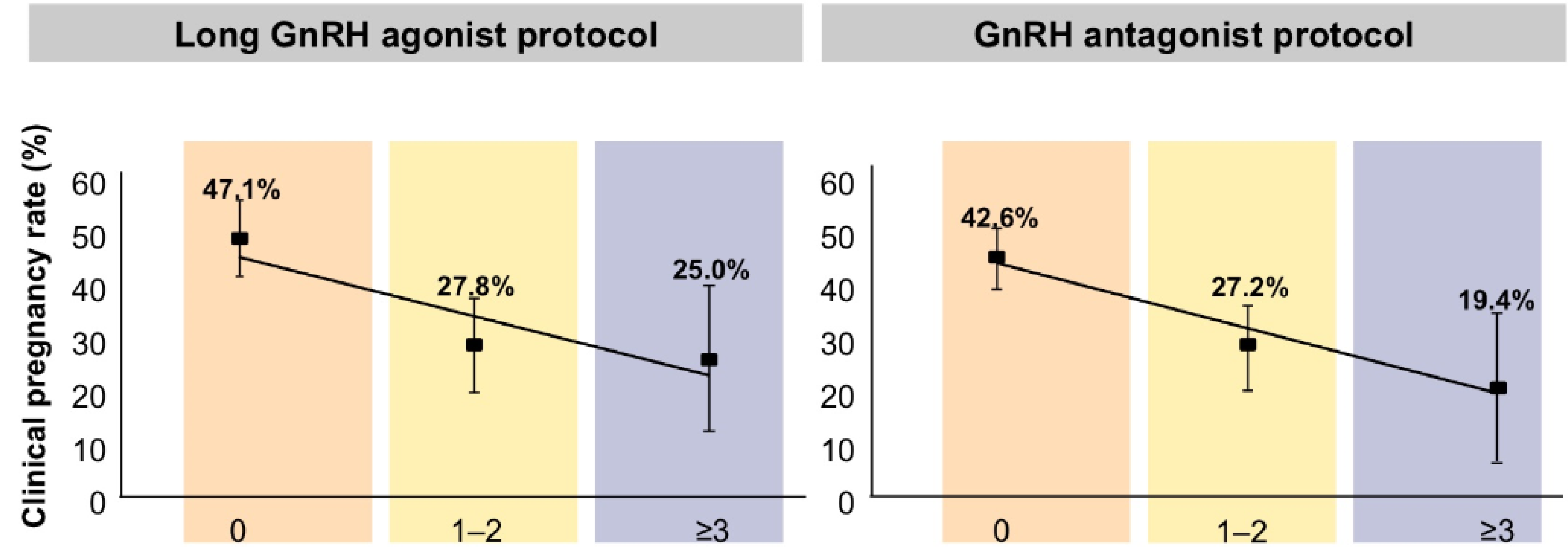
Does elevated late follicular phase progesterone affect pregnancy rates?

Yes	No
Randall, et al. 1996 Shulman, et al. 1996 Younis, et al. 1998 and 2001 Bosch, et al. 2003 Ozcakir, et al. 2004 Li, et al. 2008 Bosch, et al. 2010 **Venetis, et al. 2013** **Venetis, et al. 2015**	Ubaldi, et al. 1996 Fanchin, et al. 1997 Moffitt, et al. 1997 Martinez, et al. 2004 **Venetis, et al. 2007** **Martinez, et al. 2016**

Monitorização

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

Elevação precoce da P4 antes do *trigger* com hCG

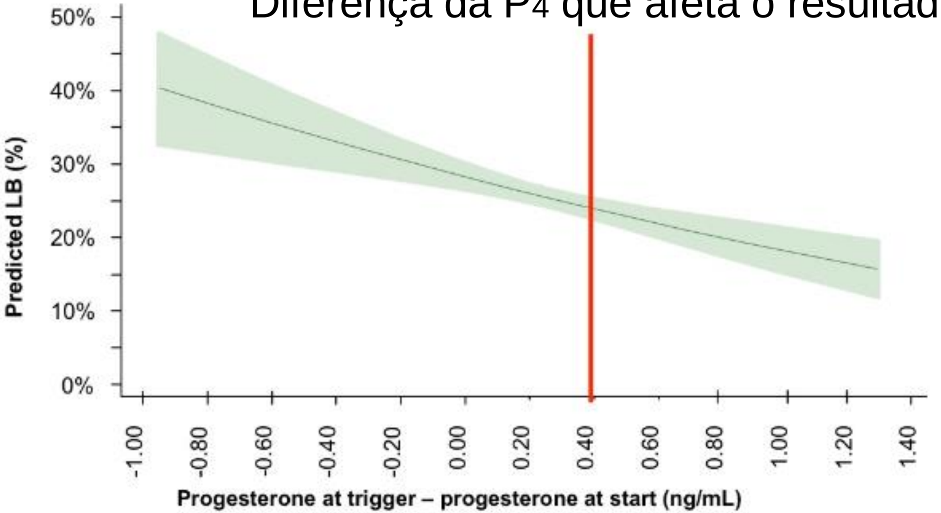


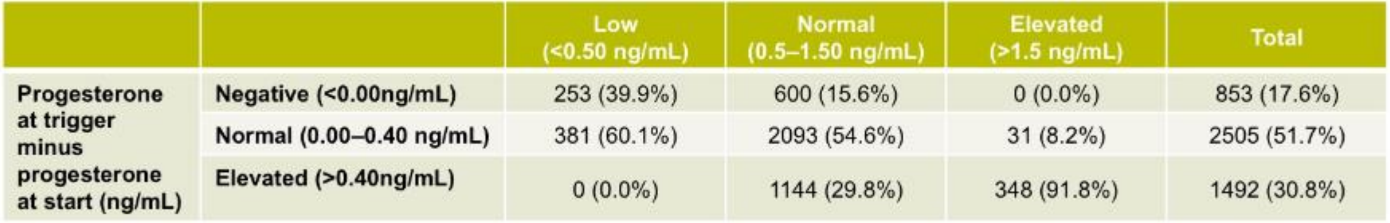
1. Huang CC, et al. Hum Reprod 2012;27:2036–2045.

Days of pre-hCG serum progesterone elevation >1 ng/mL

Monitorização

Diferença da P_4 que afeta o resultado?

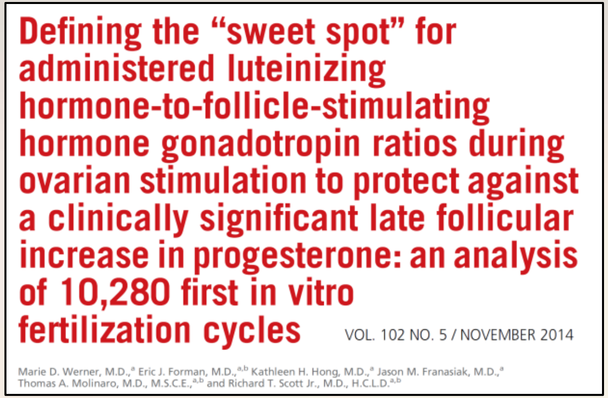




		Low (<0.50 ng/mL)	Normal (0.5–1.50 ng/mL)	Elevated (>1.5 ng/mL)	Total
Progesterone at trigger minus progesterone at start (ng/mL)	**Negative (<0.00ng/mL)**	253 (39.9%)	600 (15.6%)	0 (0.0%)	853 (17.6%)
	Normal (0.00–0.40 ng/mL)	381 (60.1%)	2093 (54.6%)	31 (8.2%)	2505 (51.7%)
	Elevated (>0.40ng/mL)	0 (0.0%)	1144 (29.8%)	348 (91.8%)	1492 (30.8%)

1. Unpublished data; Santos-Ribeiro S, et al. 2018 (under review).

P4 e estímulo ovulatório

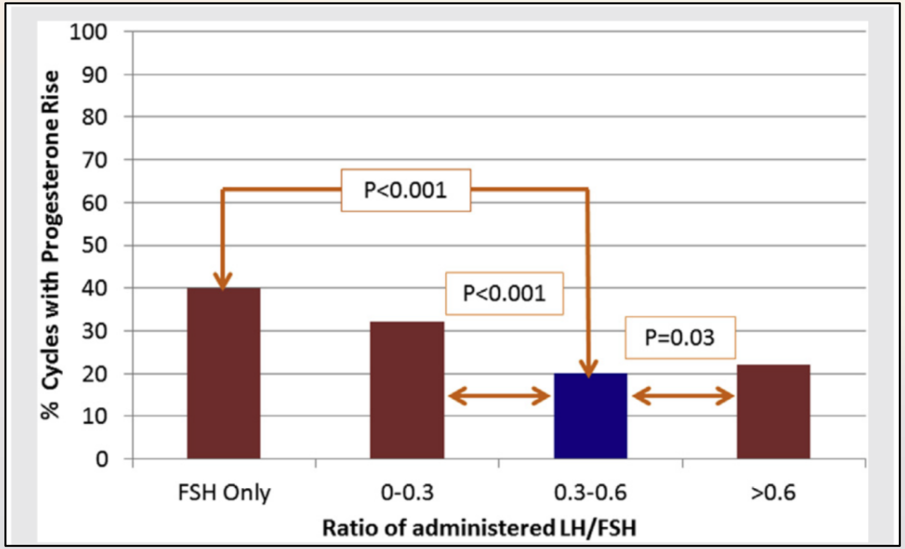


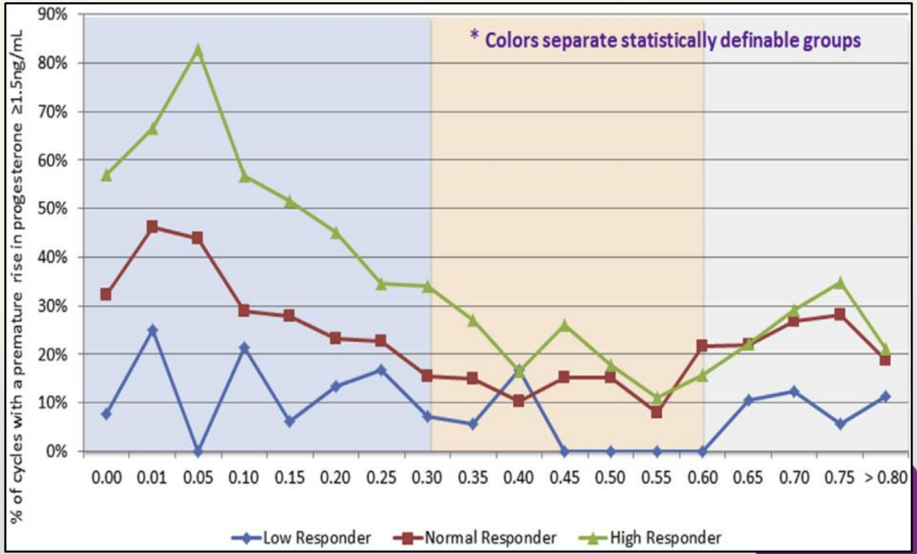
Defining the "sweet spot" for administered luteinizing hormone-to-follicle-stimulating hormone gonadotropin ratios during ovarian stimulation to protect against a clinically significant late follicular increase in progesterone: an analysis of 10,280 first in vitro fertilization cycles

VOL. 102 NO. 5 / NOVEMBER 2014

Marie D. Werner, M.D.,[a] Eric J. Forman, M.D.,[a,b] Kathleen H. Hong, M.D.,[a] Jason M. Franasiak, M.D.,[a]
Thomas A. Molinaro, M.D., M.S.C.E.,[a,b] and Richard T. Scott Jr., M.D., H.C.L.D.[a,b]

Patient(s): 10,280 patients undergoing their first IVF cycle.
Main Outcome Measure(s): The ratio of exogenous LH-to-FSH throughout stimulation and association with absolute serum P level >1.5 ng/mL on the day of hCG administration.



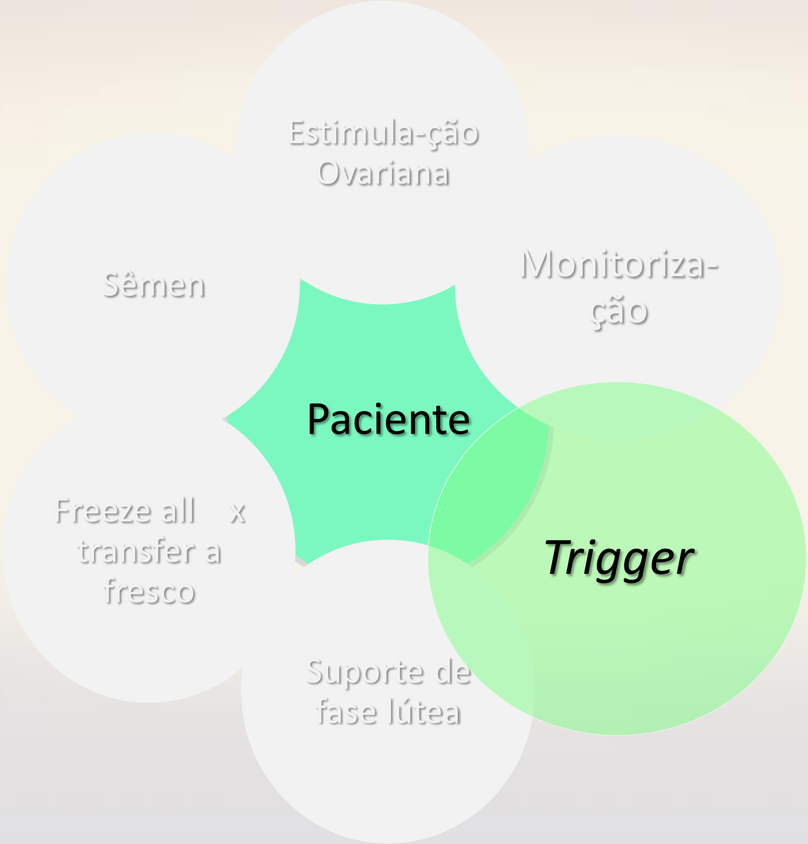


Monitorização

- Quando e quanto ser considerado aumento de P4?
- Valor único ou diferença?
- Valor único ou tempo de exposição?
- Variação conforme o estímulo ovulatório?
- *Freeze all* ??

WELCOME
TO THE REAL WORLD

Sucesso na FIV / ICSI



Estimula-ção Ovariana

Sêmen

Monitoriza-ção

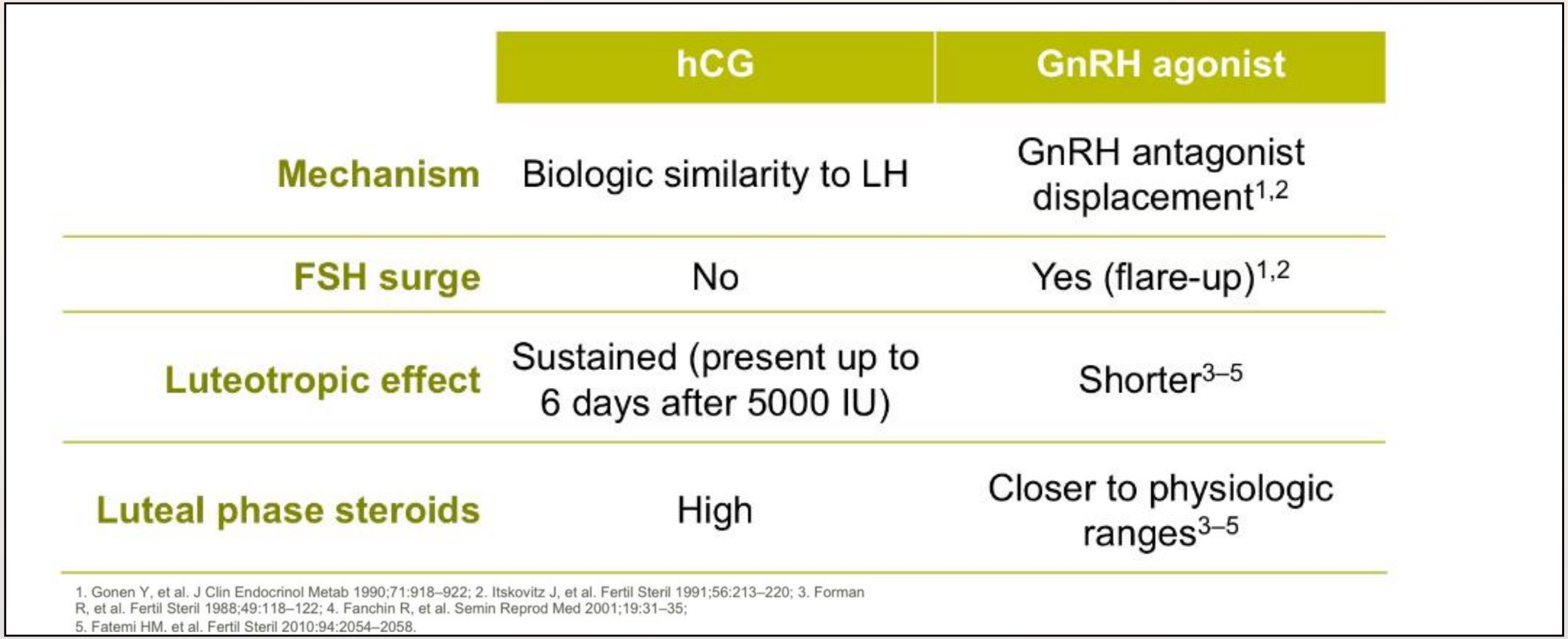
Paciente

Freeze all x transfer a fresco

Trigger

Suporte de fase lútea

Trigger com hCG: *golden standard*



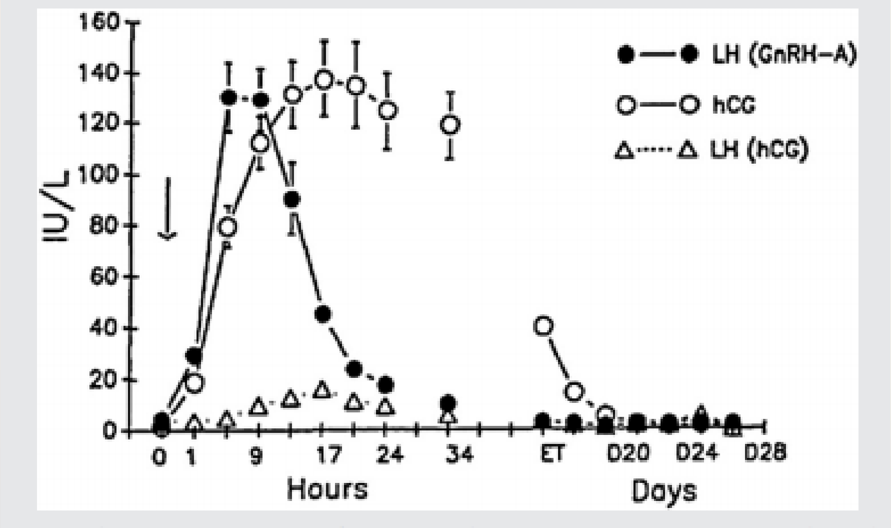
	hCG	GnRH agonist
Mechanism	Biologic similarity to LH	GnRH antagonist displacement[1,2]
FSH surge	No	Yes (flare-up)[1,2]
Luteotropic effect	Sustained (present up to 6 days after 5000 IU)	Shorter[3–5]
Luteal phase steroids	High	Closer to physiologic ranges[3–5]

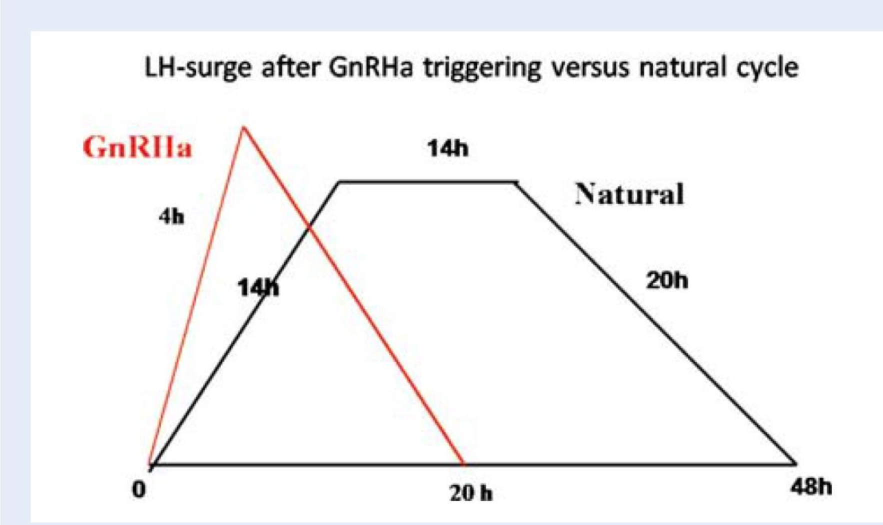
1. Gonen Y, et al. J Clin Endocrinol Metab 1990;71:918–922; 2. Itskovitz J, et al. Fertil Steril 1991;56:213–220; 3. Forman R, et al. Fertil Steril 1988;49:118–122; 4. Fanchin R, et al. Semin Reprod Med 2001;19:31–35;
5. Fatemi HM. et al. Fertil Steril 2010:94:2054–2058.

Trigger

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

LH *vs.* hCG *vs.* GnRH

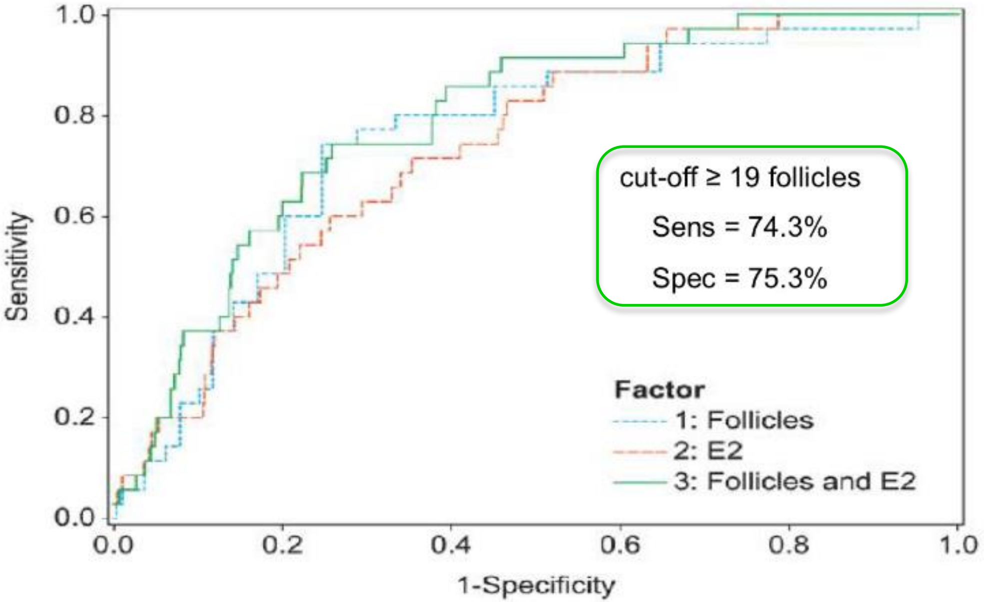



LH-surge after GnRHa triggering versus natural cycle
GnRHa
4h
14h
Natural
14h
20h
0
20 h
48h

Casper R.F., Fertil Steril vol 103, No. 4, April 2015

Trigger - SHEO

No. de folículos ≥ 11 mm no dia do hCG pode predizer SHEO grave



cut-off ≥ 19 follicles

Sens = 74.3%

Spec = 75.3%

- Large combined dataset n=2,433 patients
- GnRH-antagonist protocol
- 35 cases severe OHSS (1.4%)
- Positive predictive value, 4.2 %
- Negative predictive value, 99.5 %

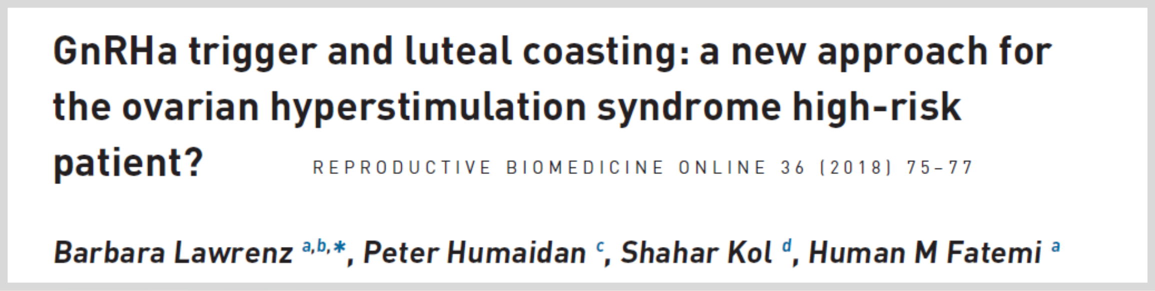
For moderate or severe OHSS, the optimal cut-off point was ≥17 follicles.
Sensitivity=68.9%; Specificity=66.7%; AUC = 0.732; PPV, 6.0%; NPV, 98.6%
1. Griesinger G, PLoS One 2016;11:e0149615

Trigger - GnRH

GnRHa trigger: LH-like luteal - mais fisiológico

- Leuprolide acetate: 1,0 - 2,0 mg
- Triptorelin: 0,1 - 0,2 mg
- Buserelin: 0,5 mg

Trigger - hCG



GnRHa trigger and luteal coasting: a new approach for the ovarian hyperstimulation syndrome high-risk patient?

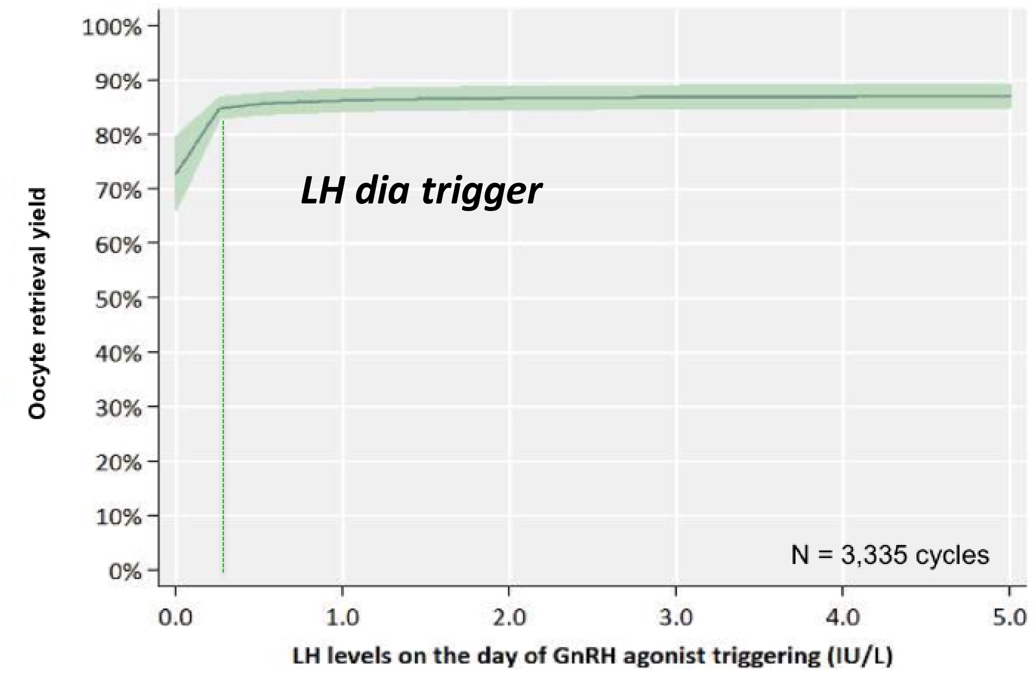
REPRODUCTIVE BIOMEDICINE ONLINE 36 (2018) 75–77

Barbara Lawrenz [a,b,*], Peter Humaidan [c], Shahar Kol [d], Human M Fatemi [a]

- ***Daily monitoring of serum progesterone*** concentrations
- Once progesterone concentrations drop ***below 30 nmol/l (10 ng/mL)***
- Administration of a rescue ***bolus of hCG (1.500 UI)***

Trigger - nível de LH

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



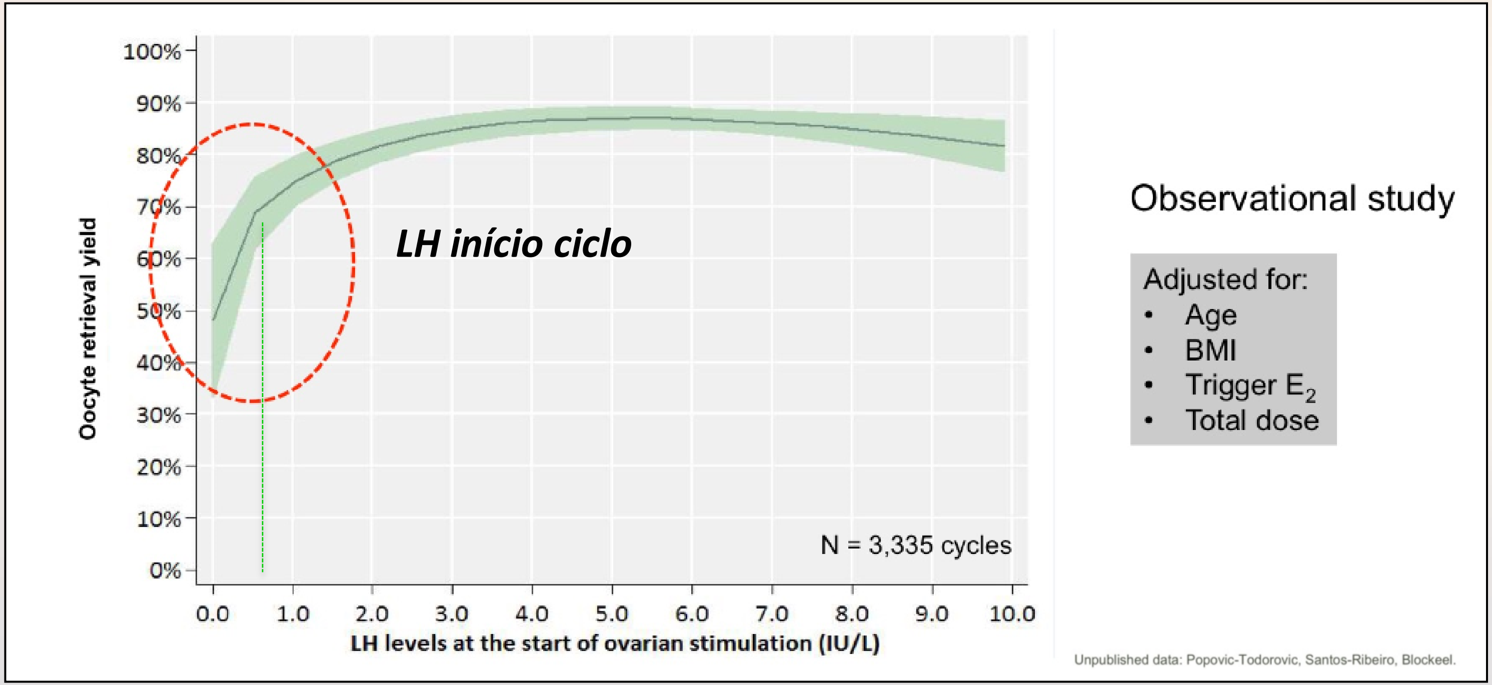
LH dia trigger

Observational study

Adjusted for:
- Age
- BMI
- Trigger E_2
- Total dose

Unpublished data: Popovic-Todorovic, Santos-Ribeiro, Blockeel.

Trigger - nível de LH



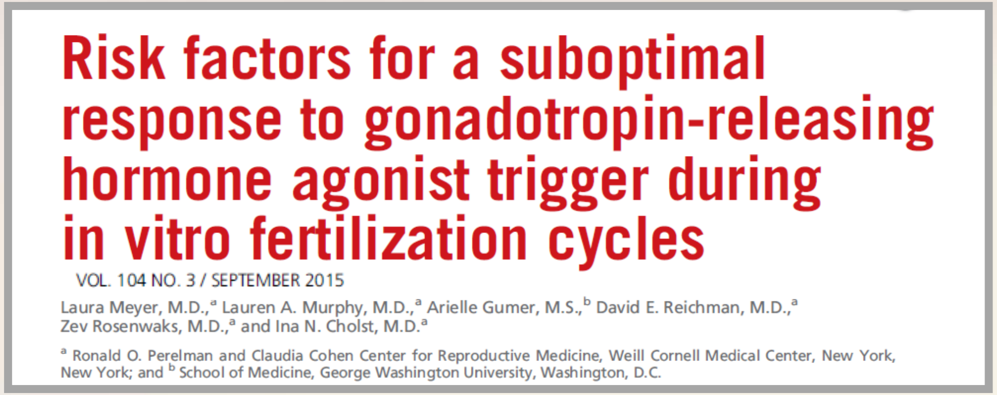
LH início ciclo

Observational study

Adjusted for:
- Age
- BMI
- Trigger E_2
- Total dose

Unpublished data: Popovic-Todorovic, Santos-Ribeiro, Blockeel.

Dual trigger: *resposta inadequada*



Risk factors for a suboptimal response to gonadotropin-releasing hormone agonist trigger during in vitro fertilization cycles

VOL. 104 NO. 3 / SEPTEMBER 2015

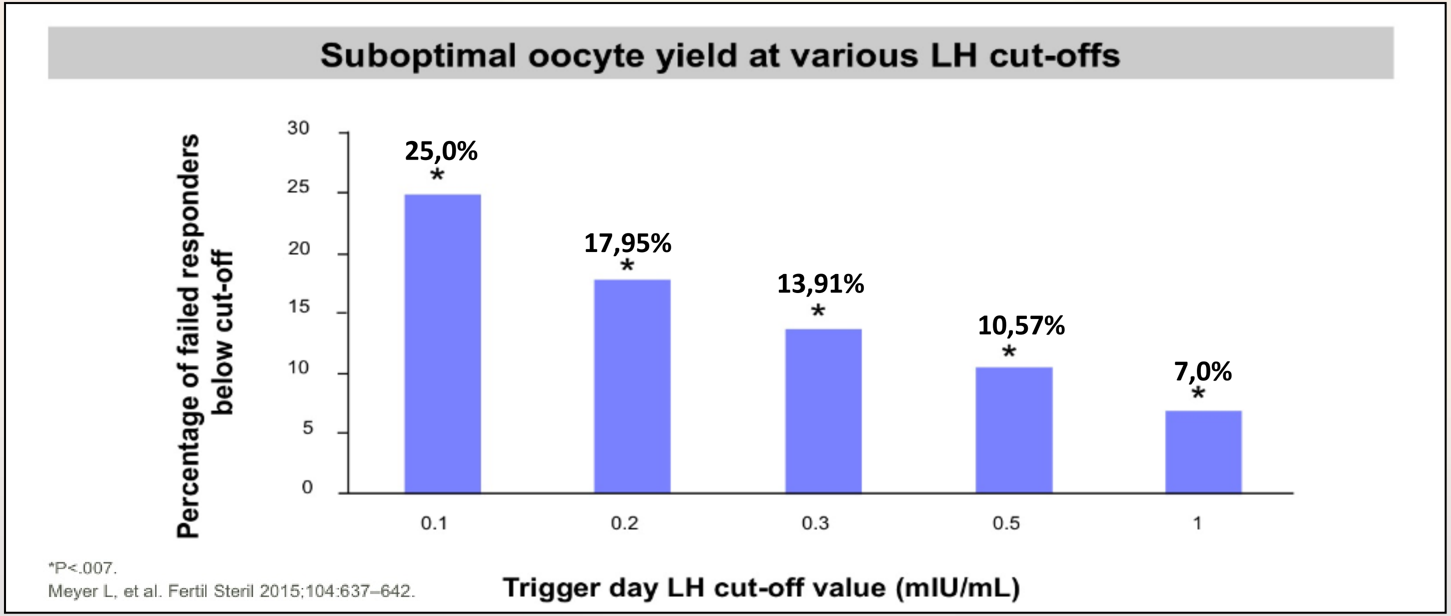
Laura Meyer, M.D.,[a] Lauren A. Murphy, M.D.,[a] Arielle Gumer, M.S.,[b] David E. Reichman, M.D.,[a]
Zev Rosenwaks, M.D.,[a] and Ina N. Cholst, M.D.[a]

[a] Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, Weill Cornell Medical Center, New York, New York; and [b] School of Medicine, George Washington University, Washington, D.C.

- Resposta sub-ótima: LH ≤ 15 mUI/mL 8-12 hs após o GnRH *trigger*
- *Leuprolide 2,0 mg + 1.000-3.000 UI hCG*

Dual trigger: *resposta inadequada*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

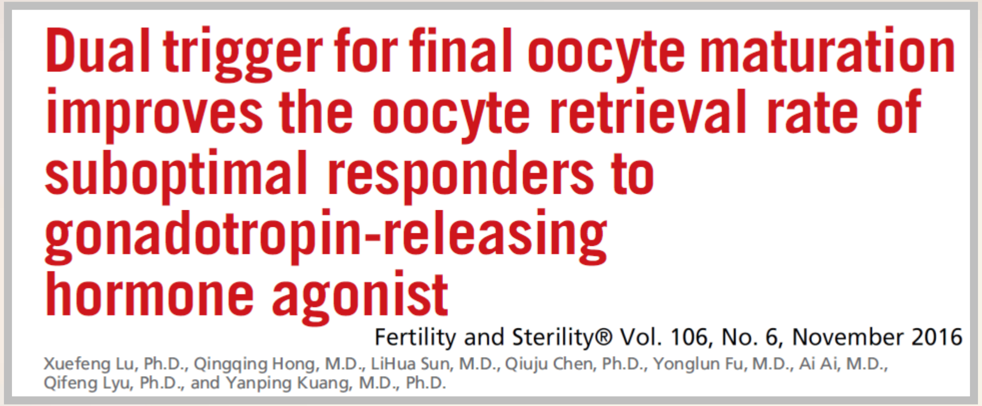


*P<.007.
Meyer L, et al. Fertil Steril 2015;104:637–642.

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

Dual trigger: *resposta inadequada*

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



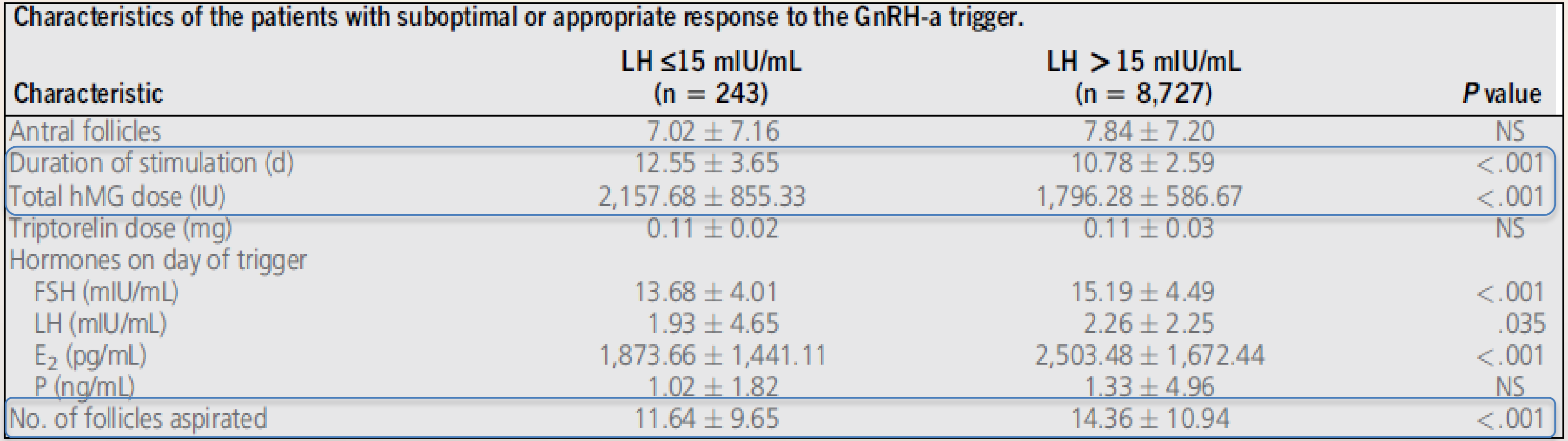
Dual trigger for final oocyte maturation improves the oocyte retrieval rate of suboptimal responders to gonadotropin-releasing hormone agonist

Fertility and Sterility® Vol. 106, No. 6, November 2016

Xuefeng Lu, Ph.D., Qingqing Hong, M.D., LiHua Sun, M.D., Qiuju Chen, Ph.D., Yonglun Fu, M.D., Ai Ai, M.D.,
Qifeng Lyu, Ph.D., and Yanping Kuang, M.D., Ph.D.

- Resposta sub-ótima: LH ≤ 15 mUI/mL ~ 10 hs após o GnRH *trigger*
- *Triptorrelina 0,1 mg + 1.000-5.000 UI hCG*

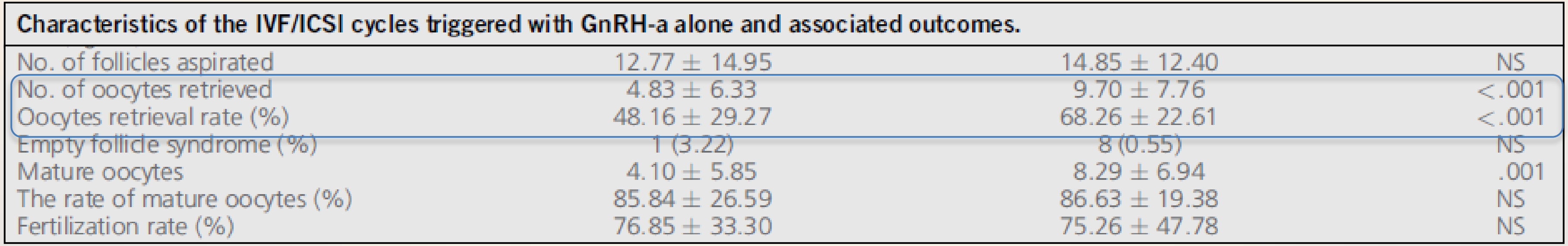
Dual trigger: *resposta inadequada*



Characteristics of the patients with suboptimal or appropriate response to the GnRH-a trigger.

Characteristic	LH ≤15 mIU/mL (n = 243)	LH >15 mIU/mL (n = 8,727)	*P* value
Antral follicles	7.02 ± 7.16	7.84 ± 7.20	NS
Duration of stimulation (d)	12.55 ± 3.65	10.78 ± 2.59	<.001
Total hMG dose (IU)	2,157.68 ± 855.33	1,796.28 ± 586.67	<.001
Triptorelin dose (mg)	0.11 ± 0.02	0.11 ± 0.03	NS
Hormones on day of trigger			
FSH (mIU/mL)	13.68 ± 4.01	15.19 ± 4.49	<.001
LH (mIU/mL)	1.93 ± 4.65	2.26 ± 2.25	.035
E_2 (pg/mL)	1,873.66 ± 1,441.11	2,503.48 ± 1,672.44	<.001
P (ng/mL)	1.02 ± 1.82	1.33 ± 4.96	NS
No. of follicles aspirated	11.64 ± 9.65	14.36 ± 10.94	<.001

Dual trigger: *resposta inadequada*

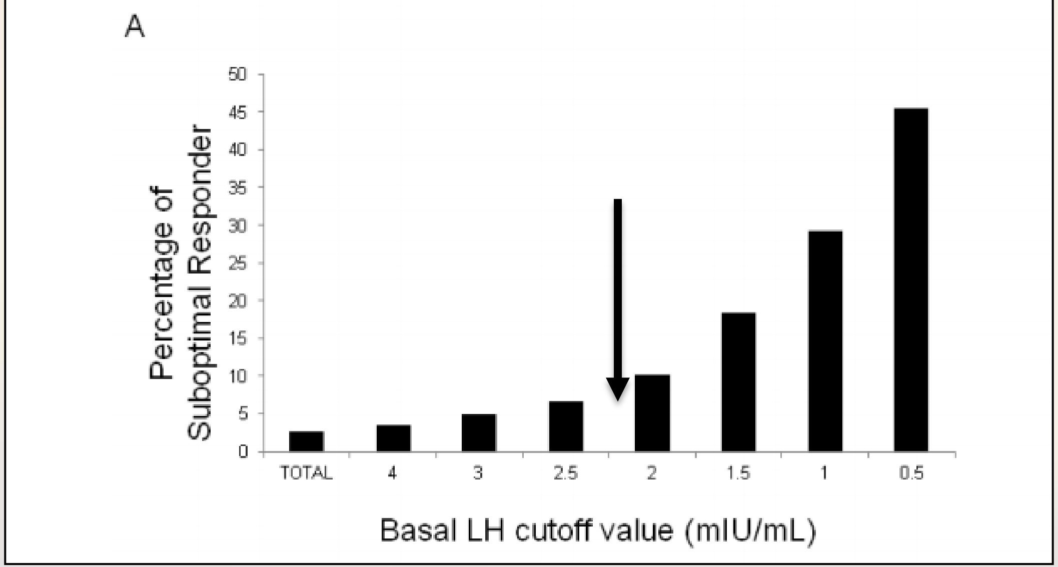


Characteristics of the IVF/ICSI cycles triggered with GnRH-a alone and associated outcomes.

No. of follicles aspirated	12.77 ± 14.95	14.85 ± 12.40	NS
No. of oocytes retrieved	4.83 ± 6.33	9.70 ± 7.76	<.001
Oocytes retrieval rate (%)	48.16 ± 29.27	68.26 ± 22.61	<.001
Empty follicle syndrome (%)	1 (3.22)	8 (0.55)	NS
Mature oocytes	4.10 ± 5.85	8.29 ± 6.94	.001
The rate of mature oocytes (%)	85.84 ± 26.59	86.63 ± 19.38	NS
Fertilization rate (%)	76.85 ± 33.30	75.26 ± 47.78	NS

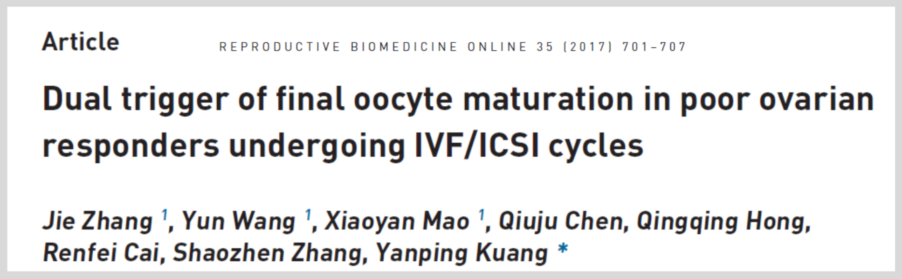
Dual trigger: *resposta inadequada*

Fertility and Sterility® Vol. 106, No. 6, November 2016



A lower basal LH level ***(LH < 2.27 mIU/mL)*** is a useful predictor of a suboptimal response to GnRH-a trigger.

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*

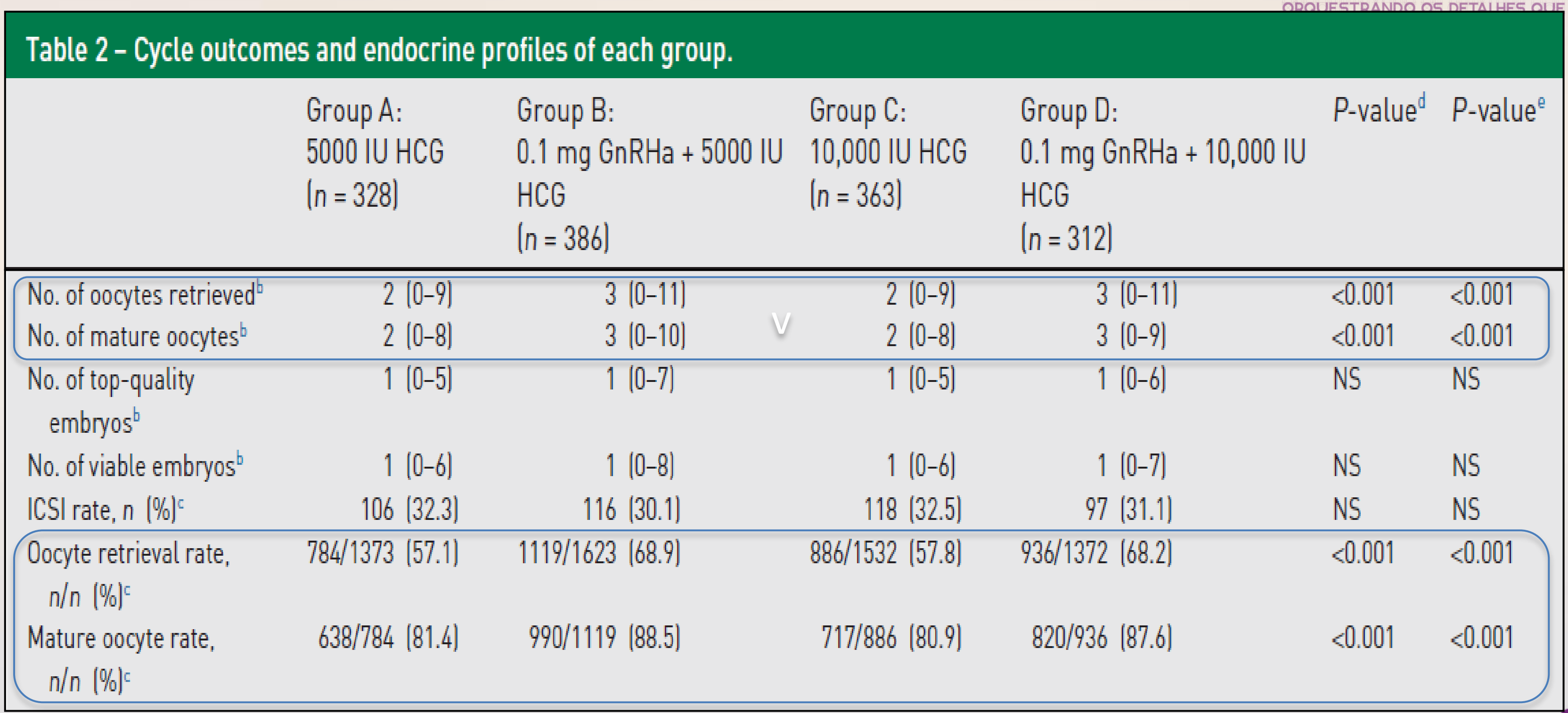
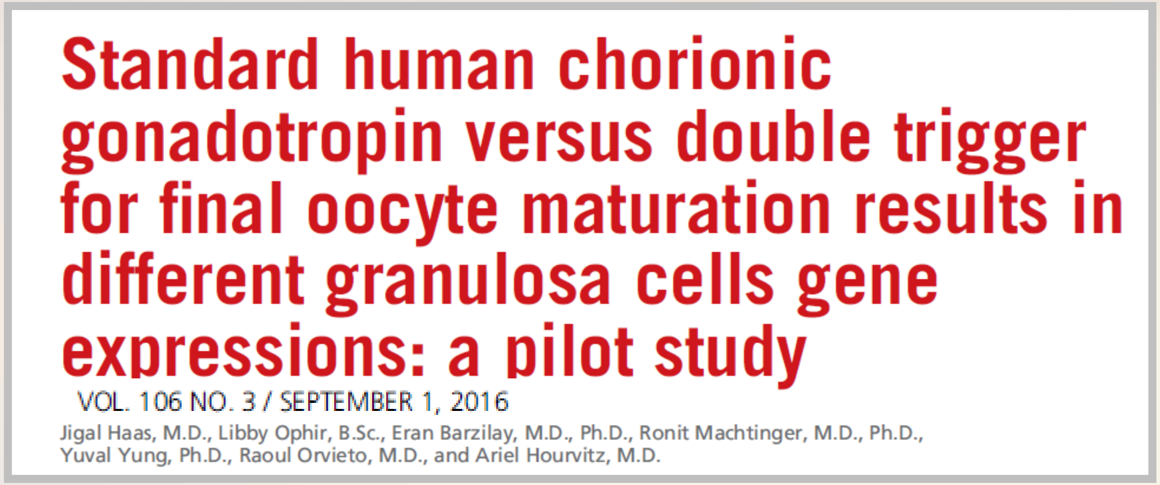


Table 2 – Cycle outcomes and endocrine profiles of each group.

	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 = 312)	P-value[d]	P-value[e]
No. of oocytes retrieved[b]	2 (0–9)	3 (0–11)	2 (0–9)	3 (0–11)	<0.001	<0.001
No. of mature oocytes[b]	2 (0–8)	3 (0–10)	2 (0–8)	3 (0–9)	<0.001	<0.001
No. of top-quality embryos[b]	1 (0–5)	1 (0–7)	1 (0–5)	1 (0–6)	NS	NS
No. of viable embryos[b]	1 (0–6)	1 (0–8)	1 (0–6)	1 (0–7)	NS	NS
ICSI rate, n (%)[c]	106 (32.3)	116 (30.1)	118 (32.5)	97 (31.1)	NS	NS
Oocyte retrieval rate, n/n (%)[c]	784/1373 (57.1)	1119/1623 (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).

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.***

Considerações no uso do *GnRH trigger*

Cuidados para uma recuperação oocitária inadequada

- ***Fatores de risco:***

- Mulheres magras e com longo tempo de uso ACO
- Mulheres com ciclos menstruais irregulares
- Estimulações longas, com altas doses de Gns
- LH quase indetectável no início do ciclo
- Valores baixos de LH no dia do trigger

Considerações no uso do *GnRH trigger*

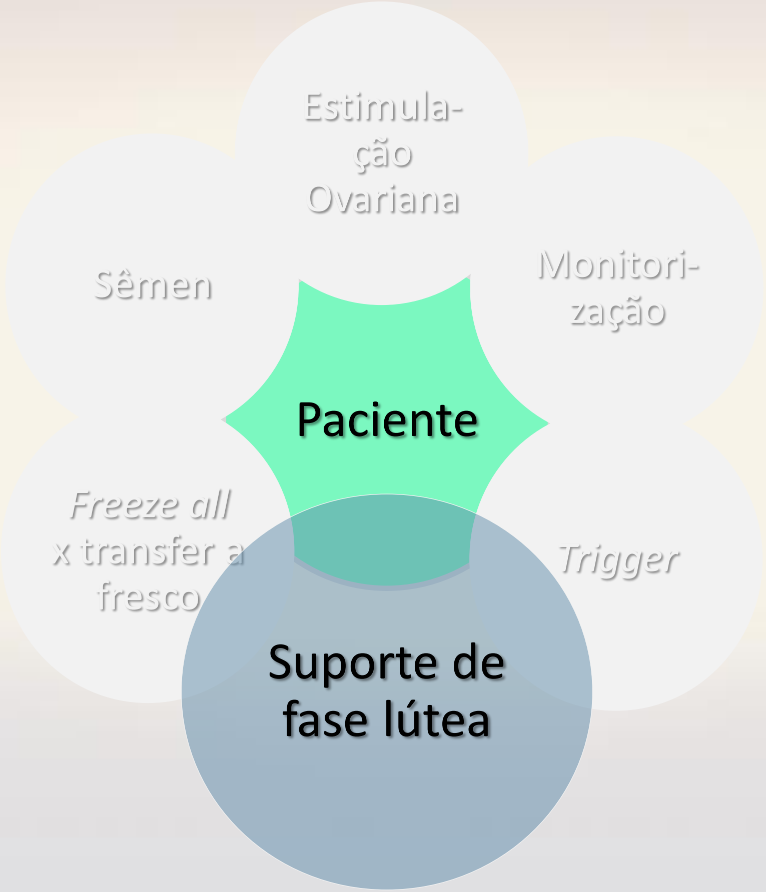
Diferentes abordagens

- ***Hiperestímulo:*** GnRH trigger + *freeze all*
- ***Pobre resposta ou resposta inadequada:*** *dual trigger*
- ***Resposta adequada e trigger com GnRH:*** suporte modificado de fase lútea

Sucesso na FIV / ICSI

FERTILITY TALKS

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Estimulação Ovariana

Monitorização

Trigger

Suporte de fase lútea

Freeze all x transfer a fresco

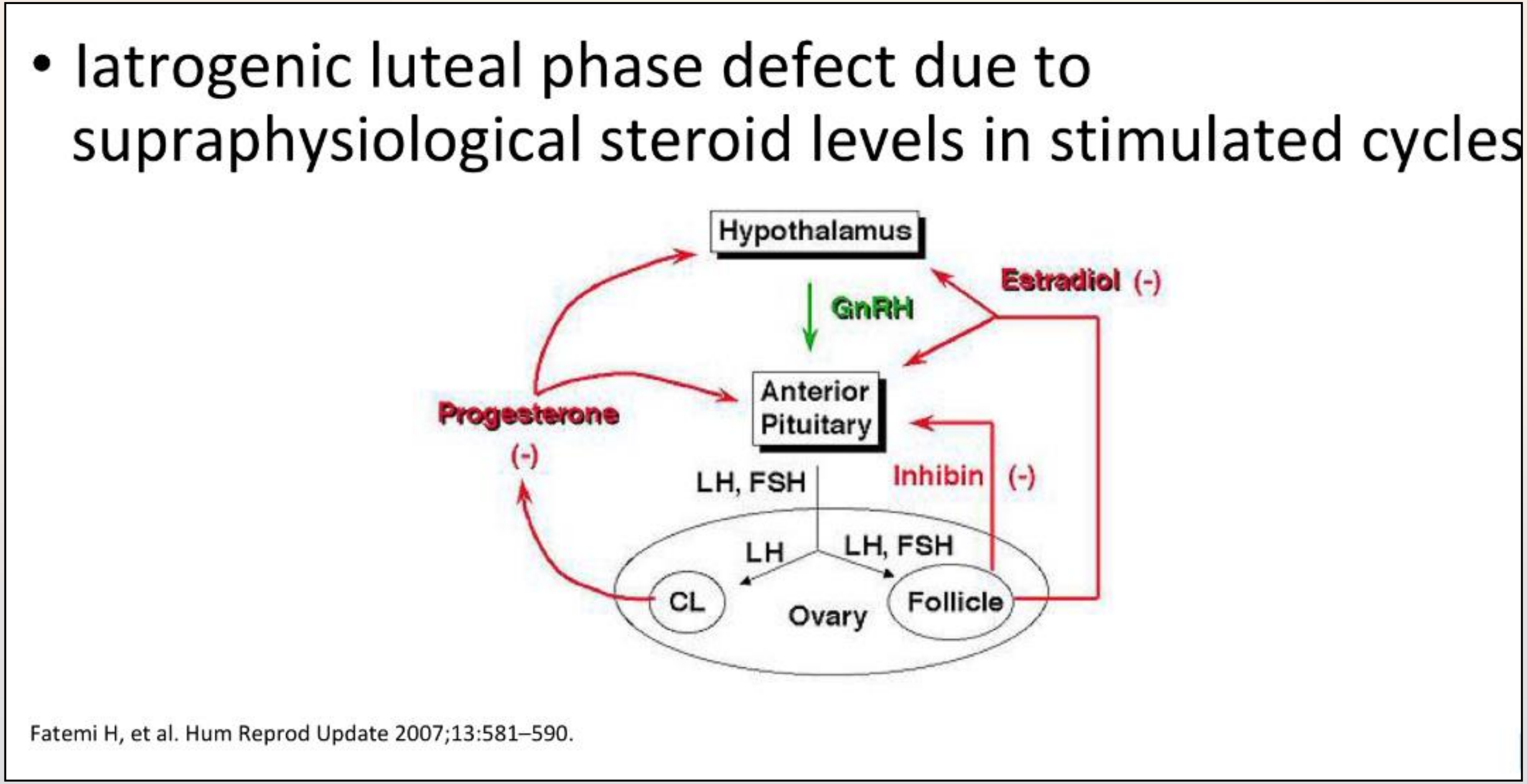
Sêmen

Paciente

MERCK

Suporte da Fase Lútea

Papel da PROGESTERONA



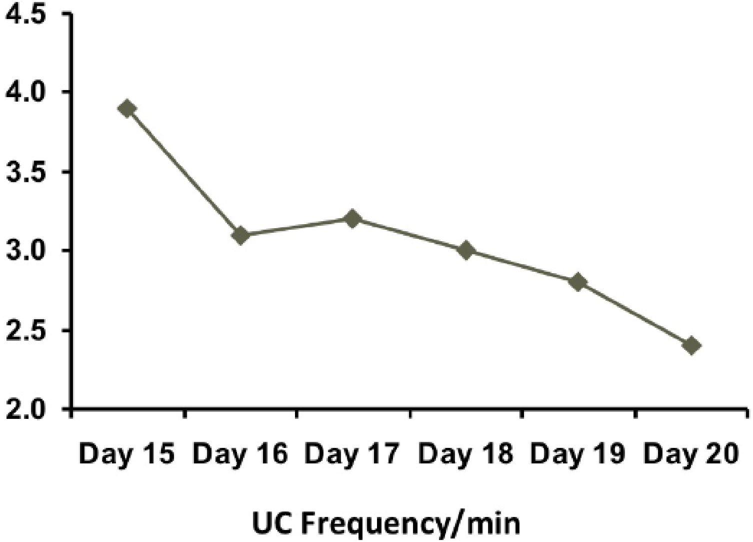
- Iatrogenic luteal phase defect due to supraphysiological steroid levels in stimulated cycles

Hypothalamus
GnRH
Estradiol (-)
Anterior Pituitary
Progesterone (-)
Inhibin (-)
LH, FSH
LH
LH, FSH
CL
Ovary
Follicle

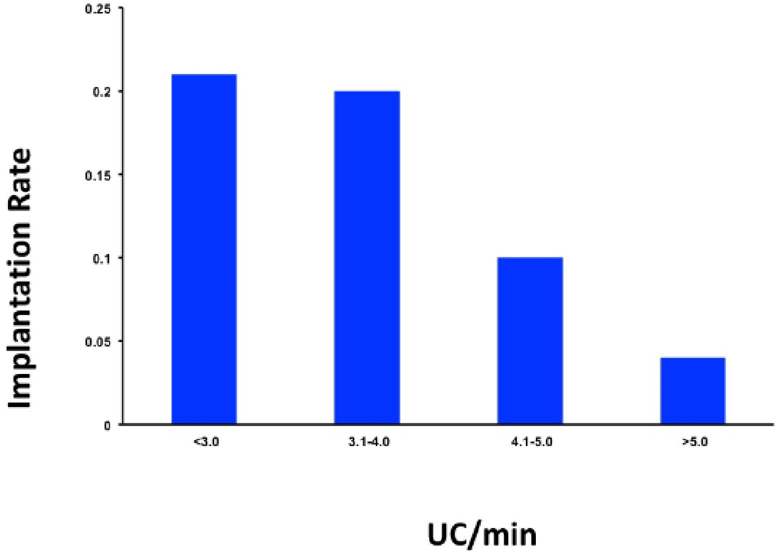
Fatemi H, et al. Hum Reprod Update 2007;13:581–590.

Suporte da Fase Lútea

Papel da PROGESTERONA



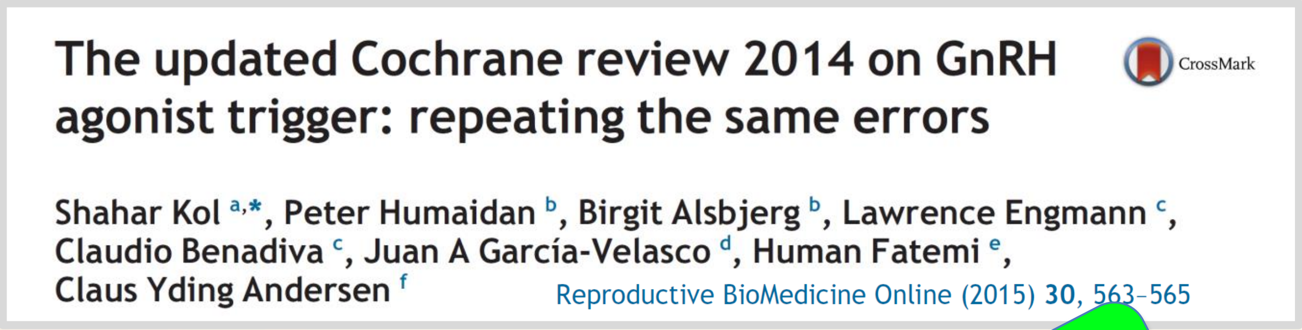
(De Ziegler et al, 1996)



(Fanchin R, et al. Hum Reprod 1998;13:1968-1974)

Suporte da Fase Lútea

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



The updated Cochrane review 2014 on GnRH agonist trigger: repeating the same errors

Shahar Kol [a,*], Peter Humaidan [b], Birgit Alsbjerg [b], Lawrence Engmann [c], Claudio Benadiva [c], Juan A García-Velasco [d], Human Fatemi [e], Claus Yding Andersen [f]

Reproductive BioMedicine Online (2015) **30**, 563–565

Suportes de fase lútea
NÃO comparáveis!!!!

- Cochrane 2010 and 2014: *GnRH agonist t* m detrimento as taxas de bebes nascidos
- Modificação no sup fase lúlea é mandatório para a manutenção de ansferência de embrião a fresco

Suporte da Fase Lútea

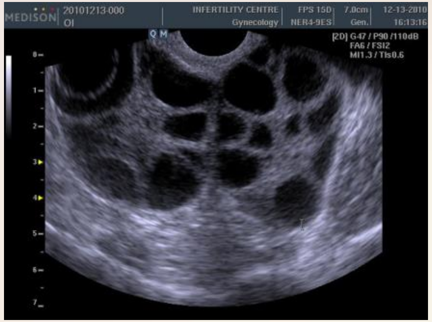
Trigger com agonista GnRH em ciclos de antagonistas necessita especial atenção no suporte da fase lútea

Bolus HCG OPU-day

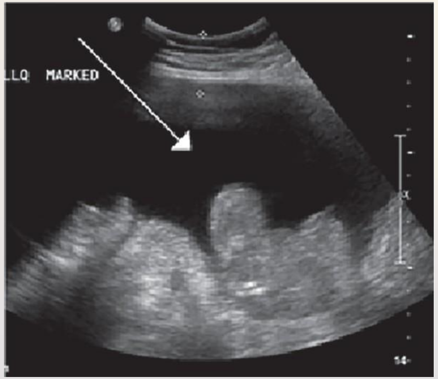
Intense Progesterone-Estradiol Luteal support

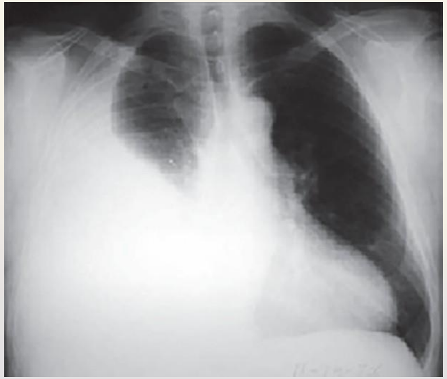
- *hCG : 1.500 IU no dia da punção dos ovócitos*
- *E_2 oral ou transdérmico: (200 mcg E_2 trans / 4 mg oral) +
PROG vaginal (600 – 800 mg/dia) iniciados no dia da punção ovócitos*

Suporte da Fase Lútea


MEDISON
20101213-000
OI
INFERTILITY CENTRE
Gynecology
FPS 15D
NER4-9ES
7.0cm
Gen.
12-13-2010
16:13:16
Q M
[2D] G47 / P90 /110dB
FA6 / FSI2
MI1.3 / TIs0.6

- *Suporte modificado de fase lútea não elimina o risco de SHEO*

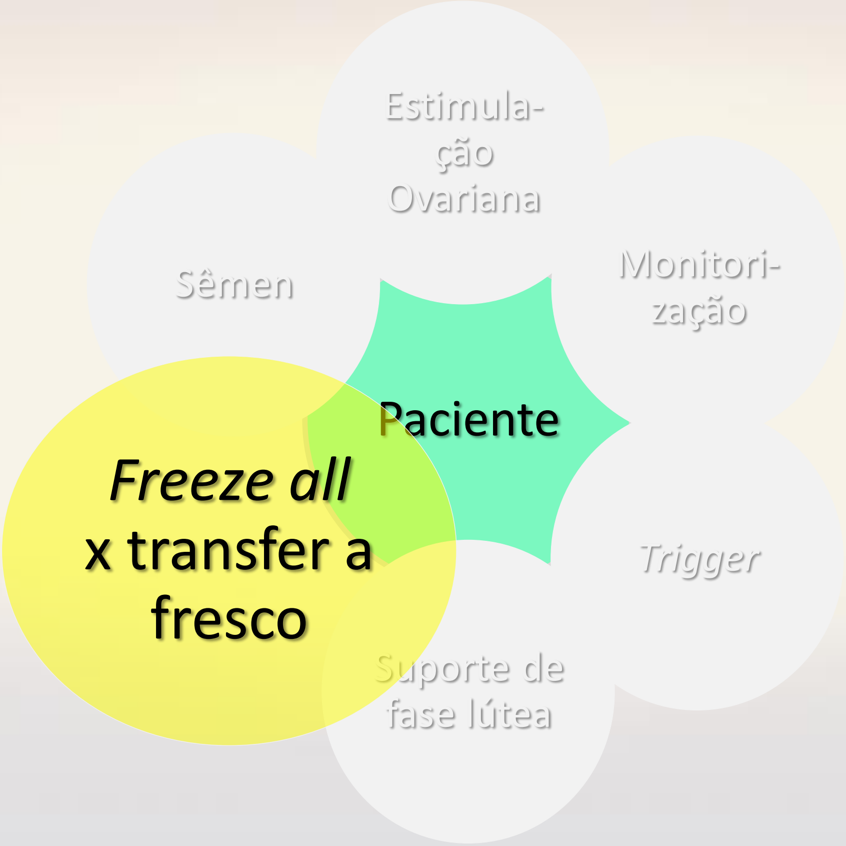




- *SHEO tardio: gestação múltipla*

1. Devroey P, et al. Hum Reprod 2011;26:2593–2597; 2.Fatemi H, et al. Fertil Steril 2014;101:1008–1011.

Sucesso na FIV / ICSI



Estimulação Ovariana

Monitorização

Trigger

Suporte de fase lútea

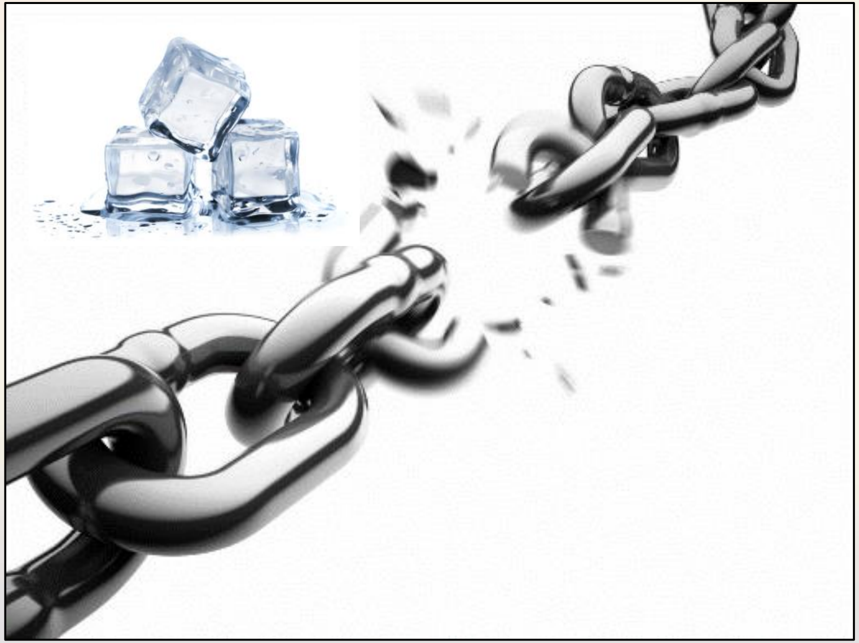
Sêmen

Paciente

Freeze all x transfer a fresco

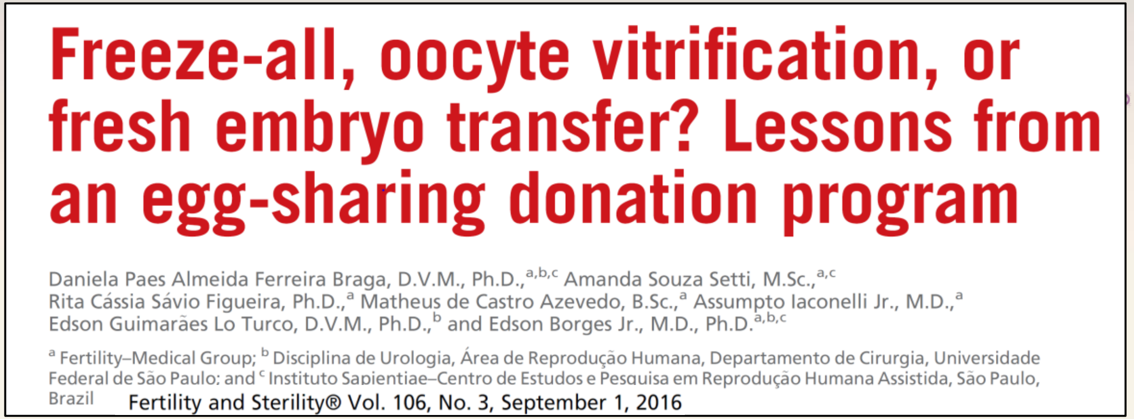
Freeze all

Estimulação ovariana



Transferência embrionária

Freeze all

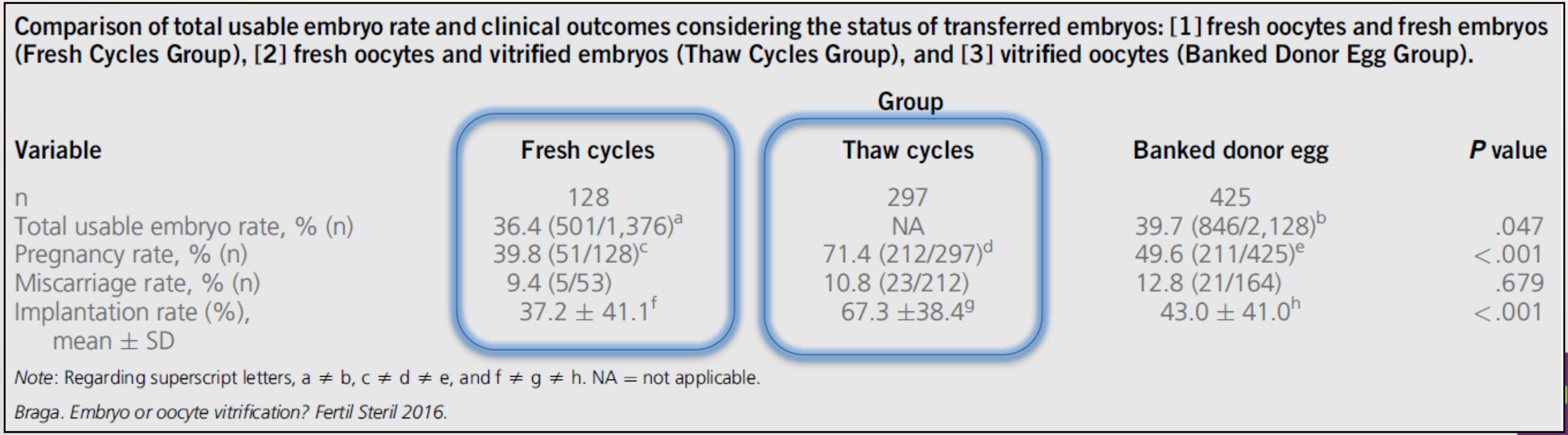


Freeze-all, oocyte vitrification, or fresh embryo transfer? Lessons from an egg-sharing donation program

Daniela Paes Almeida Ferreira Braga, D.V.M., Ph.D.,[a,b,c] Amanda Souza Setti, M.Sc.,[a,c]
Rita Cássia Sávio Figueira, Ph.D.,[a] Matheus de Castro Azevedo, B.Sc.,[a] Assumpto Iaconelli Jr., M.D.,[a]
Edson Guimarães Lo Turco, D.V.M., Ph.D.,[b] and Edson Borges Jr., M.D., Ph.D.[a,b,c]

[a] Fertility–Medical Group; [b] Disciplina de Urologia, Área de Reprodução Humana, Departamento de Cirurgia, Universidade Federal de São Paulo; and [c] Instituto Sapientiae–Centro de Estudos e Pesquisa em Reprodução Humana Assistida, São Paulo, Brazil

Fertility and Sterility® Vol. 106, No. 3, September 1, 2016



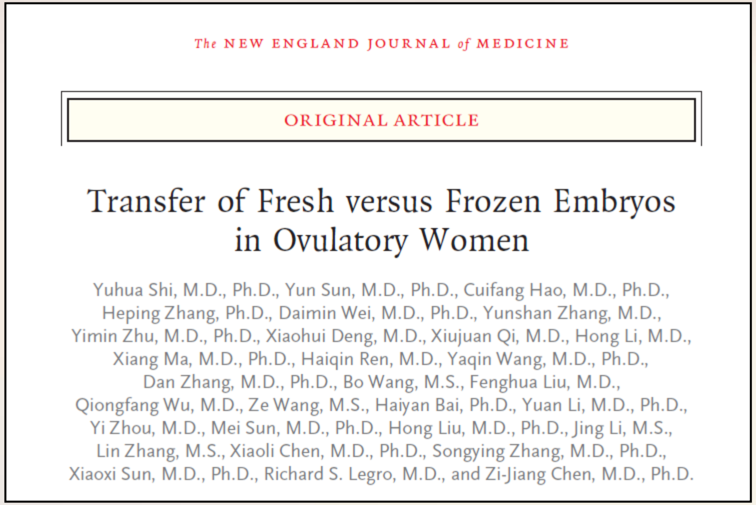
Comparison of total usable embryo rate and clinical outcomes considering the status of transferred embryos: [1] fresh oocytes and fresh embryos (Fresh Cycles Group), [2] fresh oocytes and vitrified embryos (Thaw Cycles Group), and [3] vitrified oocytes (Banked Donor Egg Group).

	Group			
Variable	**Fresh cycles**	**Thaw cycles**	**Banked donor egg**	***P* value**
n	128	297	425	
Total usable embryo rate, % (n)	36.4 (501/1,376)[a]	NA	39.7 (846/2,128)[b]	.047
Pregnancy rate, % (n)	39.8 (51/128)[c]	71.4 (212/297)[d]	49.6 (211/425)[e]	<.001
Miscarriage rate, % (n)	9.4 (5/53)	10.8 (23/212)	12.8 (21/164)	.679
Implantation rate (%), mean ± SD	37.2 ± 41.1[f]	67.3 ±38.4[g]	43.0 ± 41.0[h]	<.001

Note: Regarding superscript letters, a ≠ b, c ≠ d ≠ e, and f ≠ g ≠ h. NA = not applicable.

Braga. Embryo or oocyte vitrification? Fertil Steril 2016.

Freeze all



The NEW ENGLAND JOURNAL of MEDICINE

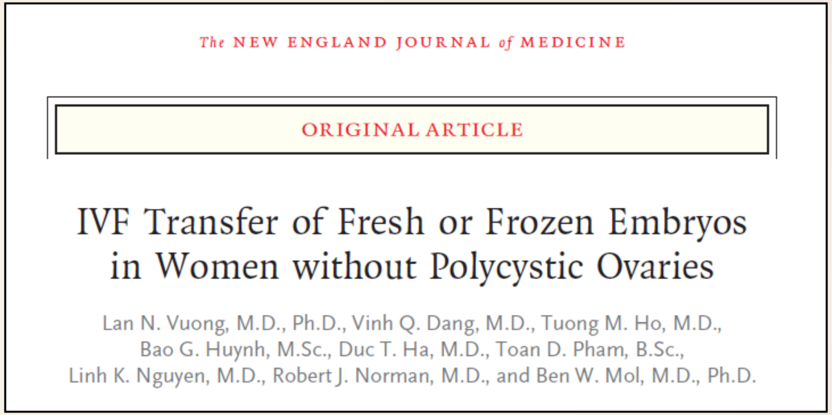
ORIGINAL ARTICLE

Transfer of Fresh versus Frozen Embryos in Ovulatory Women

Yuhua Shi, M.D., Ph.D., Yun Sun, M.D., Ph.D., Cuifang Hao, M.D., Ph.D.,
Heping Zhang, Ph.D., Daimin Wei, M.D., Ph.D., Yunshan Zhang, M.D.,
Yimin Zhu, M.D., Ph.D., Xiaohui Deng, M.D., Xiujuan Qi, M.D., Hong Li, M.D.,
Xiang Ma, M.D., Ph.D., Haiqin Ren, M.D., Yaqin Wang, M.D., Ph.D.,
Dan Zhang, M.D., Ph.D., Bo Wang, M.S., Fenghua Liu, M.D.,
Qiongfang Wu, M.D., Ze Wang, M.S., Haiyan Bai, Ph.D., Yuan Li, M.D., Ph.D.,
Yi Zhou, M.D., Mei Sun, M.D., Ph.D., Hong Liu, M.D., Ph.D., Jing Li, M.S.,
Lin Zhang, M.S., Xiaoli Chen, M.D., Ph.D., Songying Zhang, M.D., Ph.D.,
Xiaoxi Sun, M.D., Ph.D., Richard S. Legro, M.D., and Zi-Jiang Chen, M.D., Ph.D.

n engl j med 378;2 nejm.org January 11, 2018

The live-birth rate did not differ significantly between fresh-embryo transfer and frozen-embryo transfer among ovulatory women



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries

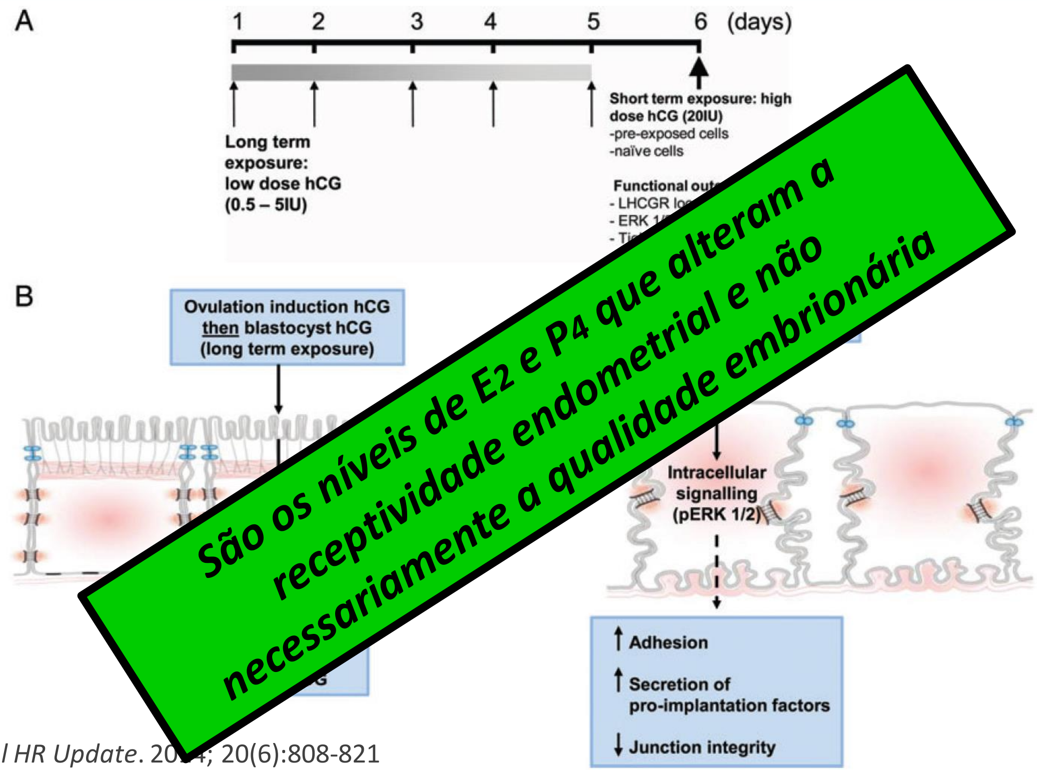
Lan N. Vuong, M.D., Ph.D., Vinh Q. Dang, M.D., Tuong M. Ho, M.D.,
Bao G. Huynh, M.Sc., Duc T. Ha, M.D., Toan D. Pham, B.Sc.,
Linh K. Nguyen, M.D., Robert J. Norman, M.D., and Ben W. Mol, M.D., Ph.D.

n engl j med 378;2 nejm.org January 11, 2018

Transfer of frozen embryos did not result in significantly higher rates of ongoing pregnancy or live birth than the transfer of fresh embryos, among women without PO.

Freeze all

FERTILITY TALKS
QUE FAZEM A DIFERENÇA.


A
1
2
3
4
5
6
(days)
Long term exposure: low dose hCG (0.5 – 5IU)
Short term exposure: high dose hCG (20IU)
-pre-exposed cells
-naïve cells
Functional out
- LHCGR lo
- ERK 1/
- Ti
B
Ovulation induction hCG then blastocyst hCG (long term exposure)
Intracellular signalling (pERK 1/2)
Adhesion
Secretion of pro-implantation factors
Junction integrity
G

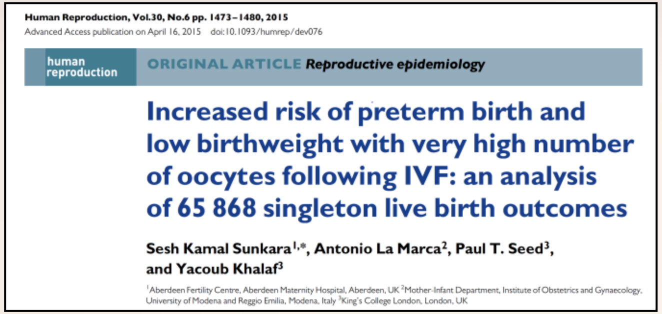
São os níveis de E_2 e P_4 que alteram a receptividade endometrial e não necessariamente a qualidade embrionária

Evans J, *et al HR Update*. 20[illegible]4; 20(6):808-821

MERCK

Freeze all

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Human Reproduction, Vol.30, No.6 pp. 1473–1480, 2015
Advanced Access publication on April 16, 2015 doi:10.1093/humrep/dev076

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes

Sesh Kamal Sunkara[1,*], Antonio La Marca[2], Paul T. Seed[3], and Yacoub Khalaf[3]

[1]Aberdeen Fertility Centre, Aberdeen Maternity Hospital, Aberdeen, UK [2]Mother-Infant Department, Institute of Obstetrics and Gynaecology, University of Modena and Reggio Emilia, Modena, Italy [3]King's College London, London, UK

- **Ciclos com transferência de embriões**
  “a fresco”
- Número de ovócitos recupe
  10 – 15 ovócitos
- Piores resultados obstétricos e perinatais

Conclusão

Aumento da morbidade neonatal consequente a níveis supra-fisiológicos hormonais

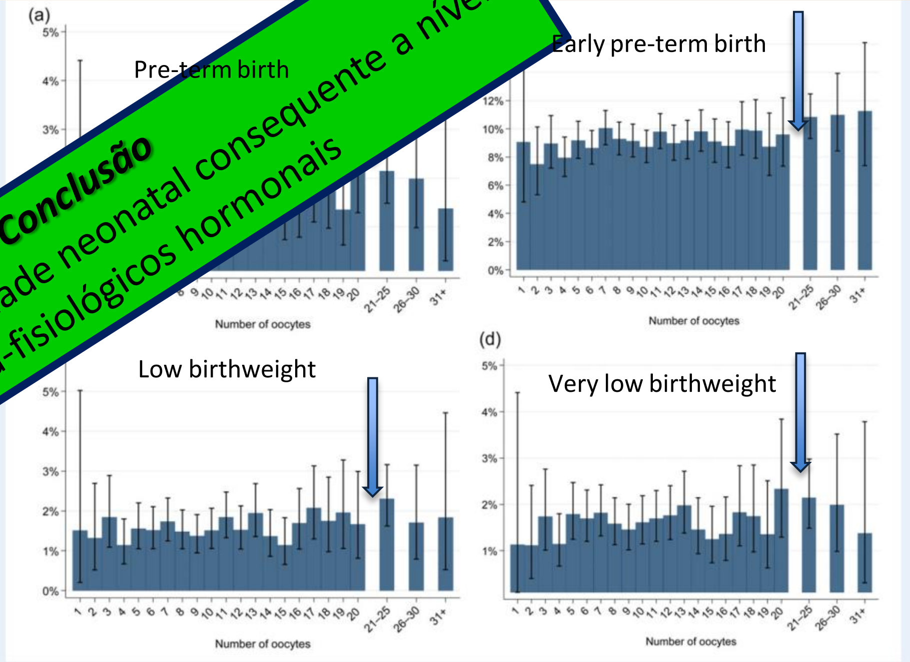
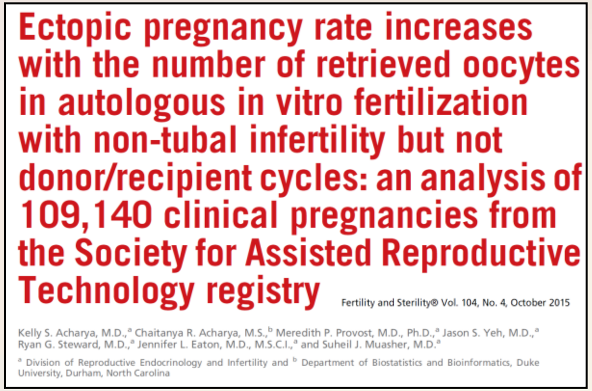


Figure 3 Association between oocyte number and adverse obstetric outcomes. (**a**) Pre-term birth. (**b**) Early preterm birth (**c**) Low birthweight (**d**) Very low birthweight.

Freeze all



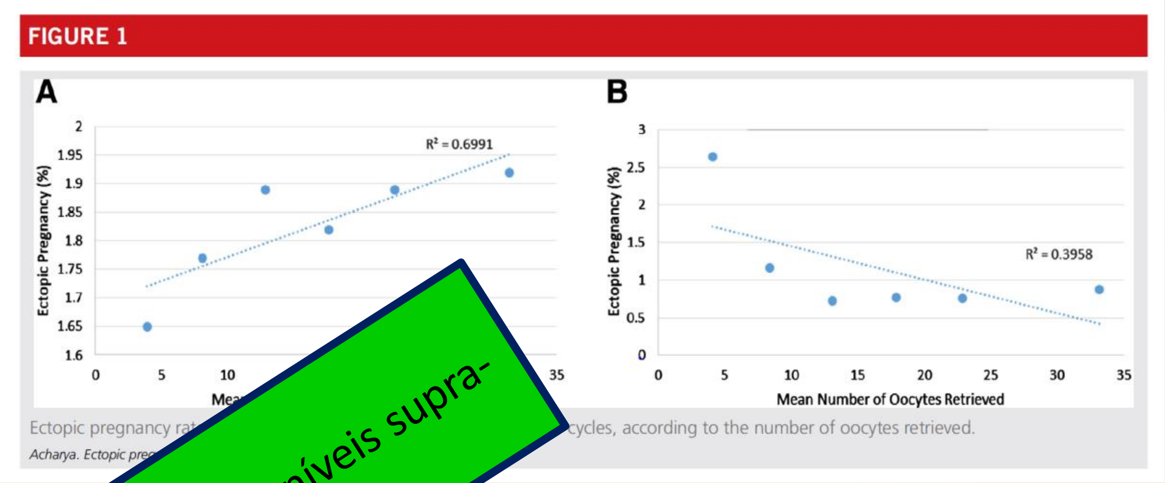
Ectopic pregnancy rate increases with the number of retrieved oocytes in autologous in vitro fertilization with non-tubal infertility but not donor/recipient cycles: an analysis of 109,140 clinical pregnancies from the Society for Assisted Reproductive Technology registry

Fertility and Sterility® Vol. 104, No. 4, October 2015

Kelly S. Acharya, M.D.,[a] Chaitanya R. Acharya, M.S.,[b] Meredith P. Provost, M.D., Ph.D.,[a] Jason S. Yeh, M.D.,[a] Ryan G. Steward, M.D.,[a] Jennifer L. Eaton, M.D., M.S.C.I.,[a] and Suheil J. Muasher, M.D.[a]

[a] Division of Reproductive Endocrinology and Infertility and [b] Department of Biostatistics and Bioinformatics, Duke University, Durham, North Carolina

FIGURE 1



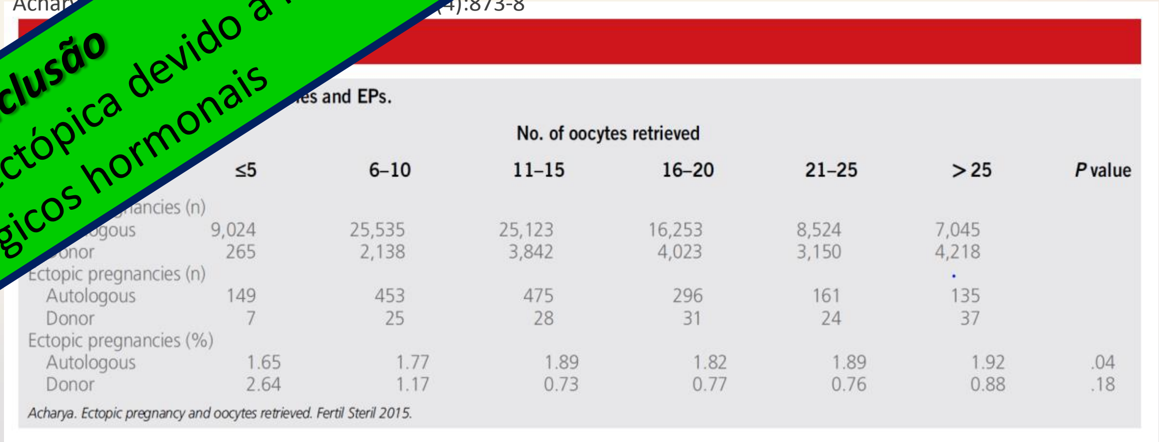
Ectopic pregnancy rat … cycles, according to the number of oocytes retrieved.

Acharya. Ectopic preg

Achar … (4):873-8

Conclusão

Aumento da gestação ectópica devido a níveis supra-fisiológicos hormonais

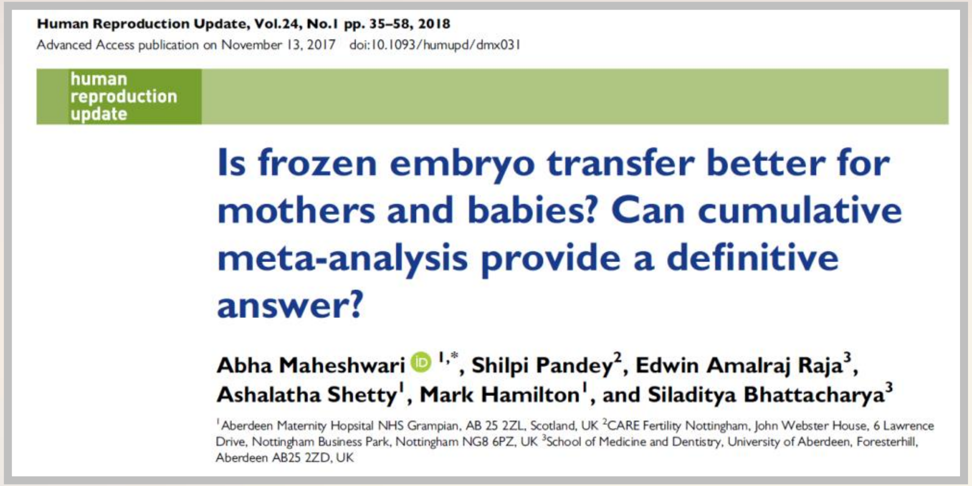


es and EPs.

	No. of oocytes retrieved						
	≤5	6–10	11–15	16–20	21–25	> 25	*P* value
ancies (n)							
ogous	9,024	25,535	25,123	16,253	8,524	7,045	
onor	265	2,138	3,842	4,023	3,150	4,218	
Ectopic pregnancies (n)							
Autologous	149	453	475	296	161	135	
Donor	7	25	28	31	24	37	
Ectopic pregnancies (%)							
Autologous	1.65	1.77	1.89	1.82	1.89	1.92	.04
Donor	2.64	1.17	0.73	0.77	0.76	0.88	.18

Acharya. Ectopic pregnancy and oocytes retrieved. Fertil Steril 2015.

Freeze all



Human Reproduction Update, Vol.24, No.1 pp. 35–58, 2018
Advanced Access publication on November 13, 2017 doi:10.1093/humupd/dmx031

human
reproduction
update

Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer?

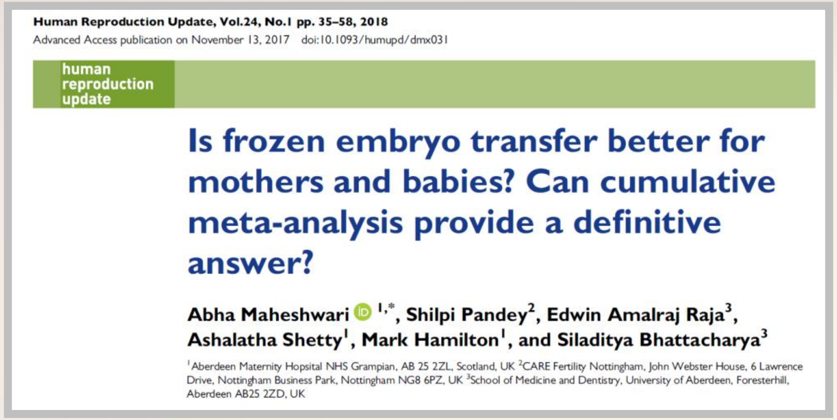
Abha Maheshwari[1,*], Shilpi Pandey[2], Edwin Amalraj Raja[3], Ashalatha Shetty[1], Mark Hamilton[1], and Siladitya Bhattacharya[3]

[1]Aberdeen Maternity Hopsital NHS Grampian, AB 25 2ZL, Scotland, UK [2]CARE Fertility Nottingham, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham NG8 6PZ, UK [3]School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

- Data Sources from Medline, EMBASE, Cochrane Central Register of Clinical Trials DARE and CINAHL (1984–2016)
- Studies comparing obstetric and perinatal outcomes in ***singleton pregnancies conceived through IVF using either fresh or frozen thawed embryos***

Freeze all

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.



Human Reproduction Update, Vol.24, No.1 pp. 35–58, 2018
Advanced Access publication on November 13, 2017 doi:10.1093/humupd/dmx031

human reproduction update

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[1] Aberdeen Maternity Hopsital NHS Grampian, AB 25 2ZL, Scotland, UK [2] CARE Fertility Nottingham, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham NG8 6PZ, UK [3] School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

Frozen-thawed embryos:

- ***lower relative risk*** *(RR) of preterm delivery (0.90; 95% CI 0.84–0.97),*
- *low birth weight (0.72; 95% CI 0.67–0.77) and small for gestational age (0.61; 95% CI 0.56–0.67)*
- ***increased risk (RR)*** *of hypertensive disorders of pregnancy (1.29; 95% CI 1.07–1.56),*
- *large for gestational age (1.54; 95% CI 1.48–1.61) and*
- *high birth weight (1.85; 95% CI 1.46–2.33).*

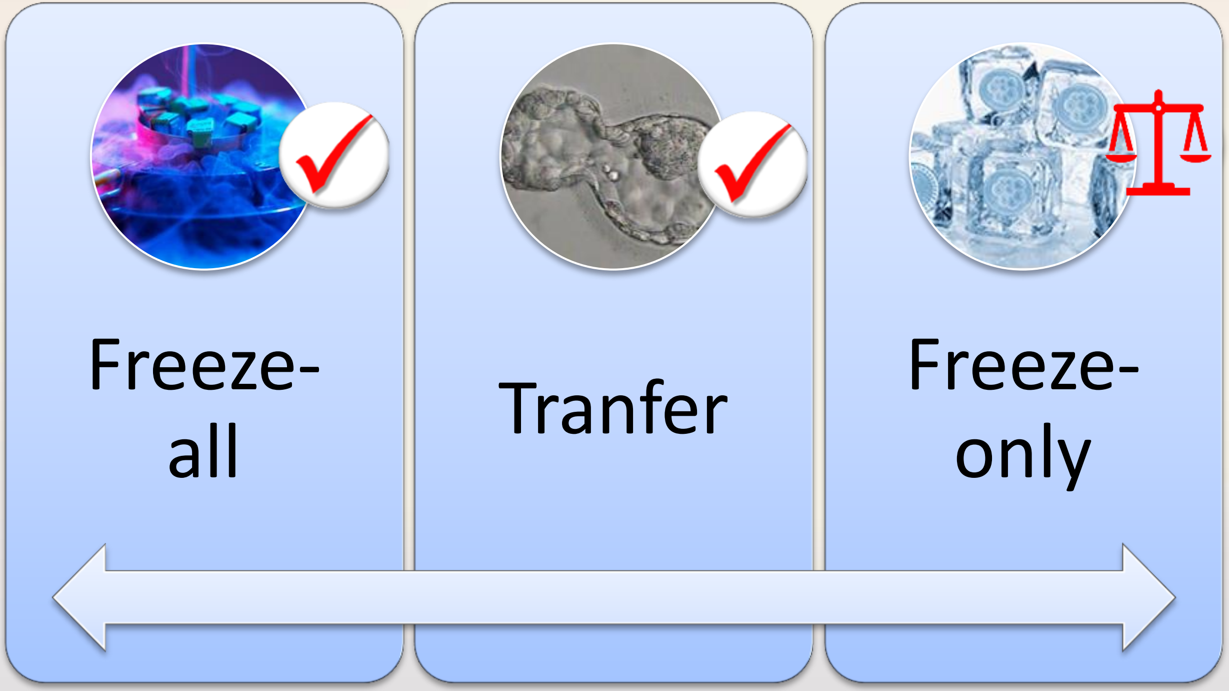
Freeze all

WELCOME
TO THE REAL WORLD

- A segmentação do ciclo (crio + transfer em ciclo subsequente) pode não ser aceitável para todas os envolvidos devido a considerações legais, éticas ou econômicas.

- A criopreservação pode produzir alterações moleculares en genes chaves e transcriptos, que ainda não são detectáveis pelos métodos diagnósticos atuais, com consequências de longo prazo ainda desconhecidas para as crianças nascidas provenientes de embriões congelados/descongelados (*Kopeika et al.,2015).*

Freeze all

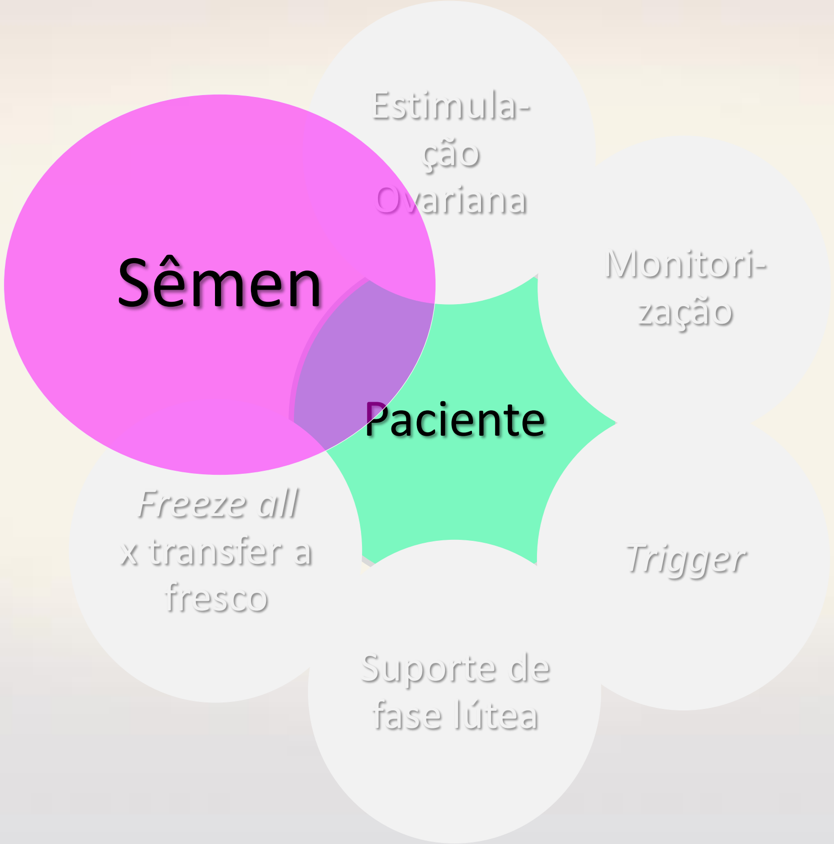


Freeze-all ✓

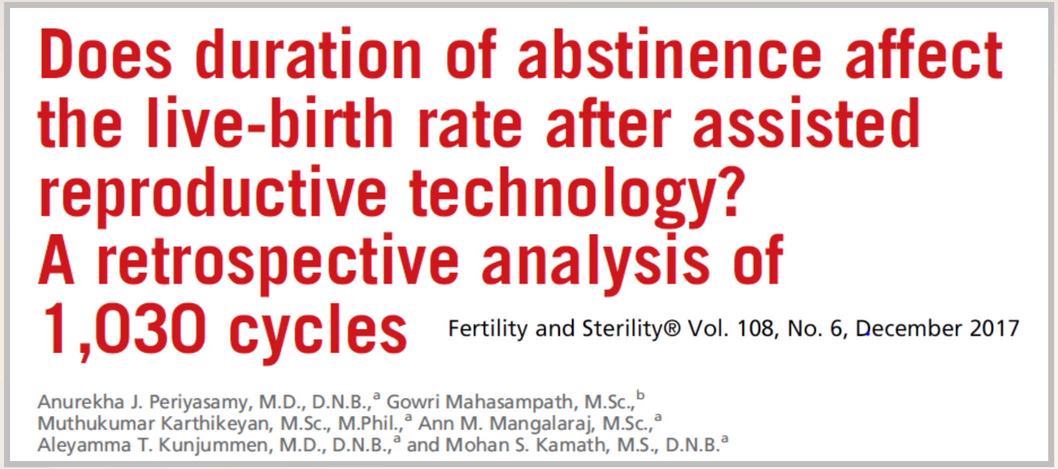
Tranfer ✓

Freeze-only ⚖

Sucesso na FIV / ICSI


Estimulação Ovariana
Sêmen
Monitorização
Paciente
Freeze all x transfer a fresco
Trigger
Suporte de fase lútea

Sêmen



Does duration of abstinence affect the live-birth rate after assisted reproductive technology? A retrospective analysis of 1,030 cycles

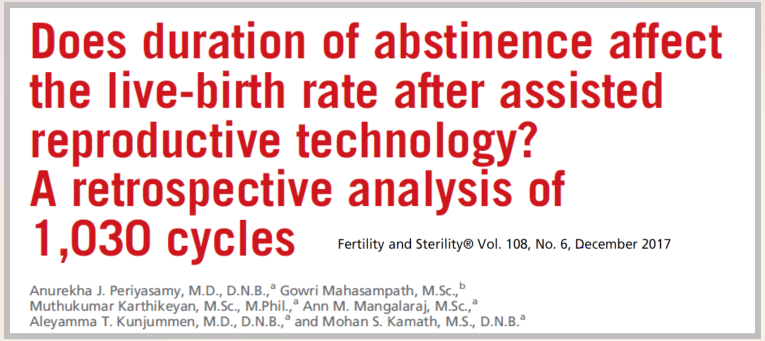
Fertility and Sterility® Vol. 108, No. 6, December 2017

Anurekha J. Periyasamy, M.D., D.N.B.,[a] Gowri Mahasampath, M.Sc.,[b]
Muthukumar Karthikeyan, M.Sc., M.Phil.,[a] Ann M. Mangalaraj, M.Sc.,[a]
Aleyamma T. Kunjummen, M.D., D.N.B.,[a] and Mohan S. Kamath, M.S., D.N.B.[a]

Patient(s): A total 1,030 ART cycles evaluated from 2011 to 2015.

Intervention(s): Group I, abstinence period 2–7 days, and group II, abstinence period >7 days, were compared. Two subgroups Ia (2–4 days) and Ib (5–7 days) were also compared with group II.

Sêmen



Does duration of abstinence affect the live-birth rate after assisted reproductive technology? A retrospective analysis of 1,030 cycles

Fertility and Sterility® Vol. 108, No. 6, December 2017

Anurekha J. Periyasamy, M.D., D.N.B.,[a] Gowri Mahasampath, M.Sc.,[b]
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Aleyamma T. Kunjummen, M.D., D.N.B.,[a] and Mohan S. Kamath, M.S., D.N.B.[a]

Conclusion(s):

An abstinence period of ***more than 7 days*** may impact ART outcomes adversely when compared with an abstinence period of 2–7 days.

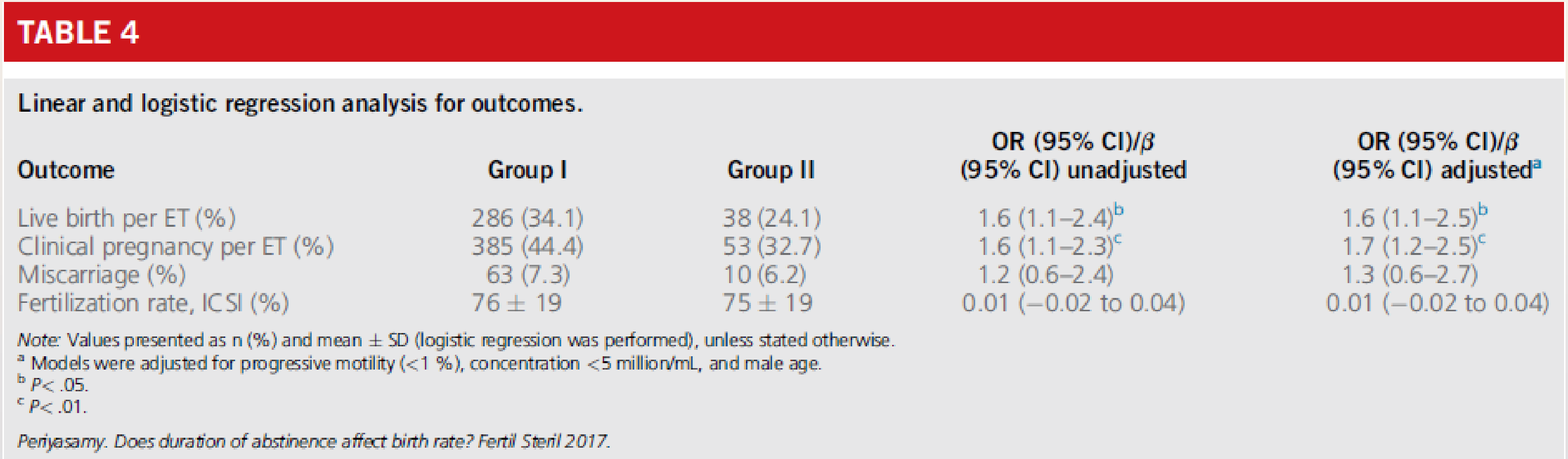


TABLE 4

Linear and logistic regression analysis for outcomes.

Outcome	Group I	Group II	OR (95% CI)/β (95% CI) unadjusted	OR (95% CI)/β (95% CI) adjusted[a]
Live birth per ET (%)	286 (34.1)	38 (24.1)	1.6 (1.1–2.4)[b]	1.6 (1.1–2.5)[b]
Clinical pregnancy per ET (%)	385 (44.4)	53 (32.7)	1.6 (1.1–2.3)[c]	1.7 (1.2–2.5)[c]
Miscarriage (%)	63 (7.3)	10 (6.2)	1.2 (0.6–2.4)	1.3 (0.6–2.7)
Fertilization rate, ICSI (%)	76 ± 19	75 ± 19	0.01 (−0.02 to 0.04)	0.01 (−0.02 to 0.04)

Note: Values presented as n (%) and mean ± SD (logistic regression was performed), unless stated otherwise.

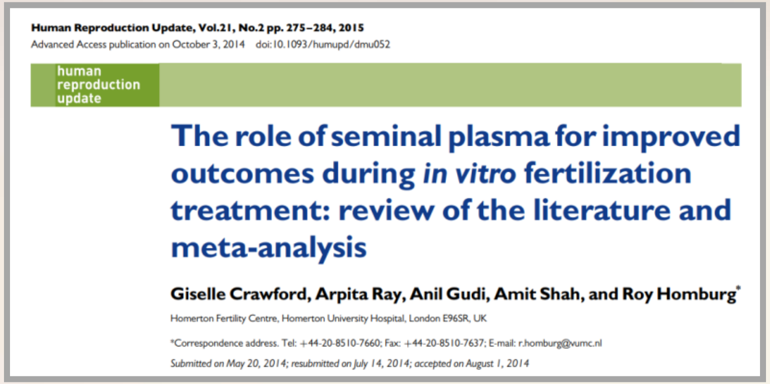
[a] Models were adjusted for progressive motility (<1 %), concentration <5 million/mL, and male age.

[b] $P < .05$.

[c] $P < .01$.

Periyasamy. Does duration of abstinence affect birth rate? Fertil Steril 2017.

Sêmen



Human Reproduction Update, Vol.21, No.2 pp. 275–284, 2015
Advanced Access publication on October 3, 2014 doi:10.1093/humupd/dmu052

human
reproduction
update

The role of seminal plasma for improved outcomes during *in vitro* fertilization treatment: review of the literature and meta-analysis

Giselle Crawford, Arpita Ray, Anil Gudi, Amit Shah, and Roy Homburg*

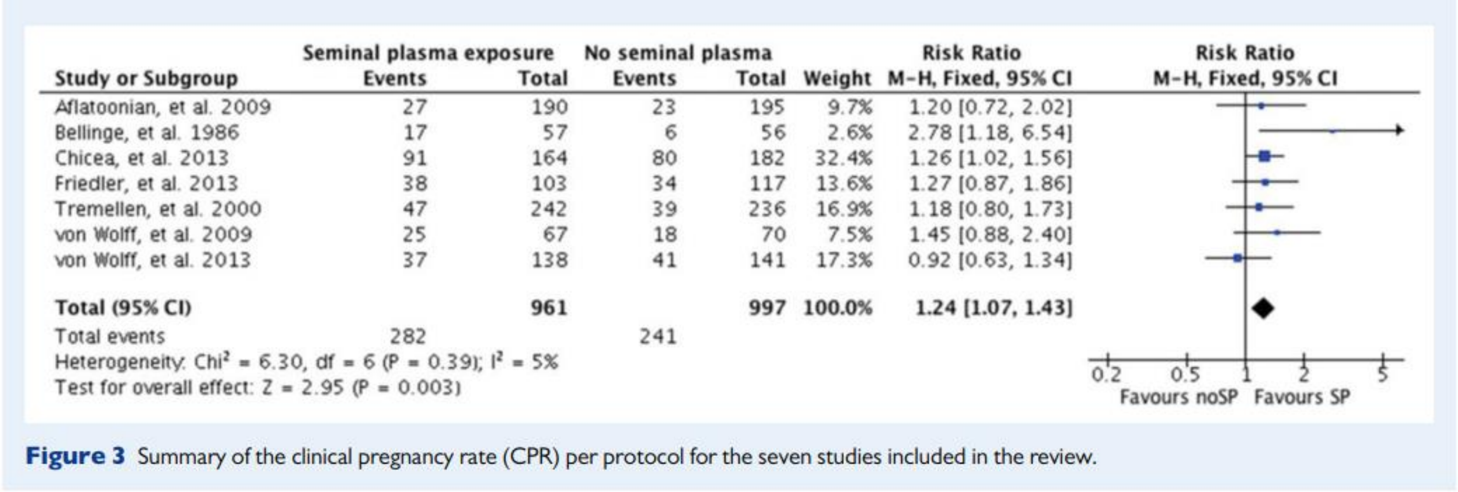
Homerton Fertility Centre, Homerton University Hospital, London E96SR, UK

*Correspondence address. Tel: +44-20-8510-7660; Fax: +44-20-8510-7637; E-mail: r.homburg@vumc.nl

Submitted on May 20, 2014; resubmitted on July 14, 2014; accepted on August 1, 2014

In total 2204 patients were included in seven RCTs.

RR 1.24, 95% CI 1.07 –1.43, P < 0.003

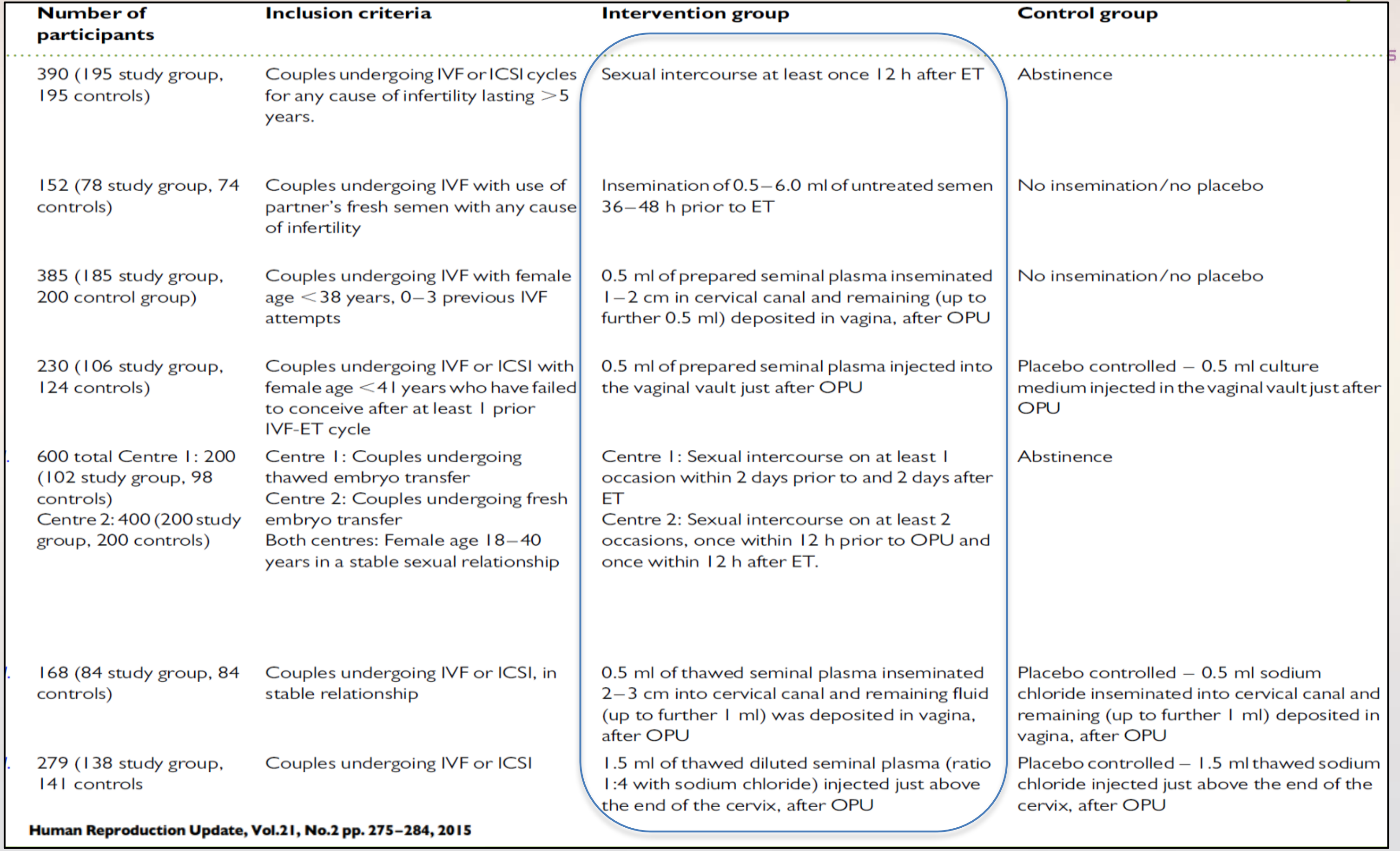


Study or Subgroup	Seminal plasma exposure Events	Seminal plasma exposure Total	No seminal plasma Events	No seminal plasma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aflatoonian, et al. 2009	27	190	23	195	9.7%	1.20 [0.72, 2.02]
Bellinge, et al. 1986	17	57	6	56	2.6%	2.78 [1.18, 6.54]
Chicea, et al. 2013	91	164	80	182	32.4%	1.26 [1.02, 1.56]
Friedler, et al. 2013	38	103	34	117	13.6%	1.27 [0.87, 1.86]
Tremellen, et al. 2000	47	242	39	236	16.9%	1.18 [0.80, 1.73]
von Wolff, et al. 2009	25	67	18	70	7.5%	1.45 [0.88, 2.40]
von Wolff, et al. 2013	37	138	41	141	17.3%	0.92 [0.63, 1.34]
Total (95% CI)		**961**		**997**	**100.0%**	**1.24 [1.07, 1.43]**
Total events	282		241			

Heterogeneity: $Chi^2 = 6.30$, df = 6 ($P = 0.39$); $I^2 = 5\%$
Test for overall effect: $Z = 2.95$ ($P = 0.003$)

Figure 3 Summary of the clinical pregnancy rate (CPR) per protocol for the seven studies included in the review.

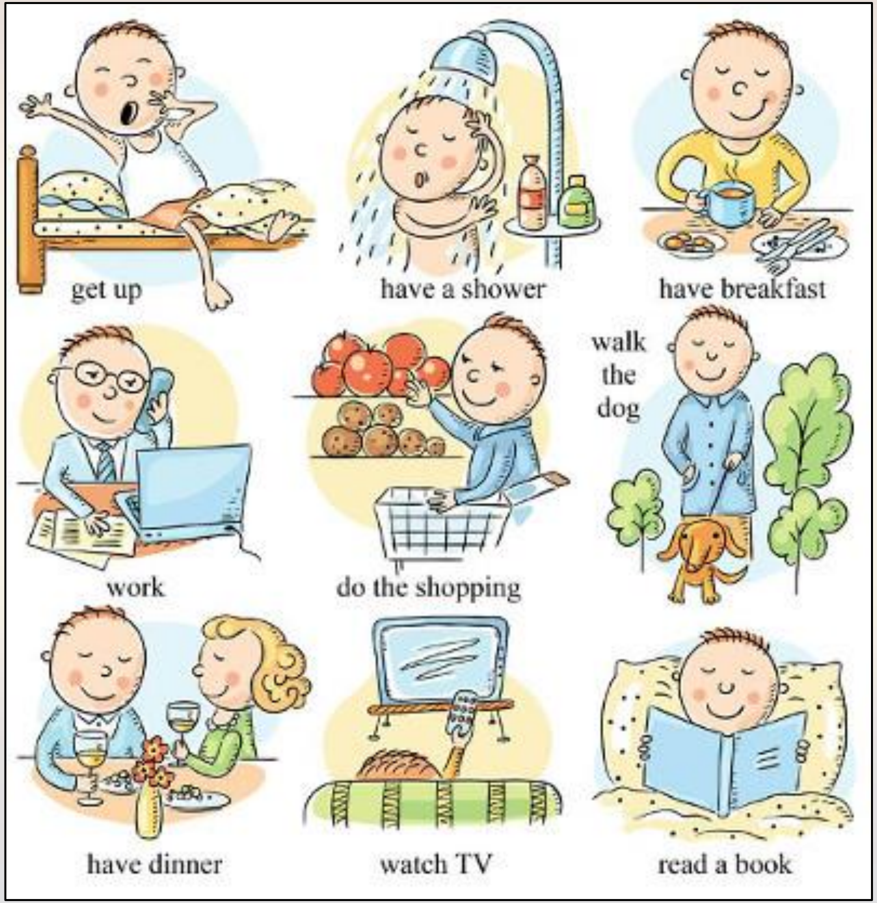
Sêmen



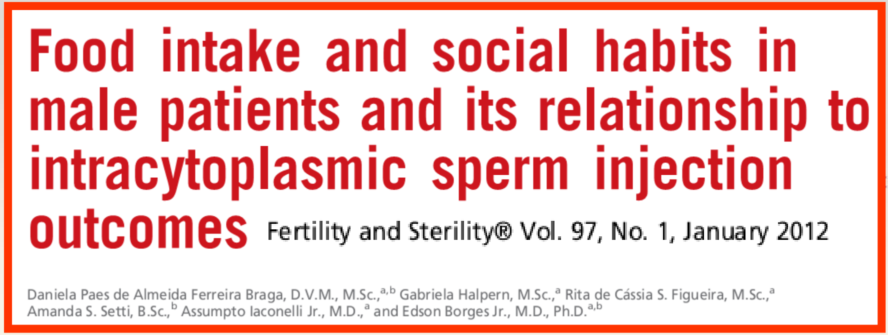
Number of participants	Inclusion criteria	Intervention group	Control group
390 (195 study group, 195 controls)	Couples undergoing IVF or ICSI cycles for any cause of infertility lasting >5 years.	Sexual intercourse at least once 12 h after ET	Abstinence
152 (78 study group, 74 controls)	Couples undergoing IVF with use of partner's fresh semen with any cause of infertility	Insemination of 0.5–6.0 ml of untreated semen 36–48 h prior to ET	No insemination/no placebo
385 (185 study group, 200 control group)	Couples undergoing IVF with female age <38 years, 0–3 previous IVF attempts	0.5 ml of prepared seminal plasma inseminated 1–2 cm in cervical canal and remaining (up to further 0.5 ml) deposited in vagina, after OPU	No insemination/no placebo
230 (106 study group, 124 controls)	Couples undergoing IVF or ICSI with female age <41 years who have failed to conceive after at least 1 prior IVF-ET cycle	0.5 ml of prepared seminal plasma injected into the vaginal vault just after OPU	Placebo controlled – 0.5 ml culture medium injected in the vaginal vault just after OPU
600 total Centre 1: 200 (102 study group, 98 controls) Centre 2: 400 (200 study group, 200 controls)	Centre 1: Couples undergoing thawed embryo transfer Centre 2: Couples undergoing fresh embryo transfer Both centres: Female age 18–40 years in a stable sexual relationship	Centre 1: Sexual intercourse on at least 1 occasion within 2 days prior to and 2 days after ET Centre 2: Sexual intercourse on at least 2 occasions, once within 12 h prior to OPU and once within 12 h after ET.	Abstinence
168 (84 study group, 84 controls)	Couples undergoing IVF or ICSI, in stable relationship	0.5 ml of thawed seminal plasma inseminated 2–3 cm into cervical canal and remaining fluid (up to further 1 ml) was deposited in vagina, after OPU	Placebo controlled – 0.5 ml sodium chloride inseminated into cervical canal and remaining (up to further 1 ml) deposited in vagina, after OPU
279 (138 study group, 141 controls	Couples undergoing IVF or ICSI	1.5 ml of thawed diluted seminal plasma (ratio 1:4 with sodium chloride) injected just above the end of the cervix, after OPU	Placebo controlled – 1.5 ml thawed sodium chloride injected just above the end of the cervix, after OPU

Human Reproduction Update, Vol.21, No.2 pp. 275–284, 2015

Hábitos


get up
have a shower
have breakfast
work
do the shopping
walk the dog
have dinner
watch TV
read a book

ORQUESTRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

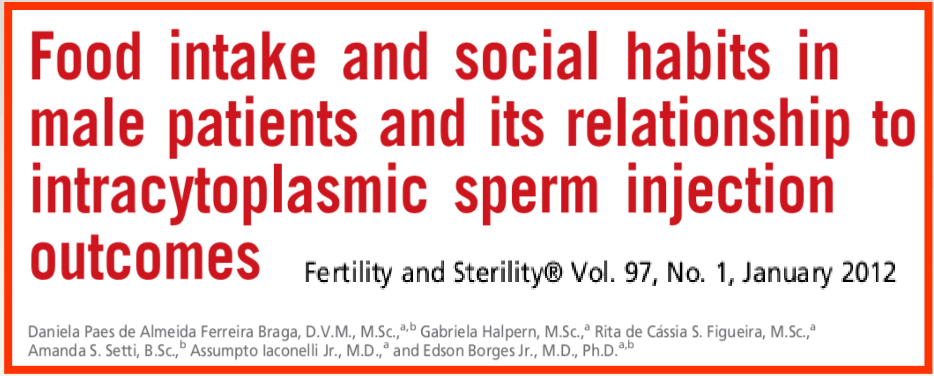


Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes

Fertility and Sterility® Vol. 97, No. 1, January 2012

Daniela Paes de Almeida Ferreira Braga, D.V.M., M.Sc.,[a,b] Gabriela Halpern, M.Sc.,[a] Rita de Cássia S. Figueira, M.Sc.,[a] Amanda S. Setti, B.Sc.,[b] Assumpto Iaconelli Jr., M.D.,[a] and Edson Borges Jr., M.D., Ph.D.[a,b]

- *Sperm concentration*: negatively influenced by BMI and alcohol consumption and positively influenced by cereal consumption and number of meals per day
- Motility: negatively influenced by BMI, alcohol consumption, and smoking habit, and positively influenced by the consumption of fruits and cereals
- Morphology: not affected by any food consumption or social habit



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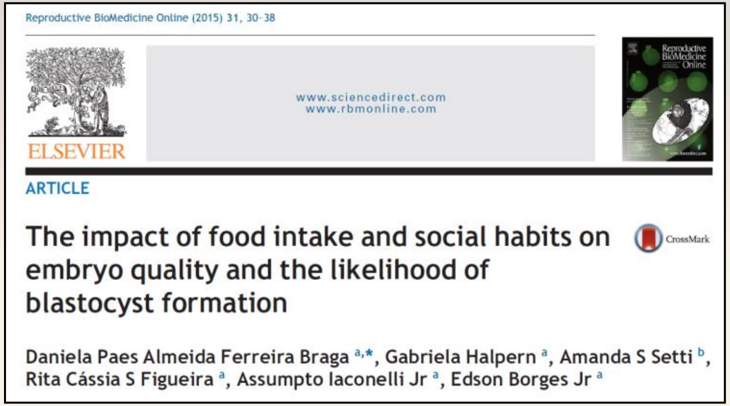
STRANDO OS DETALHES QUE FAZEM A DIFERENÇA.

- *Alcohol:* *negative influence on the fertilization rate*
- *Read met and weight-loss diet:* negative influence on implantation rate and decrease the chance of pregnancy
- *Miscarriage*: not affected



Reproductive BioMedicine Online (2015) 31, 30-38

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ARTICLE

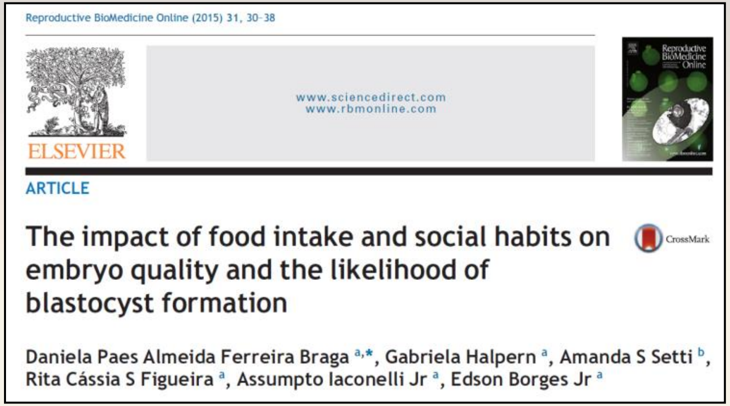
The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation

Daniela Paes Almeida Ferreira Braga [a,*], Gabriela Halpern [a], Amanda S Setti [b], Rita Cássia S Figueira [a], Assumpto Iaconelli Jr [a], Edson Borges Jr [a]

❖ *2659 embryos – 269 ICSI cycles*

- Embryo quality at the cleavage stage: negative influence by alcohol and smoking; positive influence by ceral, vegetables and fruits

- *Blastocyst*: negative influence by consumption of red meat, weight-loss diet, alcohol and cigarrete; positive influence by consumption of fruits and fish.



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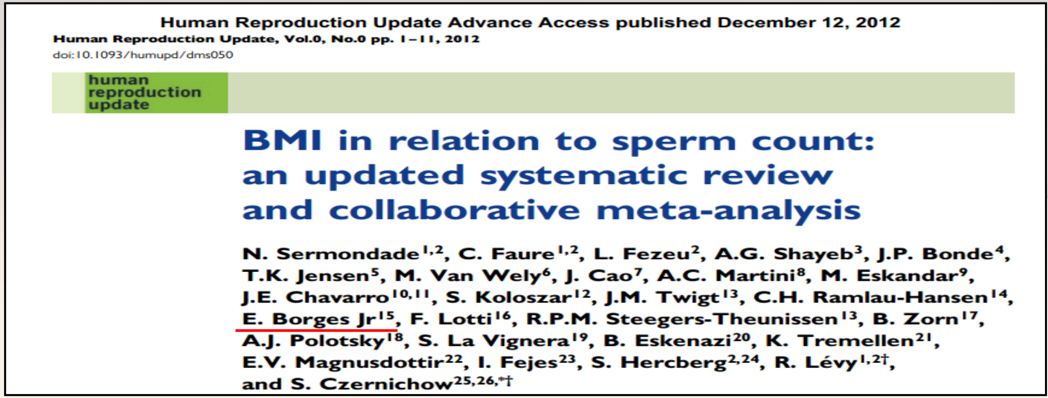
- *Read meat and BMI: negatite influence on implantancion and pregnancy*
- Weight-loss diet: *negative influence on implantation*



Human Reproduction Update Advance Access published December 12, 2012
Human Reproduction Update, Vol.0, No.0 pp. 1–11, 2012
doi:10.1093/humupd/dms050

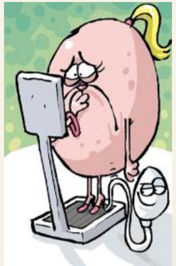
human
reproduction
update

BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis

N. Sermondade[1,2], C. Faure[1,2], L. Fezeu[2], A.G. Shayeb[3], J.P. Bonde[4], T.K. Jensen[5], M. Van Wely[6], J. Cao[7], A.C. Martini[8], M. Eskandar[9], J.E. Chavarro[10,11], S. Koloszar[12], J.M. Twigt[13], C.H. Ramlau-Hansen[14], E. Borges Jr[15], F. Lotti[16], R.P.M. Steegers-Theunissen[13], B. Zorn[17], A.J. Polotsky[18], S. La Vignera[19], B. Eskenazi[20], K. Tremellen[21], E.V. Magnusdottir[22], I. Fejes[23], S. Hercberg[2,24], R. Lévy[1,2†], and S. Czernichow[25,26,*†]

ANDO OS DETALHES QUE FAZEM A DIFERENÇA.

- ***21 estudos, 13.077 homens da população geral e em investigação de infertilidade***
- ***Estudo da relação entre BMI e incidência de oligozoospermia / azoospermia***
- ***Comparados com homens com peso normal:***



❖ Sobpeso: OR= 1,15 (0,93-1,43)

❖ Sobrepeso: OR= 1,11 (1,01-1,21)

❖ Obeso: OR= 1,28 (1,06-1,55)

❖ Obeso mórbido: OR= 2,04 (1,59-2,62)