Influência dos níveis de progesterona na receptividade endometrial

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Janela de implantação

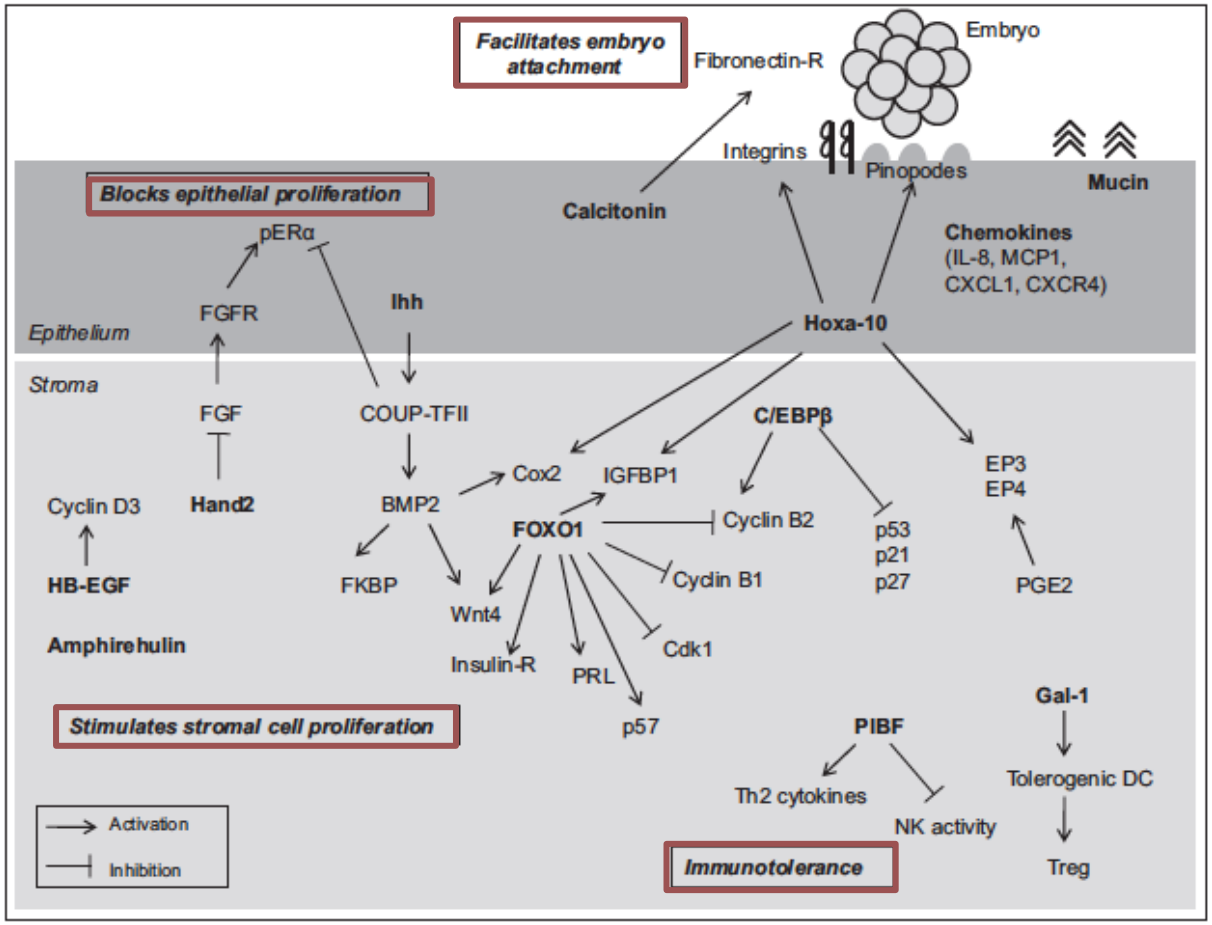

Fig. 1. Progesterone regulates endometrial receptivity and embryo attachment. Progesterone blocks the proliferative effect of oestrogen on uterine epithelial cells and facilitates uterine receptivity by its genomic actions. Progesterone modulates stromal cell proliferation, decidual growth, expression of adhesion molecules and suppresses the maternal immune system to allow embryo implantation. (Progesterone-induced molecules are shown **in bold**.)

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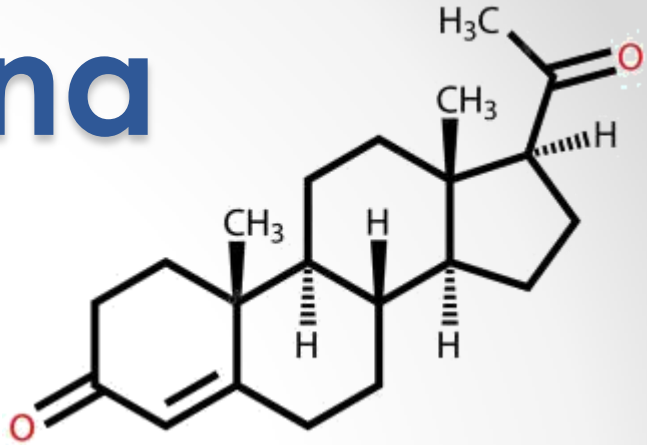
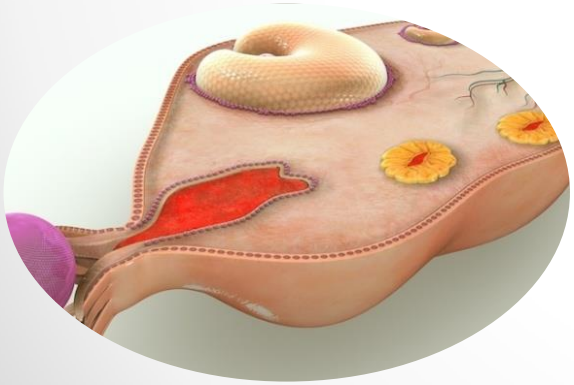
Halasz, M., Szekeres-Bartho, J/Journal of Reproductive Immunology 97 (2013) 43-50

Progesterona



- Esteróide
- **Ovários** → puberdade
- **Unidade feto-placentária** → gestação
- **Supra-renais** → menor quantidade



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Progesterona
ciclo natural

Fase folicular: 1 a 10 ng/ml

Fase ovulatória: 1ng/ml

Fase lútea: > 5 ng/ml
(FIV > 15 ng/ml)

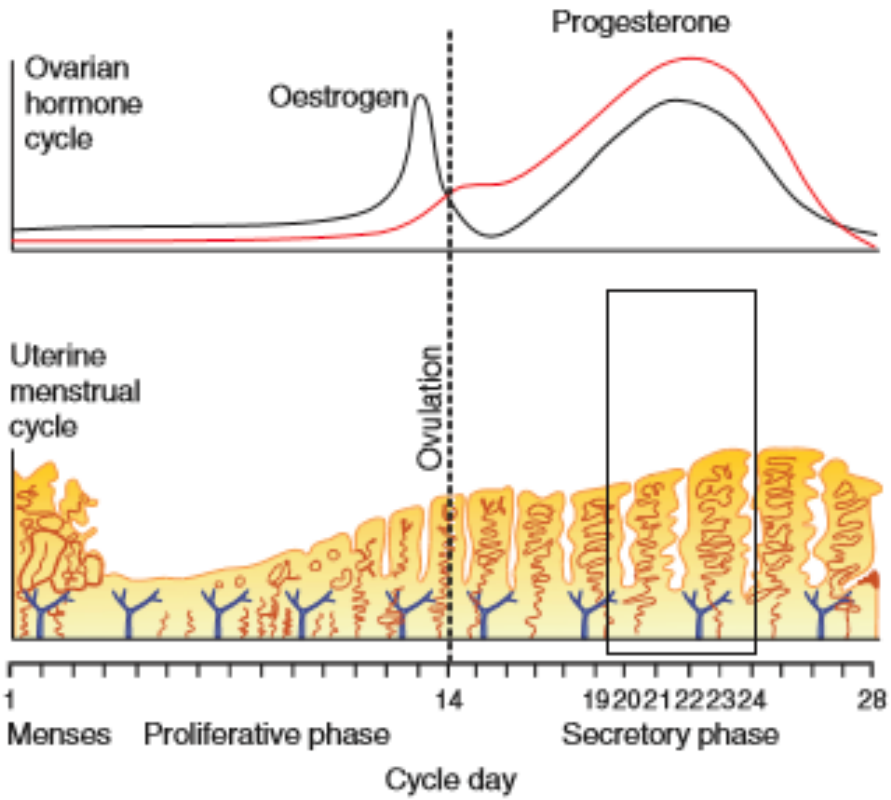

Fig. 1. Human ovarian hormone and endometrial cycles showing the 'window of receptivity' (boxed) in the endometrium.

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- Salamonsen, L.A. et al/ Reproduction, Fertility and Development, 2009

Progesterona

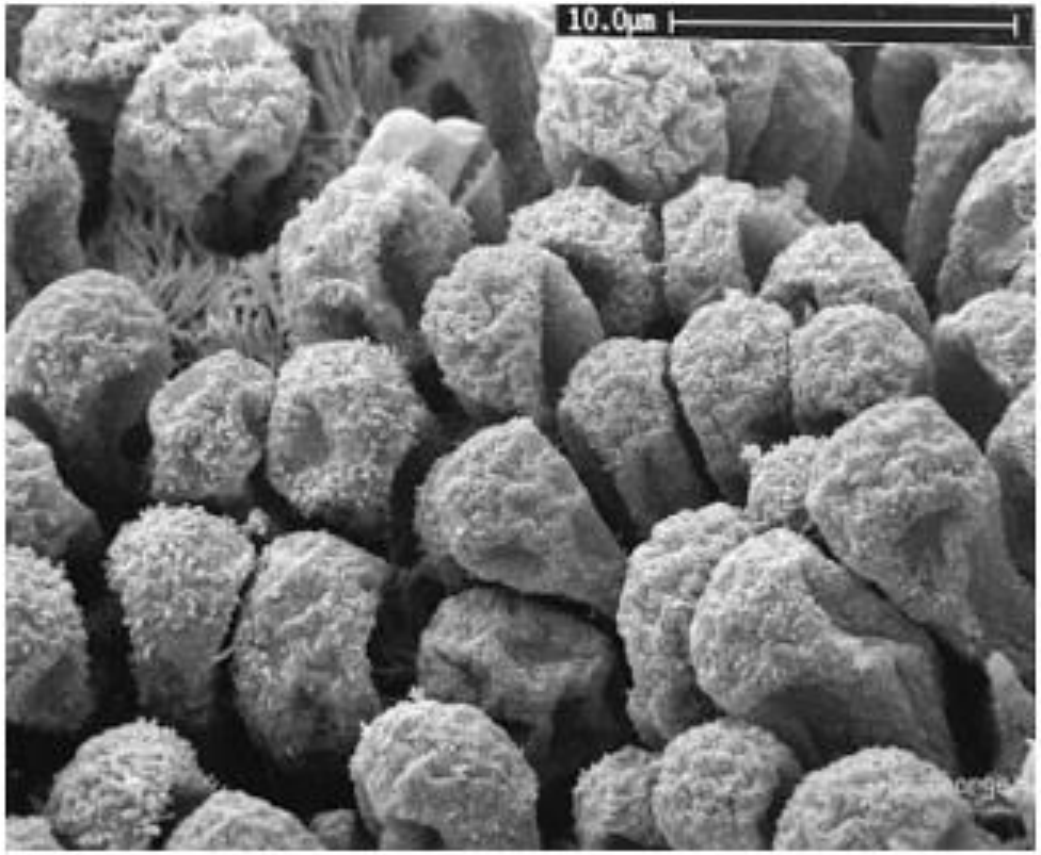

Figure 3. Micrograph of a sample taken from donor no. 9 on day 19. Note fully developed pinopodes, with many folds protruding above the the cilia seen at top left. This sample resembles a day 2[illegible] endometrium. Scale bar = 10 µm.

(Nikas, G. Hum, Reprod., 1999)

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Human Reproduction vol.14 no.3 pp.787–792, 1999

Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles

George Nikas[1,3], Osman H.Develioglu[2], James P.Toner[2] and Howard W.Jones, Jr[2]

G.Nikas

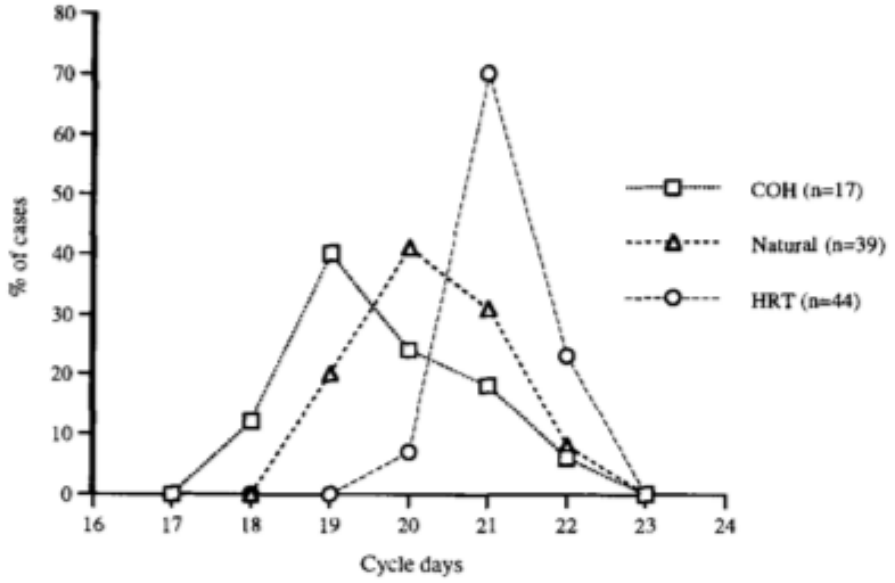

Figure 5. Differential expression of pinopodes in controlled ovarian hyperstimulation (COH) natural and hormone replacement therapy (HRT) cycles.

Ciclo natural – 21 DC

FIV – 1 a 2 dias mais cedo

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Recurrent implantation failure is another indication for the freeze-all strategy

Bruce S. Shapiro, M.D., Ph.D.[a,b]
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http://dx.doi.org/10.1016/j.fertnstert.2017.05.018

As early as 1977, even before the first live birth from in vitro fertilization, Edwards and Steptoe (5) attributed implantation failures to "abnormal endocrine conditions arising in patients treated with HMG and HCG." They discussed the advantages of avoiding the negative effects of uterine exposure to ovarian stimulation by freezing all embryos for subsequent transfers of single frozen-thawed embryos. Alas, the

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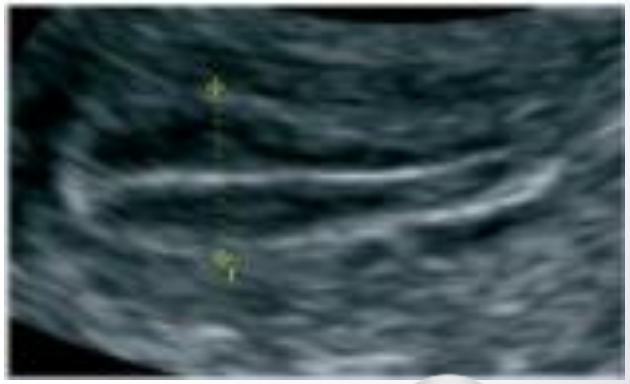
FIV

- Bloqueio hipofisário - luteinização precoce (Hofmann GE et al, 1993, Fertil Steril)
- 5 – 71% dos ciclos de FIV (Huang et al, Fertil Steril, 2012))
- Não há aumento de LH – apenas P4 - ELEVAÇÃO PRECOCE DE P4 (Harada T et al, Fertil Steril, 1996)
- **Pode ser deletério? Em quais casos?**



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Human Reproduction, Vol.24, No.6 pp. 1436–1445, 2009
Advanced Access publication on February 26, 2009 doi:10.1093/humrep/dep039

human reproduction ORIGINAL ARTICLE *Infertility*

Gene expression profile of human endometrial receptivity: comparison between natural and stimulated cycles for the same patients

D. Haouzi[1,2,3,4], S. Assou[1,3,4], K. Mahmoud[5], S. Tondeur[1,3,4], T. Rème[1,3,4], B. Hedon[2], J. De Vos[1,3,4], and S. Hamamah[1,2,3,4,6]

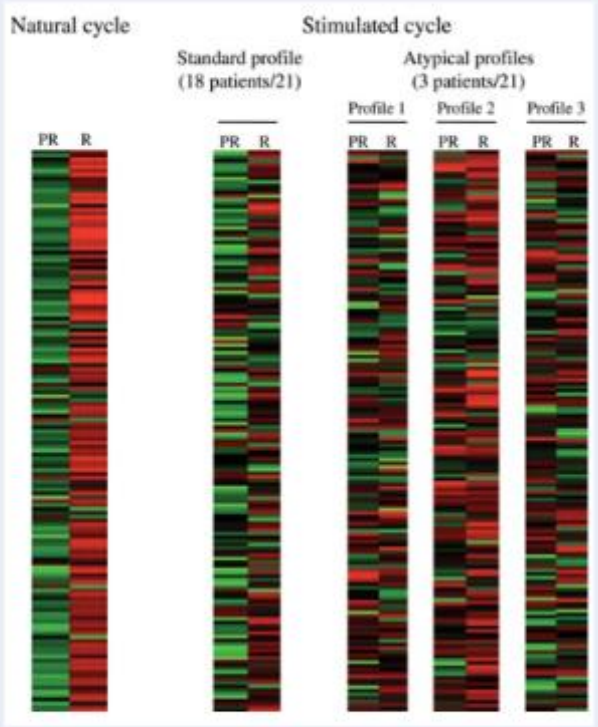

Figure 3 The two endometrium profiles during the pre-receptive (PR) and the receptive (R) stages in stimulated cycles.

The majority of patients (18/21 patients) were characterized by a common profile, called 'standard profile'. Other patients (3/21) presented an 'atypical profile'. PR, pre-receptive; R, receptive; red, up-regulated genes; green, down-regulated genes.

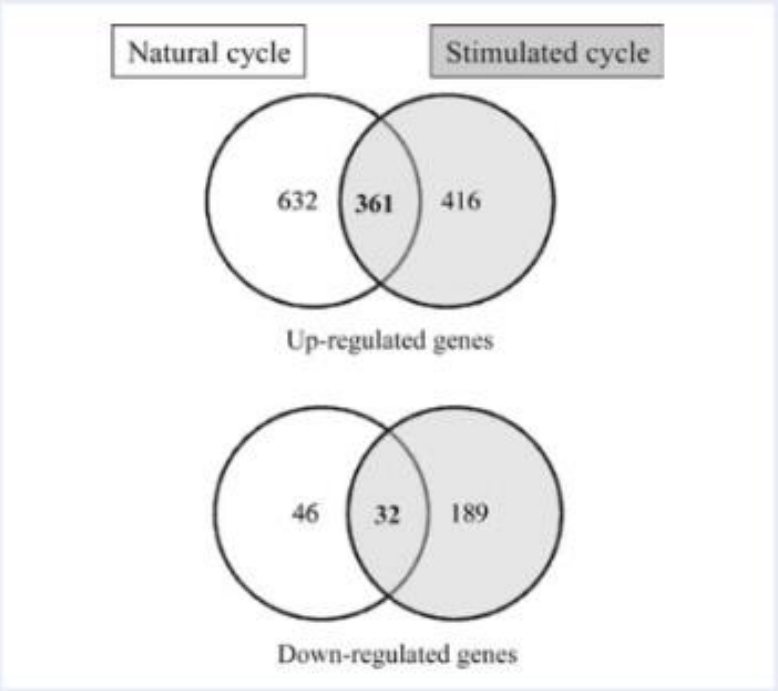

Figure 4 Venn diagram of transcripts up-regulated and down-regulated during endometrial receptivity in the natural cycle compared with the stimulated cycle.

Each list of genes was determined with the SAM software with a FDR [illegible] and an FC > 2.

human reproduction ORIGINAL ARTICLE *Infertility*

Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis

E. Labarta[1,*], J.A. Martínez-Conejero[2], P. Alamá[1], J.A. Horcajadas[2], A. Pellicer[1], C. Simón[1,2], and E. Bosch[1]

Table I Oocyte donor parameters according to P levels on the day of rCG administration.

	P level < 1.5 ng/ml ($n = 6$)	P level > 1.5 ng/ml ($n = 6$)	*P*-value
Age (years)	27.5 ± 4.2	22 ± 2.2	0.017
Previous pregnancies	3/6 (50%)	1/6 (16.7%)	0.545
BMI (kg/m^2)	22.8 ± 2.7	22.4 ± 2.3	0.807
Total dose of rFSH (IU)	1550 ± 512.8	1970.8 ± 152.0	0.083
Number of oocytes retrieved	20.5 ± 6.1	23.5 ± 1.5	0.287
Days of stimulation	9.5 ± 1.9	9.6 ± 0.8	0.845
E2 (pg/ml) on day of rCG administration	2236.8 ± 808.7	2649.3 ± 801.9	0.396
P (ng/ml) on day of rCG administration	0.54 ± 0.2	2.39 ± 0.8	<0.001

Data are expressed as mean (±SD) or percentage; P, progesterone; E2, estradiol; rCG, recombinant chorionic gonadotrophin.
P-value represents the significance value of the studied comparison; $P < 0.05$ = significant.

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- Programa de ovodoação – sem alteração na taxa de gravidez (Melo, MAB et al, Human Reprod, 2006)
- Outros estudos confirmam a não influência na qualidade embrionária e formação de blastocistos, comparando transferência a fresco X descongelamento (Bukulumez et al, RBMonline 2006; Li et al, RBM online 2008)

Table 1. Clinical features and cycle outcome of ovarian stimulation between the high progesterone and normal progesterone groups in gonadotrophin-releasing hormone antagonist cycles.

	Normal progesterone (<3.97 nmol/l)	*High progesterone (≥3.97 nmol/l)*	*P-value*
No. of patients	159	92	n/a
IVF–embryo transfer pregnancy rate (%)	48.57 (68/140)	25.97 (20/77)	0.001
Fertilization rate %	66.30 ± 27.39	66.53 ± 20.46	NS
Good quantity embryo	71.13 ± 29.22	72.36 ± 29.63	NS
No. of FET patients/cycles	68	50	NS
FET pregnancy rate (%)	36.76 (25/68)	34.00 (17/50)	NS
HCG (mIU/ml)			
Cancelled cycle rate (%)	11.95 (19/159)	16.30 (15/92)	NS
IVF–embryo transfer pregnancy rate (%)	48.57 (68/140)	25.97 (20/77)	0.001
No. of FET patients/cycles	68	50	NS
FET pregnancy rate (%)	36.76 (25/68)	34.00 (17/50)	NS

ET = embryo transfer; FET = frozen embryo transfer; n/a = not applicable; NS = not statistically significant; rFSH = recombinant FSH.

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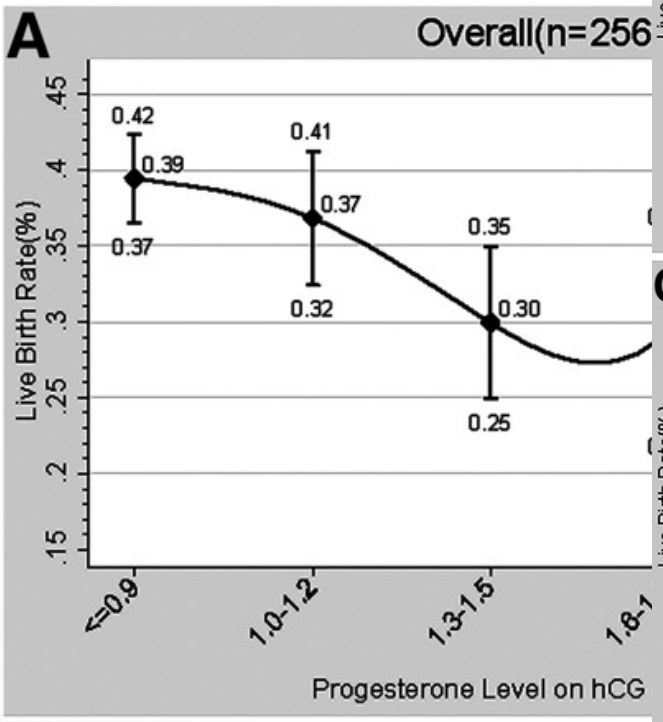
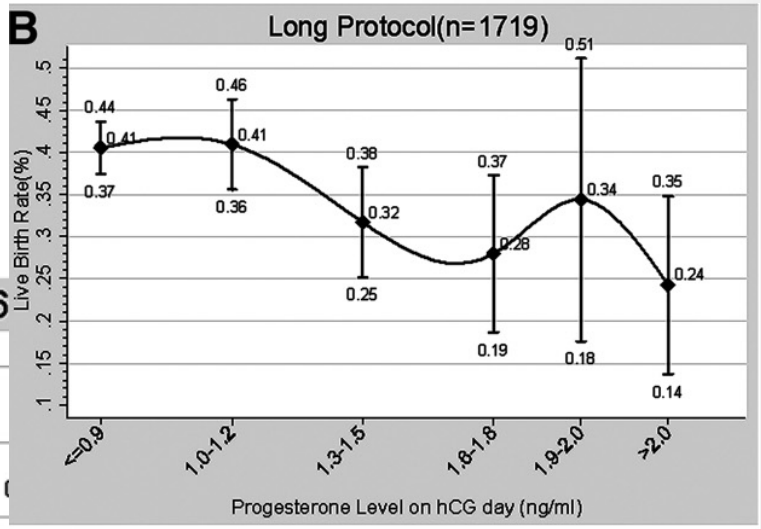
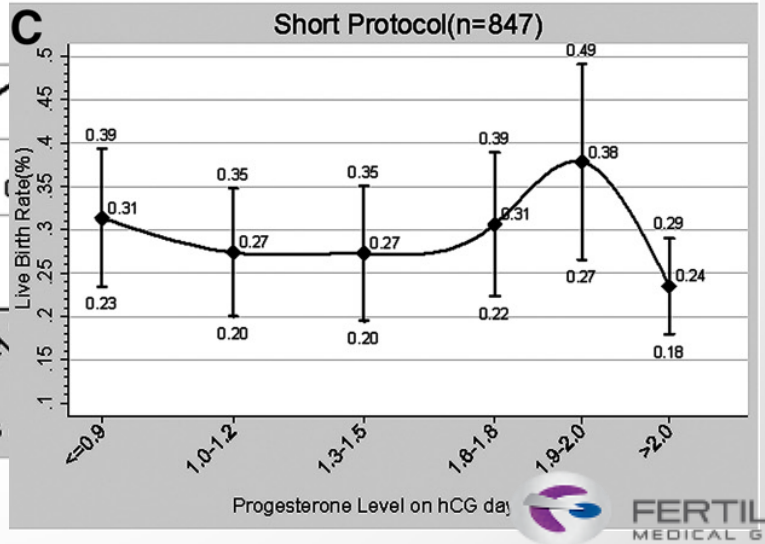
Elevação precoce de progesterona

Premature progesterone rise negatively correlated with live birth rate in IVF cycles with GnRH agonist: an analysis of 2,566 cycles

Rui Huang, M.D.,[a,b] Cong Fang, M.D.,[a] Shuyi Xu, Ph.D.,[c] Yanhong Yi, M.D.,[b] and Xiaoyan Liang, M.D.[a]







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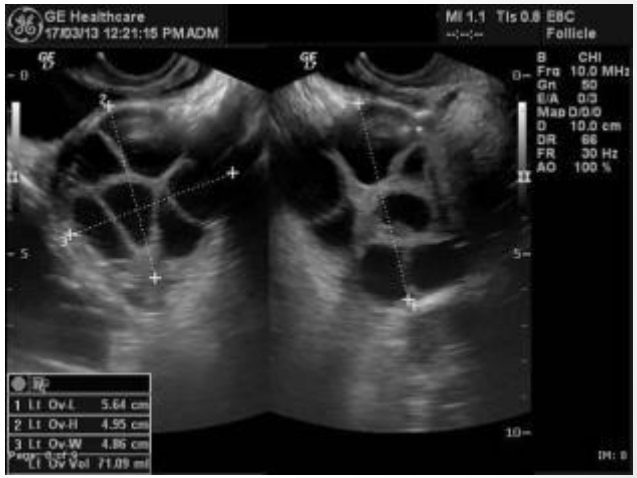
Patogenese e etiologia

hipóteses

1. Acúmulo de progesterona produzida por múltiplos foliculos em desenvolvimento.
2. Aumento da conversão de colesterol em progesterona por efeito das doses aumentadas de gonadotrofinas nas células da granulosa.
3. Luteinização precoce por aumento súbito de LH.
4. Aumento da sensibilidade ao LH.



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(Huang, Progesterone Rise and Live Birth rate. Fertil Steril 2012)

Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles

Bei Xu, Ph.D., Zhou Li, Ph.D., Hanwang Zhang, Ph.D., Lei Jin, Ph.D., Yufeng Li, Ph.D., Jihui Ai, Ph.D., and Guijin Zhu, M.D.

≤ 4 oocitos – 1,5 ng/ml

5-19 oocitos- 1,75 ng/ml

≥ 20 oocitos – 2,2 ng/ml

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Elevação precoce de progesterona

- Estratégia de congelar todos os embriões em más-respondedoras (Critérios de Bologna) se **P>1,5 ng/ml** no dia do hCG

- Sem diferença estatística

Table 1. Fresh vs. Freeze-all in poor responders

	FRESH-GROUP	FREEZE-ALL GROUP	Relative Risk (95% CI)	*p* value
N° of patients	247	131		
Age, years +/-SD	39.62 +/- 3.90	39.43 +/- 3.74		0.651
Number of embryos transferred +/- SD	1.91 +/- 0.85	1.71 +/- 0.74		0.053
Implantation rate, %	11.4%	12.3%	1.10 (0.70-1.74)	0.758
Pregnancy Rate, n(%)	49/247 (19.8%)	28/131 (21.4%)	1.08 (0.71-1.63)	0.725
Clinical Pregnancy Rate, n(%)	41/247(16.6%)	23/131 (17.6%)	1.06 (0.66-1.68)	0.814
Ongoing Pregnancy Rate, n(%)	33/247 (13.4%)	18/131 (13.7%)	1.03 (0.60-1.75)	0.918

Roque , M, Fertil. Steril. 2016

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Elevação precoce de progesterona

- Freeze-all para normorrespondedoras – 938 ciclos
- Melhor implantação (25.5% versus 19.3%, *p*=0.002) e gestação ongoing (41% versus 32%, *p*=0.004) no grupo freeze all.

Freeze-all policy in normal responders

M. Roque, M. Valle, F. Guimaraes, A.F. Kostolias, M. Sampaio, S. Geber

O-179 Tuesday, October 18, 2016 12:15 PM

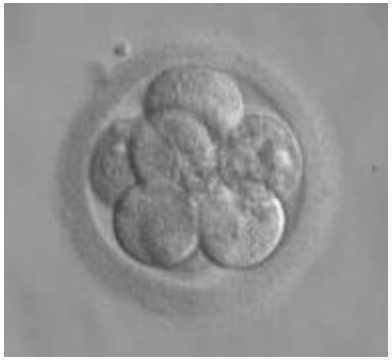
Table 1. Fresh vs. elective FET in normal responders - sub-group analysis

	Group 1(12-15 oocytes)		Group 2(8-11 oocytes)		Group 3(4-7 oocytes)	
	Fresh	**Freeze-all (*p*)**	**Fresh**	**Freeze-all (*p*)**	**Fresh**	**Freeze-all (*p*)**
N° of patients	69	109	172	140	282	166
Age, years +/- SD	33.20 +/- 5.16	33.81 +/- 3.70 (*p*=0.400)	34.98 +/- 4.74	34.32 +/- 4.72 (*p*=0.221)	36.55 +/- 4.35	35.78 +/- 4.15 (*p*=0.066)
Retrieved oocytes +/- SD	13.26 +/- 1.13	13.44 +/- 1.13 (*p*=0.305)	9.33 +/- 1.12	9.29 +/- 1.13 (*p*=0.798)	5.51 +/- 1.08	5.48 +/- 1.07 (*p*=0.811)
N° of embryos transferred +/- SD	2.28 +/- 0.68	2.25 +/- 0.56 (*p*=0.770)	2.28 +/- 0.73	2.18 +/- 0.71 (*p*=0.099)	2.34 +/- 0.81	2.22 +/- 0.60 (*p*=0.067)
Implantation Rate, %	16.6%	28.6% (***p*=0.039**)	19.6%	26.5% (***p*=0.038**)	17.4%	18.2% (*p*=0.490)
Pregnancy Rate, %	39.1%	56.9% (***p*=0.021**)	43.0%	55.0% (***p*=0.035**)	39.4%	41.6% (*p*=0.647)
ClinicalPregnancy Rate, %	33.3%	53.2% (***p*=0.009**)	40.1%	51.4% (***p*=0.047**)	34.7%	36.7% (*p*=0.671)
Ongoing Pregnancy Rate, %	31.9%	47.7% (***p*=0.035**)	34.9%	47.1% (***p*=0.029**)	30.1%	31.3% (*p*=0.793)
Relative Risk Ongoing Pregnancy-Freeze-all vs Fresh	**1.50 (1.01-2.23)**		**1.35 (1.03-1.77)**		**1.04 (0.78-1.38)**	

Elevação precoce de progesterona

- Assincronia embrião/endométrio (Kolibianakiset al, Fertil Steril, 2004)
- Fase folicular prolongada / aumento de E2
- Antecipar o Trigger
- Evitar > 2 dias ou ≥ 3 foliculos com ≥17mm em FSH/GnRH antagonista (Kyriu et al,Hum. Reprod., 2009)

Avaliar cada caso se vale a pena deixar de recuperar um número maior de oocitos maduros se podemos simplesmente congelar todos os embriões.



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Elevação precoce de progesterona

- Utilização de mild stimulation – previne elevação de E2 e P4 (Al-Azemi et al, Hum. Reprod. 2011)
- E2/P o dia do hCG, reserva ovariana normal, e transferência em D+3 X D+5.
- Melhor taxa de gestação com P<1,5ng/ml e E2/P < 0,55 em D+3, mas sem diferença em D+5. Sensibilidade 82% e especificidade de 44% (Eldingy, E.A. Fertil Steril, 2010)

Alteração temporária?

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Elevação precoce de progesterona

- Criopreservação de todos os oócitos/embriões e transferir em ciclo natural – 31,1% x 14,5% (Fatemi, HM, Fertil Steril, 2010)
- Congelar os embriões 2PN e cultivar até blastocisto no ciclo de transferência (Shapiro et al, Fertil Steril, 2010)

	Fresh embryo transfer	Thawed embryo transfer	*P* value
Blastocyst transfers	399	37	
Patient age	32.6 ± 4.2	33.8 ± 4.5	NS
Embryos transfered	2.0 ± 0.5	2.1 ± 0.6	NS
Implantation rate	25.2%	54.4%	<.0001
Ongoing pregnancies	126 (31.6%)	26 (70.3%)	<.0001

- Congelar em D+3 quando P>1,5 ng/ml e transferir após preparo endometrial com E2 e 3 dias de P. (Roque, M, Fertil Steril 2015)
- Taxa de implantação 19,9% x 26,5%
- Taxa de gestação ongoing 31,1% x 39,7%

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Conclusões

- Elevação precoce de progesterona em ciclos de FIV piora as taxas de gestação em ciclos a fresco
- O valor de corte -1,5 ng/ml no dia do hCG
- O efeito deletério na receptividade endometrial, não influencia nos parâmetros oocitarios e embrionários
- Etiologia multifatorial
- Prevenção - individualizar os protocolos, timing do trigger, monitorizar , congelar os oócitos ou embriões.

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