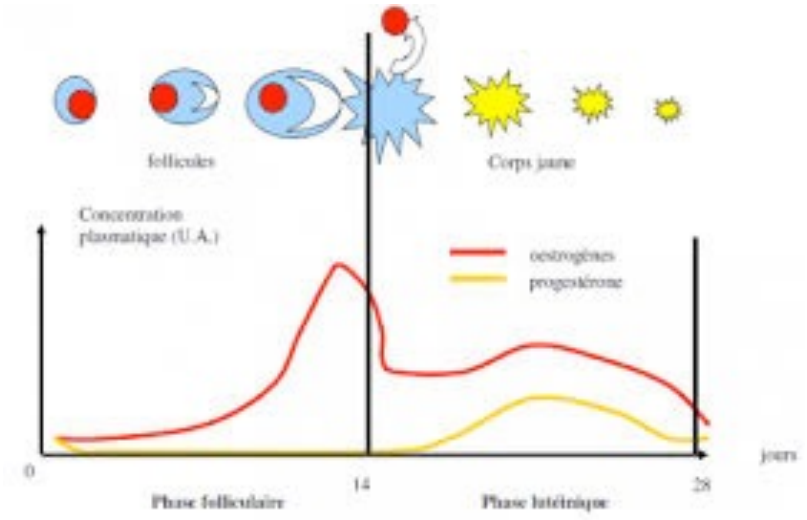
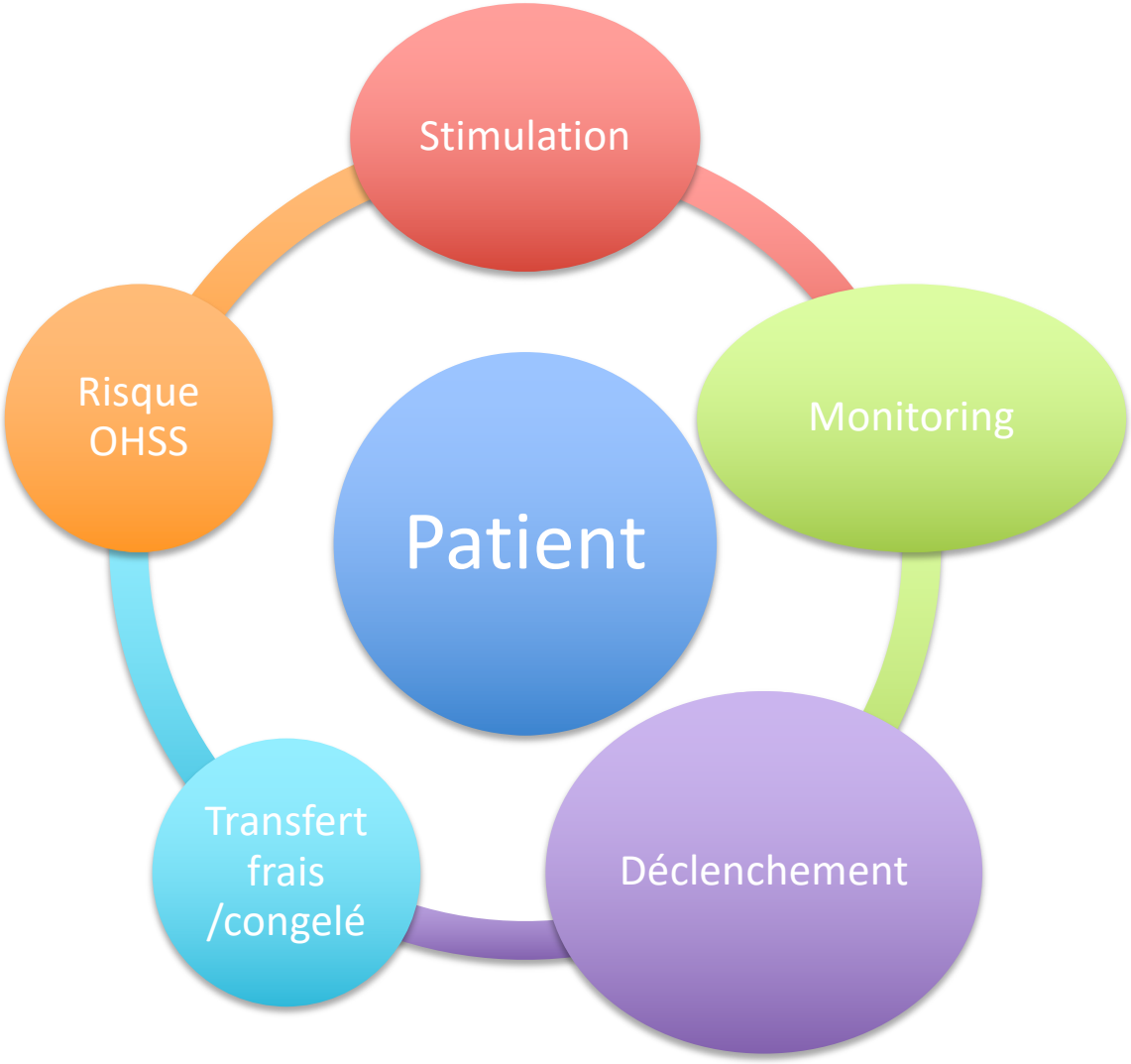


Nouveautés dans la stimulation d'ovulation et regain d'intérêt pour la phase lutéale

Anne Guivarc'h-Levêque
Clinique Mutualiste la sagesse Rennes

Evolution des pratiques



Nombre d'ovocytes optimum

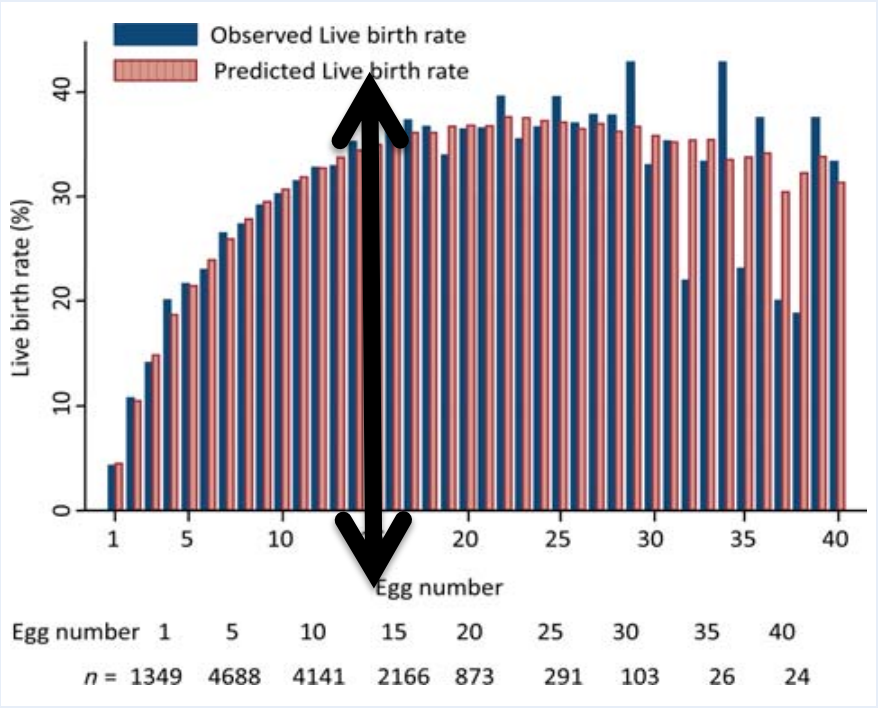


Figure 4 Observed versus predicted live birth rate in data from 2006 to 2007.

Optimum 15 ovocytes

A moduler Selon l'Age

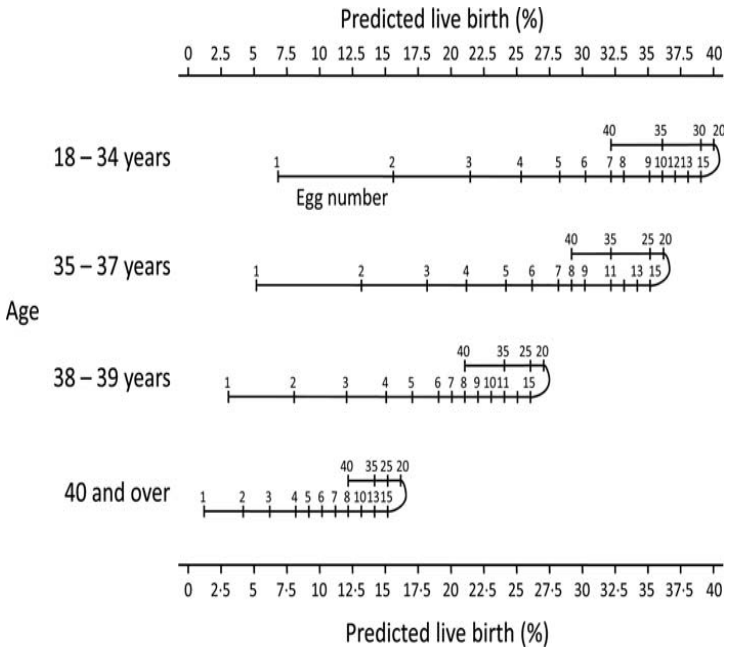
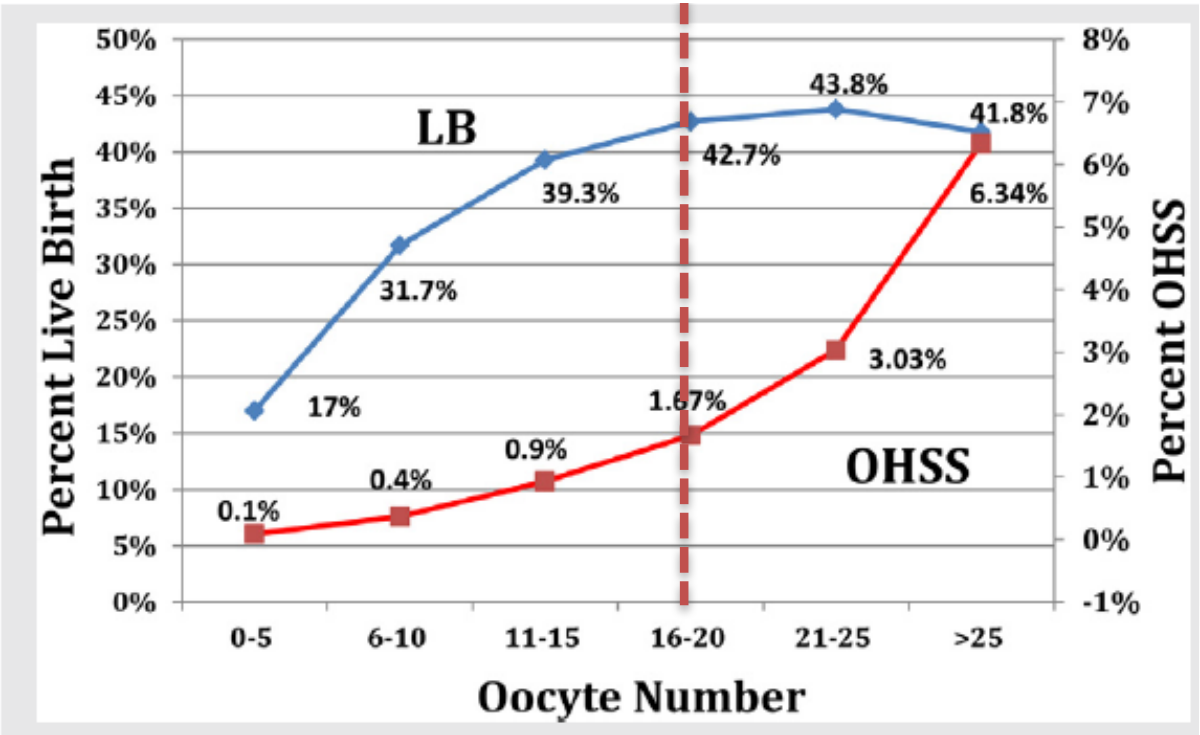


Figure 5 Nomogram to calculate predicted live birth probability given egg number and age.

Sunkara Human Reprod 2011

Risque OHSS en fonction du nombre d'ovocytes



Risque OHSS avec nombre d'ovocytes > 15

Steward RG Fertil Steril 2014

Evaluation réserve ovarienne

Table V Comparison of characteristics of the most widely used markers of ovarian reserve

Characteristics for a good marker	Age	AMH	FSH	AFC
Prediction of poor response	+	+++	++	+++
Prediction of hyper response	+	+++	−	++
Low inter-cycle variability	+++	++	−	++
Low intra-cycle variability	+++	++	−	++
Blinded to the operator	+++	+++	+++	−
Applicable to all patients (a)	+++	+++	+	+
Cheapness	+++	−	−	−

La Marca A Human Reprod 2010

Classement selon nb ovocytes

Table I IVF outcome for groups of women with different ovarian response.

	Ovarian response groups				
	Group A 1–3 oocytes *n* = 83	Group B 4–9 oocytes *n* = 471	Group C 10–15 oocytes *n* = 327	Group D >15 oocytes *n* = 218	*P*-value
Live birth in the fresh cycle*	14 (16.9%)	140 (29.7%)	111 (33.4%)	70 (32.1%)	0.02[b]
Cumulative live birth*	18 (21.7%)	187 (39.7%)	165 (50.5%)	134 (61.5%)	<0.001[b]

Faible Suboptimale Optimale Hyper

Drakopoulos Human Reprod 2016

Développement des protocoles antagonistes

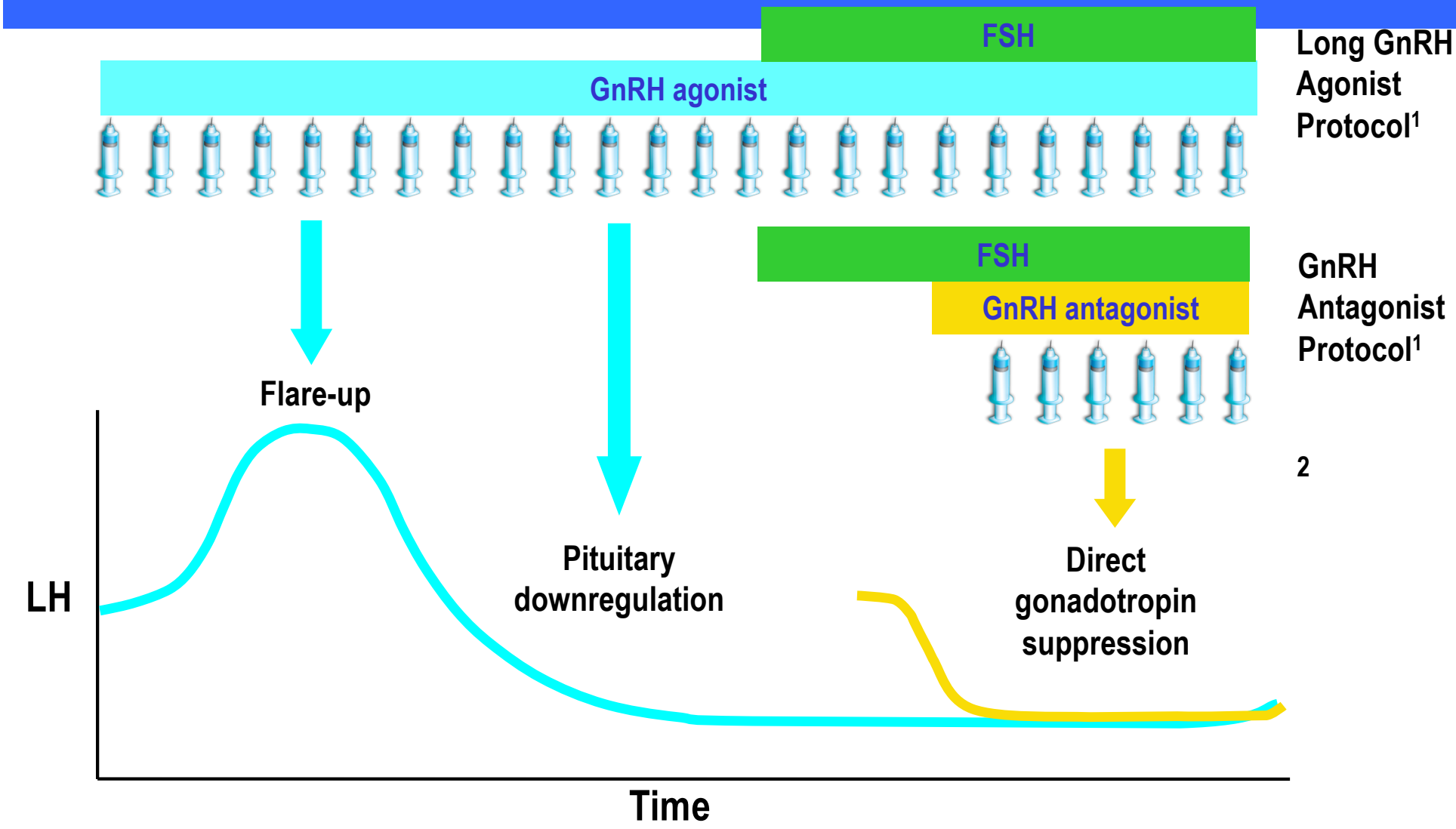
Human Reproduction, Vol.24, No.4 pp. 764–774, 2009
Advanced Access publication on January 19, 2009 doi:10.1093/humrep/den468

human reproduction OPINION

Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment

Paul Devroey[1,10], Mohamed Aboulghar[2], Juan Garcia-Velasco[3], Georg Griesinger[4], Peter Humaidan[5], Efstratios Kolibianakis[6], William Ledger[7], Candido Tomás[8], and Bart C.J.M. Fauser[9]

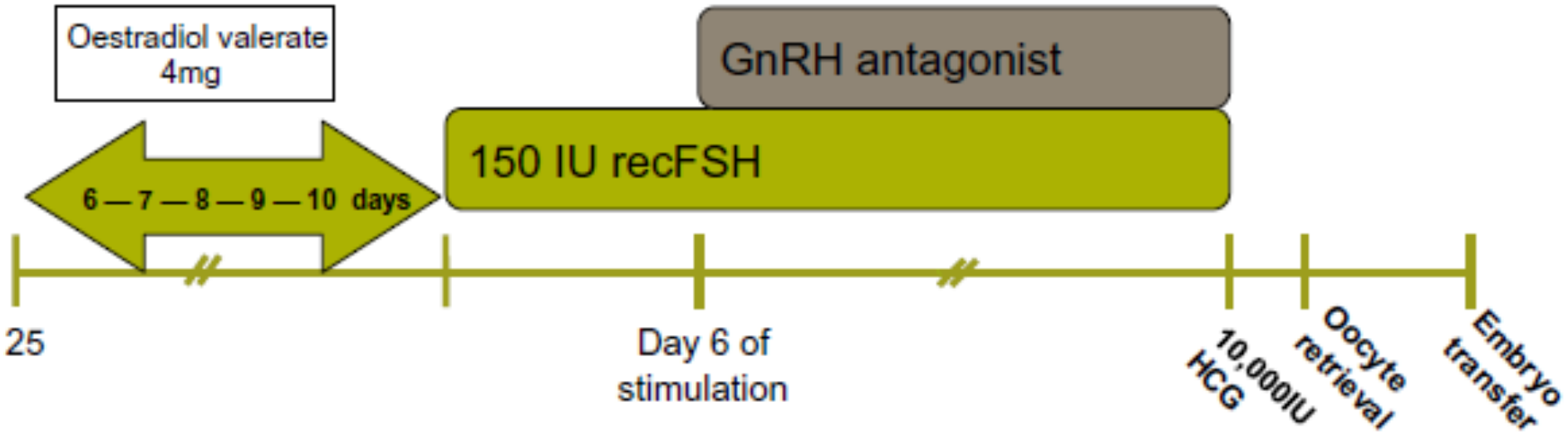
GnRH Antagonist Cycles Are Shorter Than Long GnRH Agonist Cycles



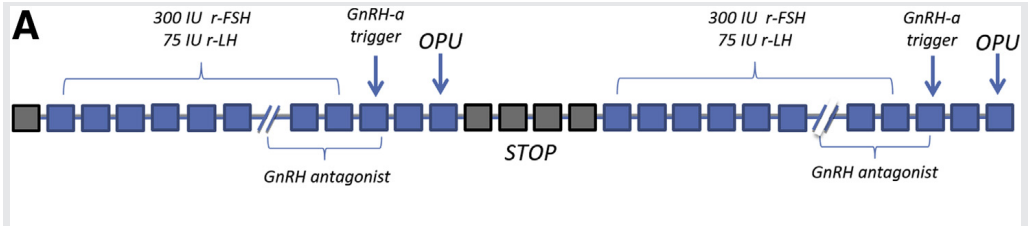
1. Adapted with permission from de Greef R et al. *Clin Pharmacol Ther*. 2010;88:79–87.
2. Adapted from Hodgen. *Contemp Rev Obstet Gynaecol*. 1990;35:10–24.

Programmation avec les antagonistes

- E_2 pretreatment (Guivarc'h, 2010, Blockeel et al., 2012, Cedrin-Durnerin et al., 2012)
- OCP pretreatment (Wei et al., 2017)



Stimulation en phase folliculaire et phase lutéale = Duostim

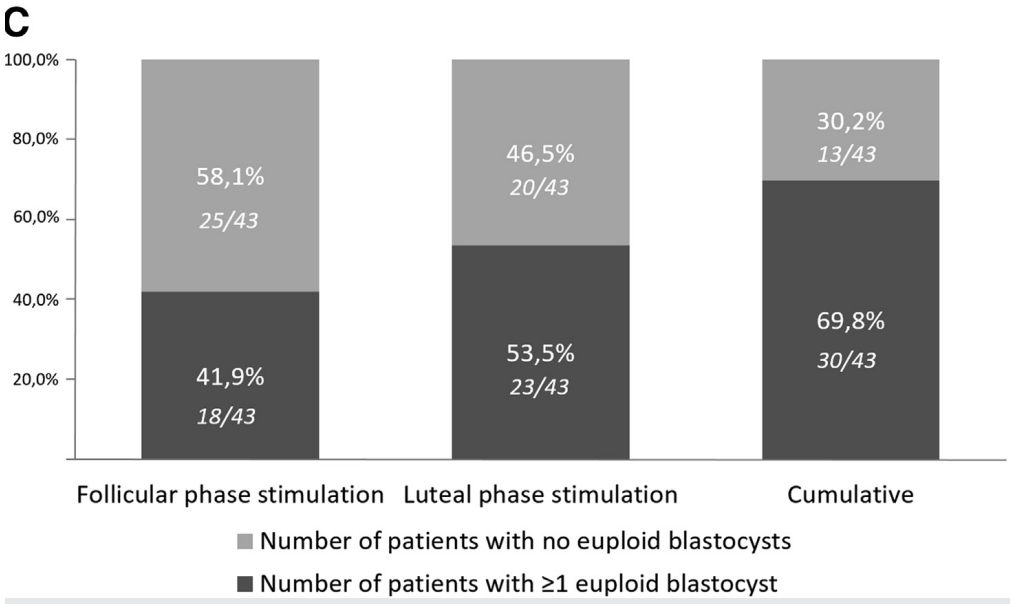


Preliminary clinical outcomes according to follicular or luteal phase stimulation.

	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.

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



Ubalfi Fertil Steril 2016

Apparition de nouvelles molécules

Dosage fonction du poids
Longue durée d'action 7J

Dosage fonction du poids et de l'AMH
Déterminée par calculateur et fixe
Cible entre 8 et 14 ovocytes

Long-acting FSH versus daily FSH for women undergoing assisted reproduction (Review)

Pouwer AW, Farquhar C, Kremer JAM

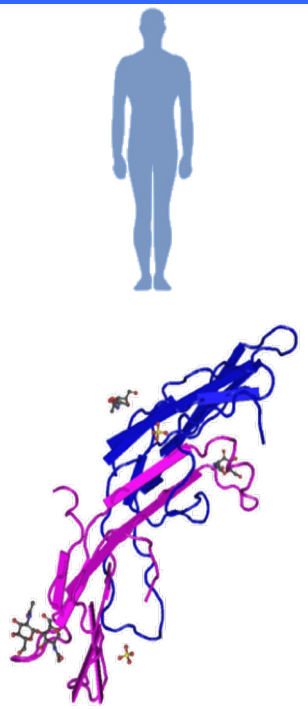
THE COCHRANE COLLABORATION

Is there a place for corifollitropin alfa in IVF/ICSI cycles? A systematic review and meta-analysis

Fertility and Sterility® Vol. 97, No. 4, April 2012

: In view of its equivalence and safety profile, corifollitropin alfa in combination with daily GnRH antagonist seems to be an alternative for daily rFSH injections in normal responder patients undergoing ovarian stimulation in IVF/ICSI treatment cycles

Follitropin delta est la première FSH recombinante humaine dérivée d'une lignée cellulaire humaine



Identical amino acid sequence as natural human FSH and existing CHO-derived rFSH products

+

Expression in a cell line of human origin

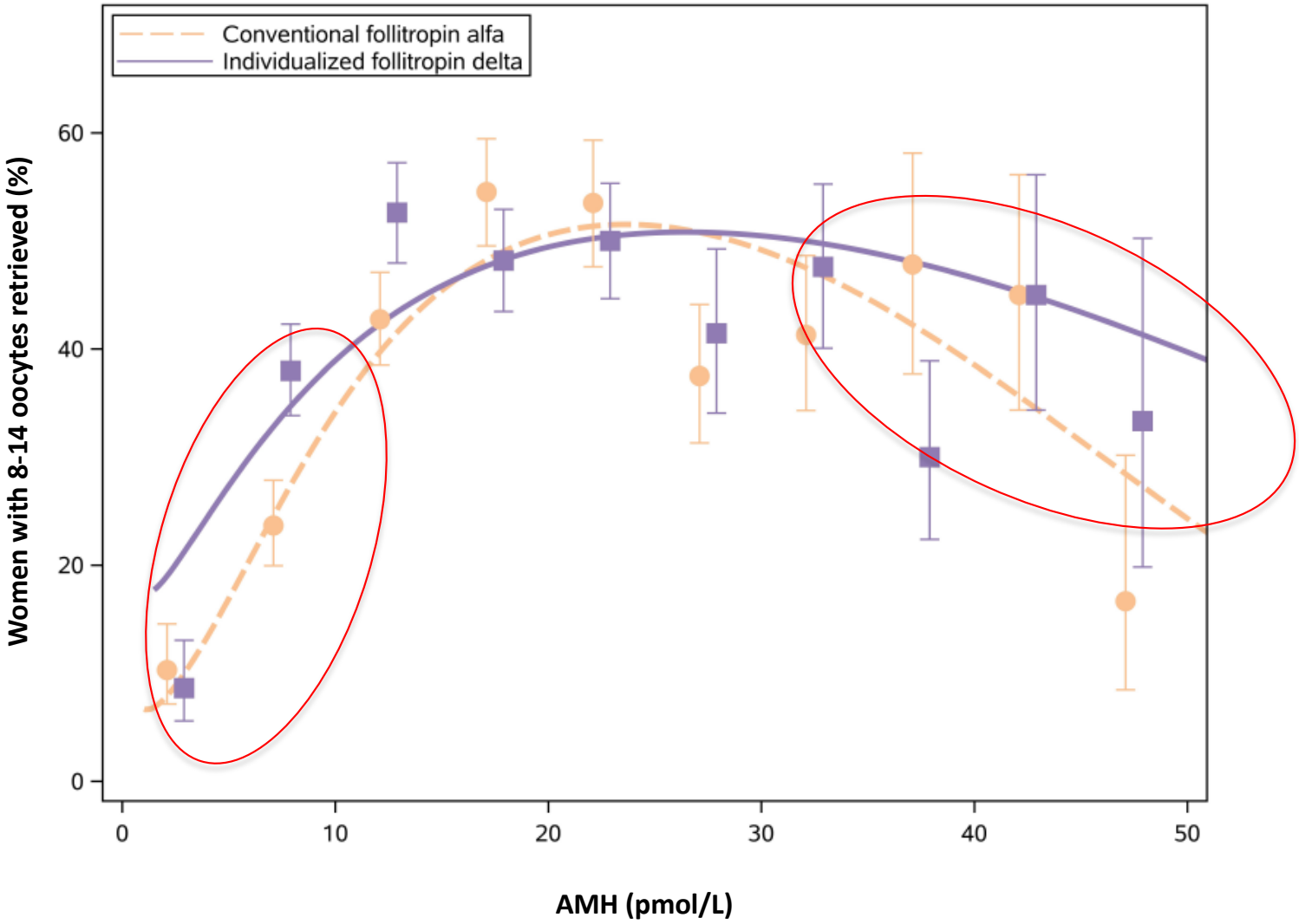
=

Glycosylation pattern that is more complex than rFSH derived from non-human, mammalian CHO cell line

- European Commission marketing authorisation of REKOVELLE® (follitropin delta) – 12 December, 2016

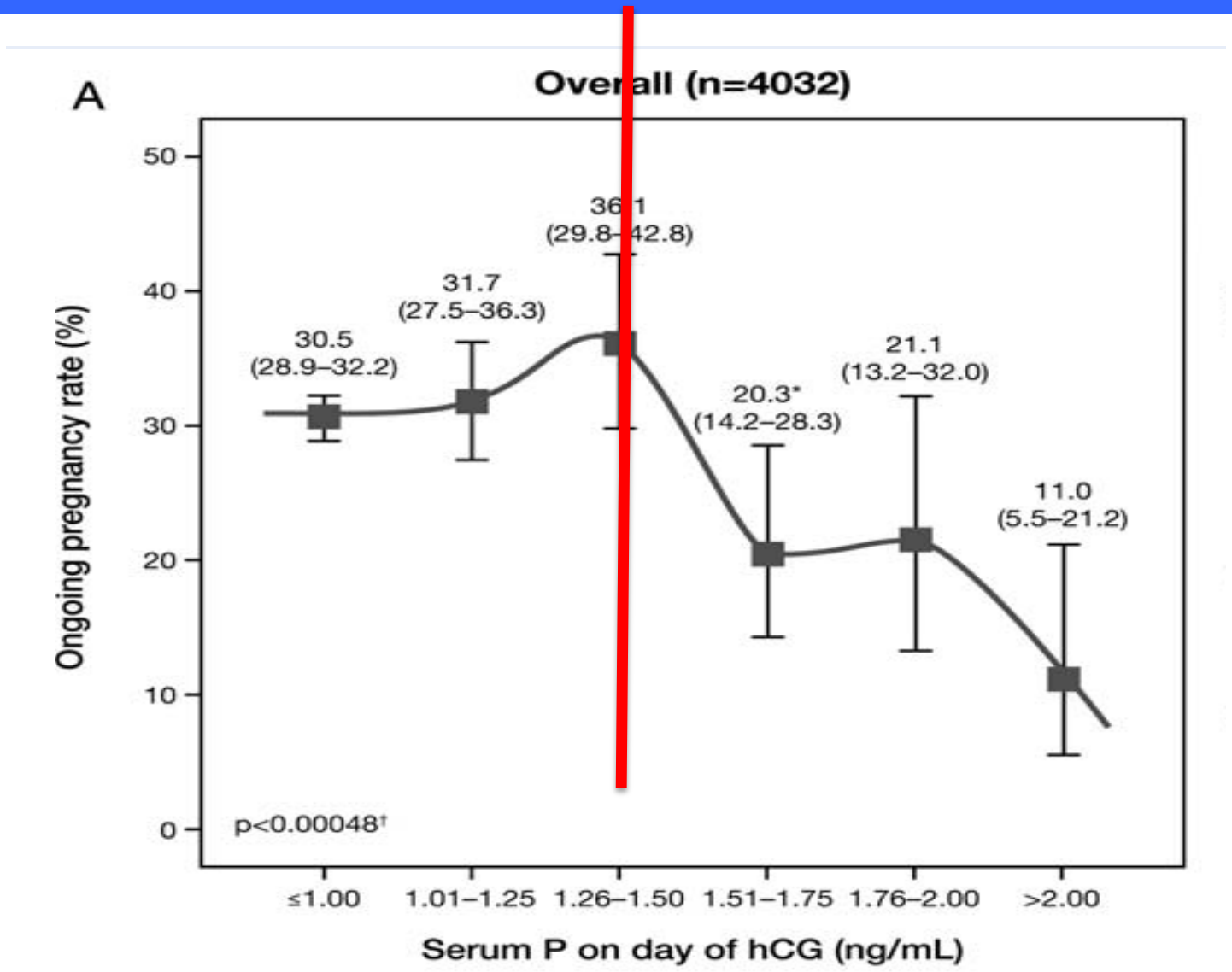
Resultats +Femmes qui ont atteint la cible de 8 à 14 ovocytes prélevés

Plus de femmes à atteindre la cible de 8à 14 ovocytes avec dosage individualisé de follitropin delta



MONITORING DE LA PROGESTÉRONE PHASE FOLL

Progestérone fin de phase folliculaire

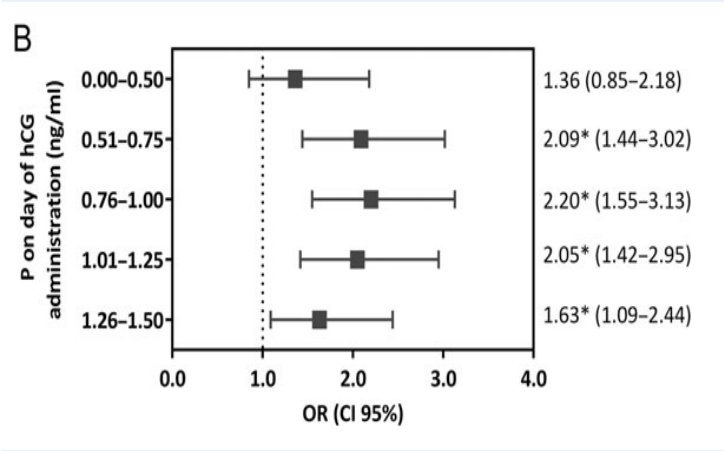


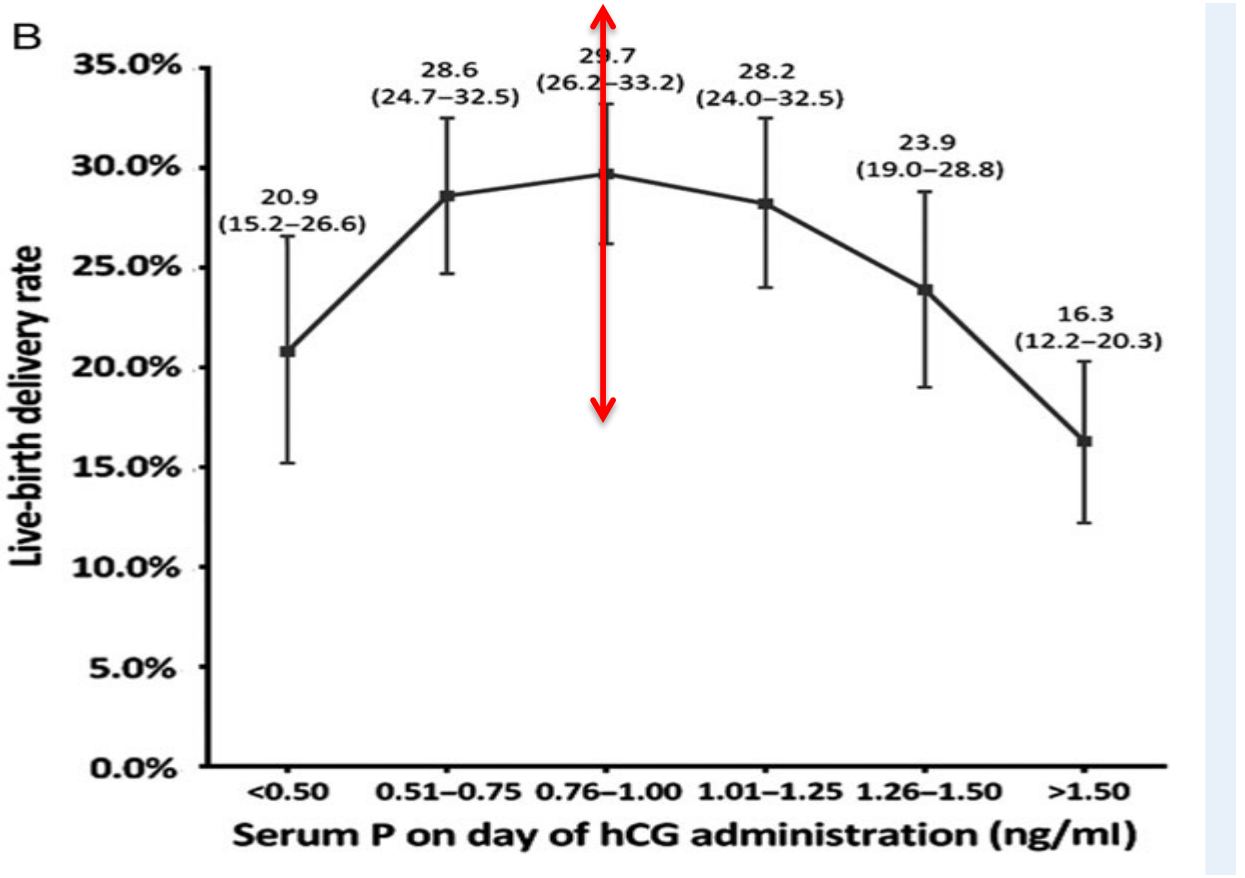
1,5

BOSCH E HR 2011

Un taux trop bas de progestérone semble également délétère

2723 cycles
1er 2ème cycle
Antag



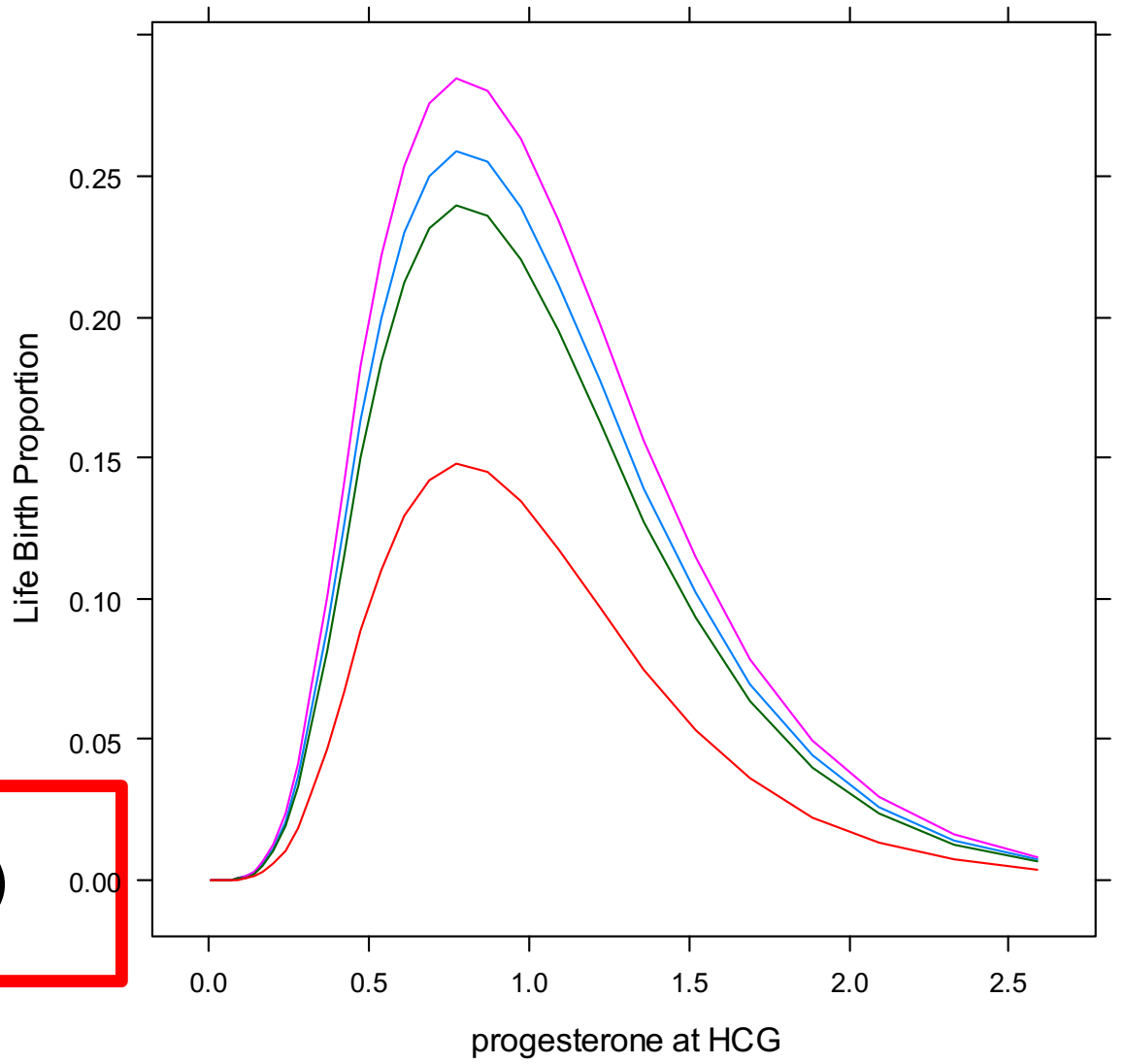


Blockeel and al Human Reprod 2014

Intervalle optimum de Pg en fin phase folliculaire

	total	
Nb cycles	5477	
Nb patientes	2192	
Age	34	19-43
Nb tent	2	±1,3
Antag	65.1	
Long Agonist	24.1	
Court Agonist	10.8	
Infert Primaire	56.6	
Infert secondaire	43.4	

Valeur optimale Pg HCG 0,8ng/ml
Baisse 34% de Lb si PgHCG ≠(0,5 - 1,1)
OR 0,66 (0,56-0,77) 33,8% effectif



A. Guivarch et al ESHRE 2017 RBMO

DÉCLENCHEMENT PAR AGONISTE DU GNRH

Pic de LH naturel et induit par agoniste

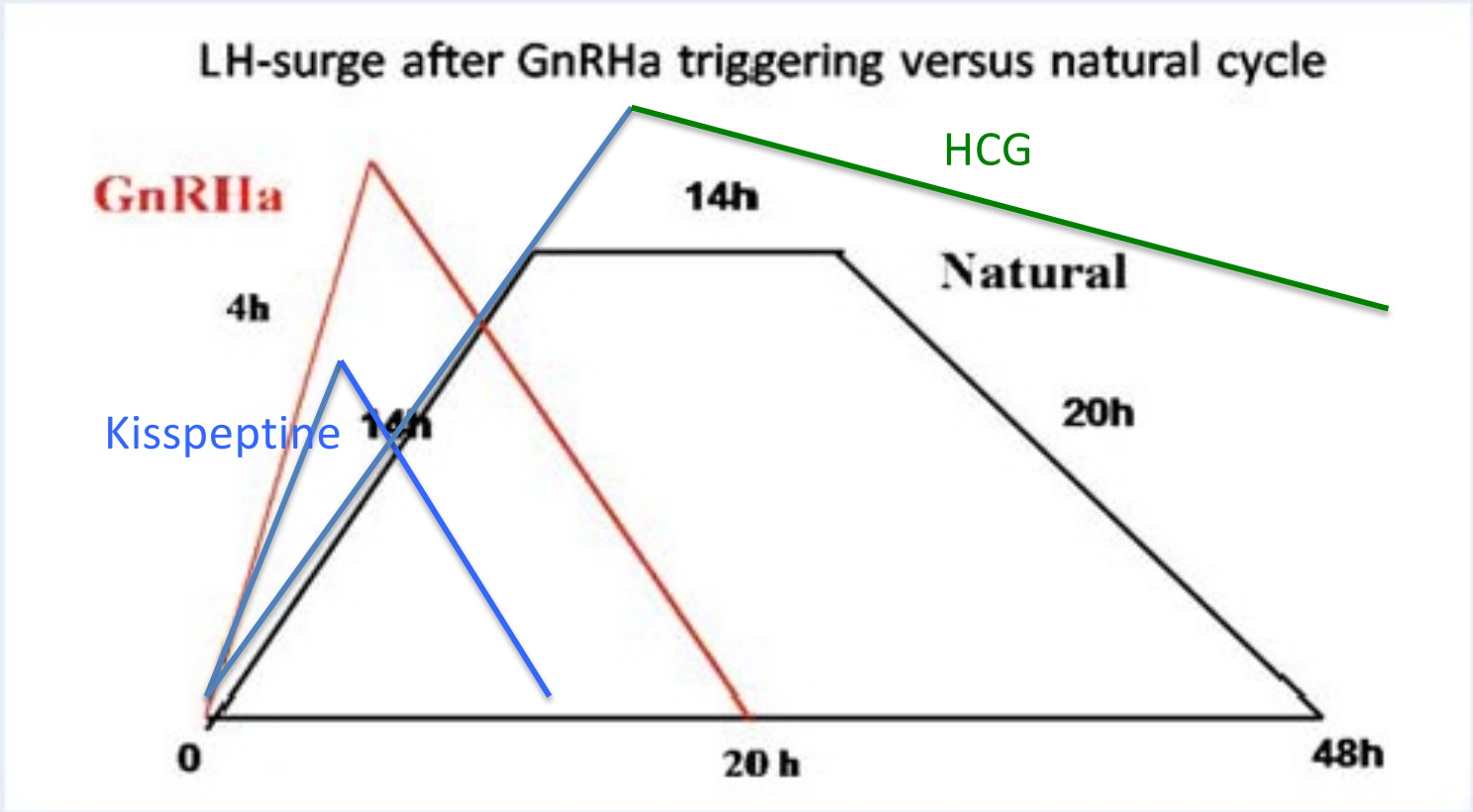
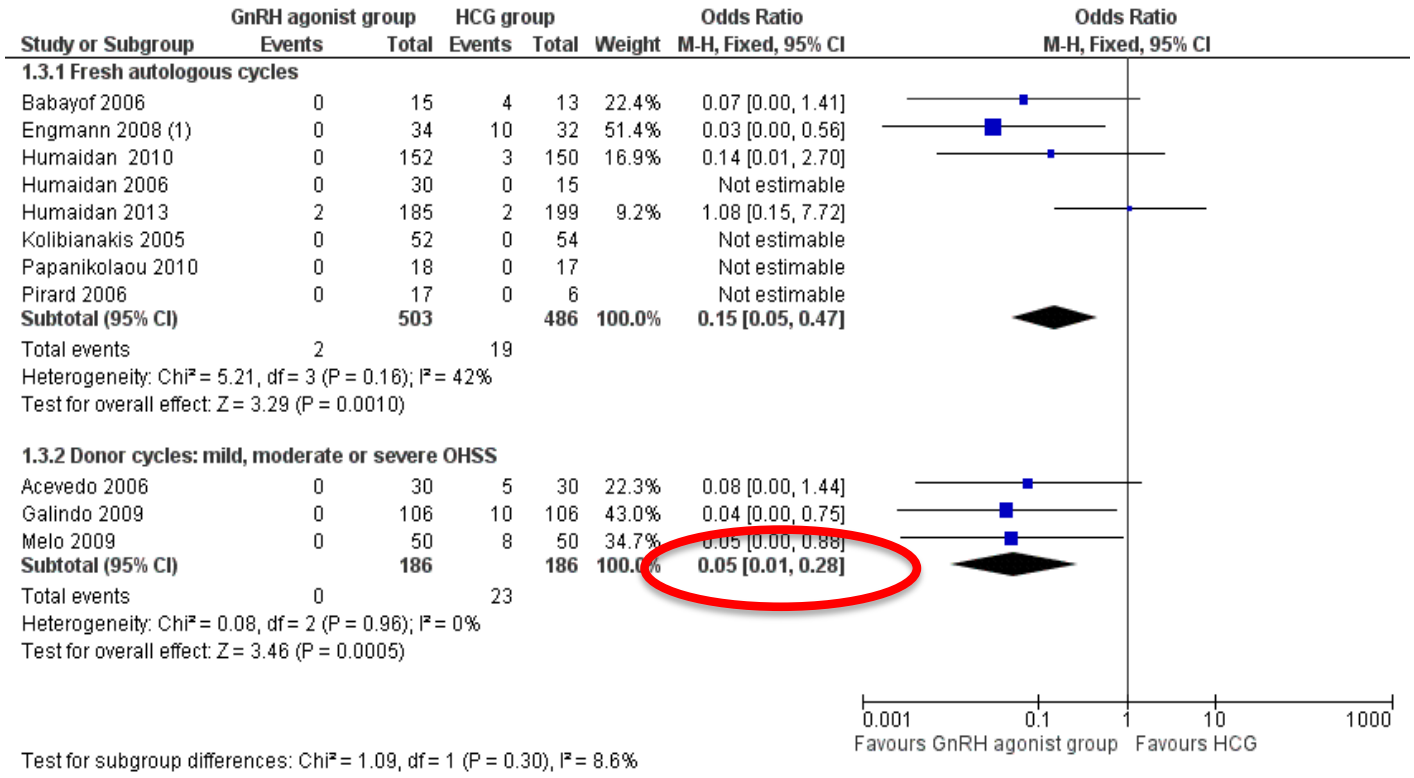


Figure 1 Differences in LH-surge after GnRH-agonist triggering when compared with a natural cycle.

Humaidan HR update 2011

Déclenchement de l'ovulation par agoniste et OHSS

Figure 5. GnRH agonist versus HCG for oocyte maturation triggering, outcome: 1.2 OHSS incidence per women randomly assigned.



Youssef M Cochrane Review 2014

Human Reproduction, Vol.26, No.10 pp. 2593–2597, 2011
Advanced Access publication on August 9, 2011 doi:10.1093/humrep/der251

human reproduction

OPINION

An OHSS-Free Clinic by segmentation of IVF treatment

Paul Devroey*, Nikolaos P. Polyzos, and Christophe Blockeel

Centre for Reproductive Medicine, UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium

*Correspondence address. Tel: +32-477-380889; Fax: +32-2-477-6649; E-mail: paul.devroey@uzbrussel.be

The use of the GnRH antagonist protocol

Ovulation triggering Agonist

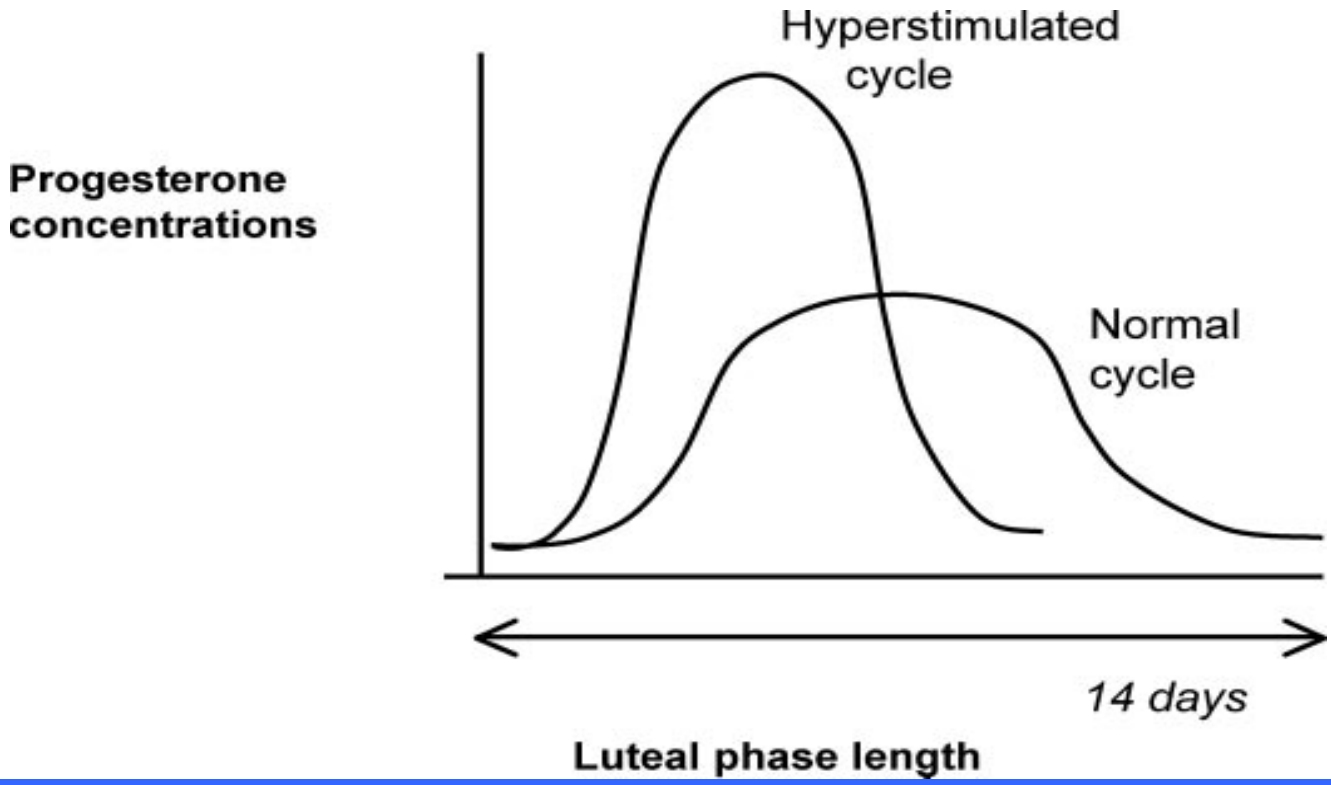
Cryopreservation of oocytes and embryos

Conclusion évolution stimulation

- Définition de la stimulation optimale
  - Nb ovo cible
- Protocoles
  - Antagoniste
  - Stimulation aléatoire folliculaire et lutéale
  - Nouvelles molécules
- Sécurité
  - Déclench ago

REGAIN D’ INTERÊT PHASE LUTEALE

Ce qui est sur pour les cycles frais !!

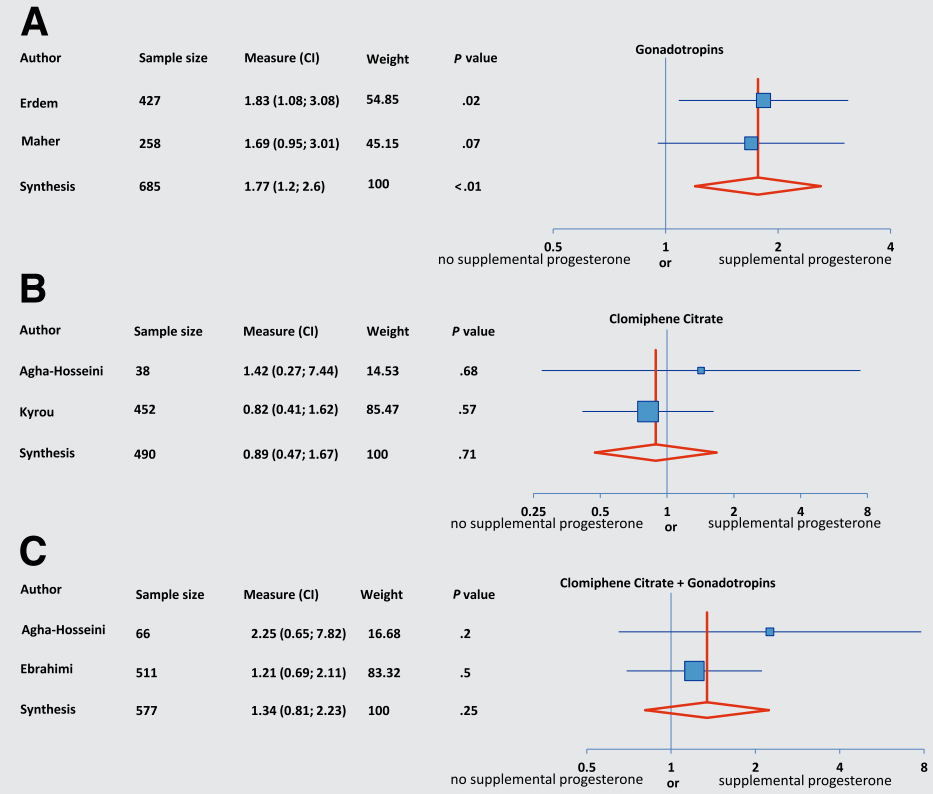


Insuffisance lutéale constante cycles hyperstimulés majorée si déclenchement agoniste

Maclon NS Endocrine reviews 2006

CYCLE DÉCLENCHÉ PAR HCG

Soutien phase lutéale hors fiv selon type de stimulation



Forrest plot of clinical pregnancy in subgroup analysis based on method of ovulation induction. (A) gonadotropins; (B) clomiphene citrate; (C) clomiphene citrate + gonadotropins. CI = confidence interval.

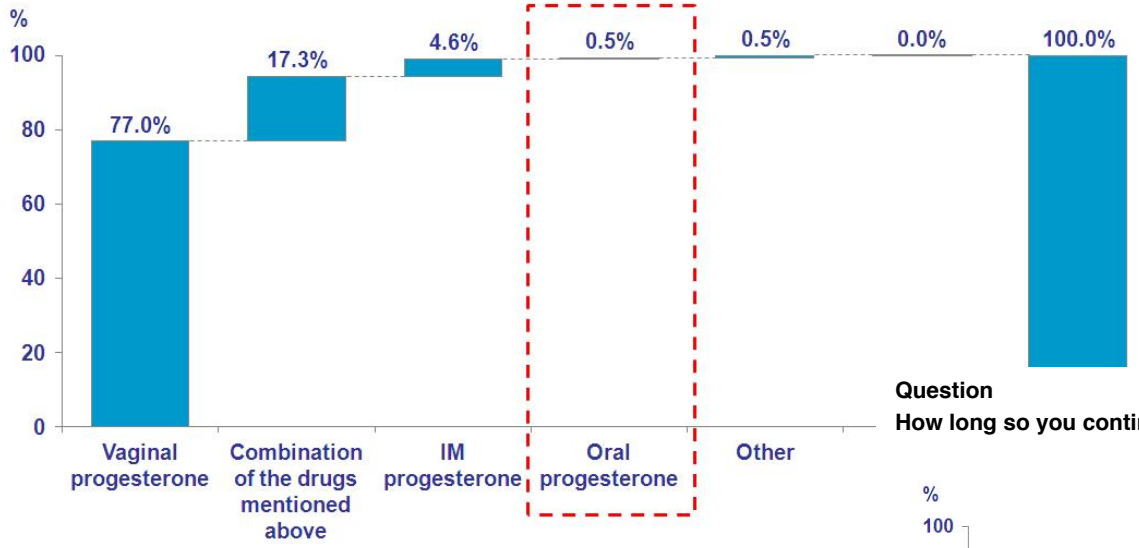
Hill. Progesterone luteal support for IUIs. Fertil Steril 2013.

Sauf si Clomid seul

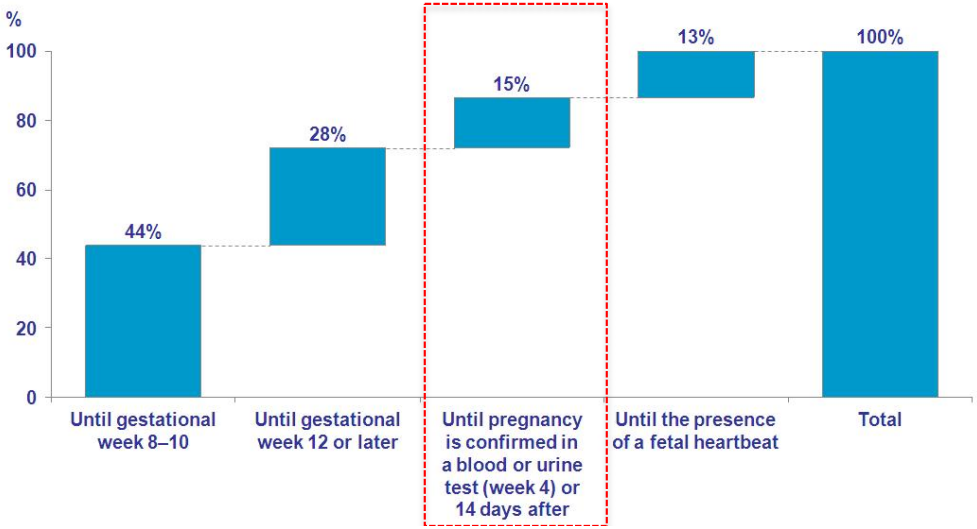
Hill Fertil Steril 2013

Quelle progestérone et quelle durée pour le soutien de la phase lutéale en FIV ?

Question:
Which agent/route is your treatment of choice to support the luteal phase



Question
How long so you continue progesterone sepplementation of the patient concieved?



IVF worldwide survey 2012

Pénibilité de la progestérone vaginale et de sa durée !

Study or Subgroup	early P cessation Events	Total	P continuation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andersen 2002	118	150	126	153	83.1%	0.96 [0.85, 1.07]
Goudge 2010	25	35	24	31	16.9%	0.92 [0.70, 1.22]
Total (95% CI)		**185**		**184**	**100.0%**	**0.95 [0.86, 1.05]**
Total events	143		150			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.97 (P = 0.33)

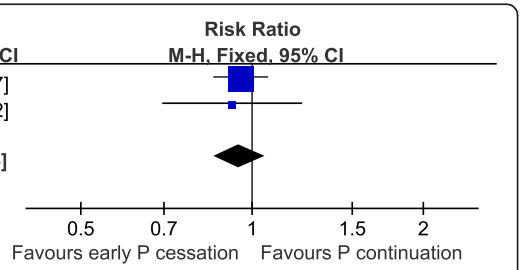


Figure 4 Live birth rate of women who underwent early P cessation versus P continuation after IVF/ICSI.

Liu et al RBEJ 2012

Y a t'il une place pour autre progestérone ?

PLOS ONE

RESEARCH ARTICLE

Subcutaneous Progesterone Is Effective and Safe for Luteal Phase Support in IVF: An Individual Patient Data Meta-Analysis of the Phase III Trials

Jakob Doblinger[1], Barbara Cometti[2], Silvia Trevisan[2], Georg Griesinger[3]*

1 Department of Obstetrics and Gynecology, Paracelsus Medical University, Salzburg, Austria, **2** IBSA Institut Biochimique SA, R&D Scientific Affairs, Lugano, Switzerland, **3** Department of Gynecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany

Human Reproduction, Vol.32, No.5 pp. 1019–1027, 2017
Advanced Access publication on March 1, 2017 doi:10.1093/humrep/dex023

human reproduction

ORIGINAL ARTICLE *Infertility*

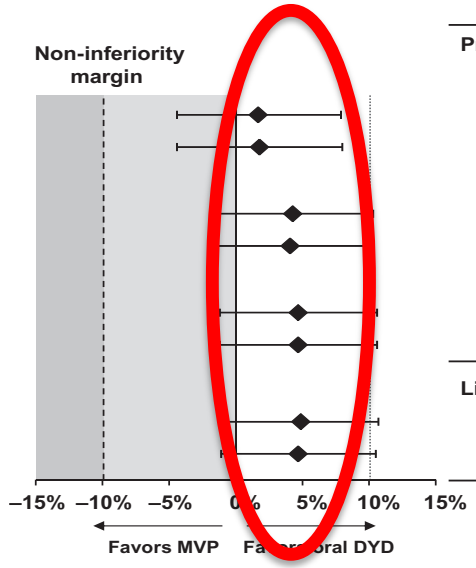
A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in *in vitro* fertilization

Herman Tournaye[1], Gennady T. Sukhikh[2], Elke Kahler[3,*], and Georg Griesinger[4]

Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?

Georg Griesinger, M.D.,[a] Christophe Blockeel, M.D.,[b] and Herman Tournaye, M.D.[b]

[a] Department of Gynecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Luebeck, Germany; and [b] Center for Reproductive Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium



Outcome	% (*n*/*N*)		Difference in pregnancy rate (Oral DYD–MVP)	95% CI
	Oral DYD	MVP		
Pregnancy rate				
4 weeks of gestation				
FAS	47.1 (234/497)	45.5 (217/477)	1.7	–4.4–7.9
PPS	47.2 (232/492)	45.5 (216/475)	1.8	–4.4–8.0
8 weeks of gestation				
FAS	39.6 (197/497)	35.4 (169/477)	4.3	–1.7–10.3
PPS	39.6 (195/492)	35.6 (169/475)	4.1	–1.9–10.1
12 weeks of gestation				
FAS	37.6 (187/497)	33.1 (158/477)	4.7	–1.2–10.6
PPS	37.6 (185/492)	33.1 (157/475)	4.7	–1.2–10.6
Live birth rate				
FAS	34.6 (172/497)	29.8 (142/477)	4.9	–0.8–10.7
PPS	34.6 (170/492)	29.9 (142/475)	4.7	–1.1–10.5

Figure 2 Pregnancy status post-treatment. Positive pregnancy rates at 4, 8 and 12 weeks of gestation, and the live birth rates are shown for both the FAS and PPS. A non-inferiority margin of 10% was used, whereby the test drug is non-inferior if the lower bound of the 95% CI excludes a difference greater than 10% in favor of the comparator.
CI, confidence interval; DYD, dydrogesterone; FAS, full analysis sample; MVP, micronized vaginal progesterone; PPS, per protocol sample.

CYCLE DECLENCHE PAR AGONISTE

Modèle Européen : population à risque

Table III **Reproductive outcome for women in the two RCTs.**

	>14 follicles	
	Group A: GnRHa trigger + 1.500 hCG	**Group B: hCG trigger**
Patients, *n*	60	58
Rate of transfer, *n* (%)	52/60 (86.7)	57/58 (98.3)
Embryos transferred. mean (SD)	1.19 (0.40)	1.19 (0.40)
Positive hCG per embryo transfer, *n* (%)	25/52 (48.1)	21/57 (36.8)
Clinical pregnancy per patient, *n* (%)	21/60 (35.0)	17/58 (29.3)
Ongoing pregnancy per patient, *n* (%)	17/60 (28.3)	15/58 (25.9)
Implantation rate, *n* (%)	22/62 (35.5)	20/68 (29.4)
Early pregnancy loss, *n* (% of positive hCG)	4/25 (16.0)	4/21 (19.0)
OHSS rate, *n* (%)	0/60 (0)	2/58 (3.4)

RR, relative risk; CI, confidence interval; OHSS, ovarian hyperstimulation syndrome.

Humaidan HR 2013

Declenchement par agoniste transfert frais modèle Européen

	population	Nb de cycles	Taux de réussite	OHSS
Radesic 2011	>14 foll >11mm S8 S9	71	52,1% G/T 1 blasto	1
Illiodromiti 2013	>14 foll >12mm JHCG AMH > E2 >	275	41,8%G/cycle 1 blasto	2
Sehyan 2013	Nb foll > 12 E2 élevé	23	17,4%G/T	6
Guivarc'h 2013	>20 foll> 11 JHCG E2>4000pg Atcd OHSS	68	39,6%G/T	1

TRANSFERT D’EMBRYON DIFFÉRÉ.

Quel est le meilleur traitement pour transfert d'embryon différé?

Table II Outcomes per embryo transfer.

	Overall	Type of frozen embryo transfer cycle		OR (95% CI)	*P*-value
		Modified natural	Artificial		
Clinical pregnancy/ET	167/734 (22.8%)	94/394 (23.9%)	75/340 (22.1%)	0.8 (0.64–1.27)	0.6
Ongoing pregnancy/ET	101/734 (13.8%)	57/394 (14.5%)	45/340 (13.2%)	0.8 (0.52–1.22)	0.3
Live birth/ET	98/734 (13.4%)	57/394 (14.5%)	41/340 (12.1%)	0.8 (0.53–1.25)	0.3

Groenenwoud HR 2016

Table IV Reproductive outcome per embryo transferred and per embryo transfer.

	Natural cycle	hMG	Relative risk	*P*-value[a]
Reproductive outcome per embryo transferred				
Total *N* embryos transferred	*n* = 332	*n* = 340		
Implantation rate (IU + EU)[b]: % (95% CI)	12.4 (9.1–16.8)	16.2 (12.4–21.1)	1.3 (95% CI 0.9–2.0)	0.191
Implantation rate with FHB[c]: % (95% CI)	10.2 (7.3–14.3)	14.1 (10.6–18.7)	1.4 (95% CI 0.9–2.1)	0.153
Live birth rate: % (95% CI)	9.6 (6.8–13.6)	13.2 (10–17.7)	1.4 (95% CI 0.9–2.2)	0.171
Reproductive outcome per embryo transfer cycle	*n* = 213 cycles	*n* = 221		
Clinical pregnancy rate (IU + EU): % (95% CI)	17.4 (12.6–24.0)	23.5 (17.9–30.9)	1.4 (95% CI 0.9–2.1)	0.159
Clinical pregnancy rate with FHB[b]: % (95% CI)	14.6 (10.2–20.7)	20.8 (15.6–27.8)	1.4 (95% CI 0.9–2.3)	0.124
Live birth rate: % (95% CI)	14.1 (9.8–20.2)	19.9 (14.8–26.8)	1.4 (95% CI 0.9–2.3)	0.145
Reproductive outcome per embryo transferred on Day 3				
Total *N* embryos transferred after cryopreservation on Day 3	*n* = 287	*n* = 293		
Implantation rate (IU + EU)[b]: % (95% CI)	12.5 (9.0–17.4)	16.7 (12.6–22.1)	1.3 (95% CI 0.9–2.1)	0.191
Implantation rate with FHB[c]: % (95% CI)	10.1 (7.0–14.6)	15.0 (11.1–20.2)	1.5 (95% CI 0.9–2.4)	0.098
Live birth rate: % (95% CI)	9.8 (6.7–14.1)	14.0 (10.3–19.0)	1.4 (95% CI 0.9–2.3)	0.142

Peeraer HR 2015

Pas de différence

ESHRE 2019 FCS et TEC

- Etude française multicentrique
- Comparaison 14421 cycles
  - cycle naturel (NC)Cycle stimulé (SC) Cycle artificiel (AC) (56%)
- FCS/ naissance
  - NC 25,6%/ 18,8%
  - SC 23,6% /19,3%
  - ***AC 36,5%/ 16,9% p<0,003***
- Augmentation du taux de FCS en cycle artificiel

Faut ’il doser la progestérone avant transfert d’embryon dévitrifié en THS ?

Human Reproduction, Vol.32, No.12 pp. 2437–2442, 2017
Advanced Access publication on October 13, 2017 doi:10.1093/humrep/dex316

human reproduction ORIGINAL ARTICLE *Infertility*

Low serum progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial preparation: a prospective study

E. Labarta[1,*], G. Mariani[1], N. Holtmann[1,2], P. Celada[1], J. Remohí[1], and E. Bosch[1]

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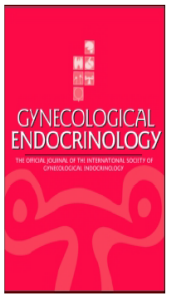

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Low serum progesterone the day prior to frozen embryo transfer of euploid embryos is associated with significant reduction in live birth rates

Gaggiotti-Marre, F. Martinez, L. Coll, S. Garcia, M. Álvarez, M. Parriego, P. Barri, N. Polyzos & B. Coroleu

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ARTICLE

Serum progesterone concentration and live birth rate in frozen–thawed embryo transfers with hormonally prepared endometrium

Isabelle Cédrin-Durnerin[1,*], Tiphaine Isnard[1], Sarah Mahdjoub[2], Charlotte Sonigo[1], Alice Seroka[1], Marjorie Comtet[1], Charlène Herbemont[3], Christophe Sifer[3], Michael Grynberg[1]

CrossMark

Si Prog < 10 ng
Réduction significative des taux de grossesse

Conclusion phase lutéale

- Cycle frais
  - Evolution vers autre voie administration progestérone ?
  - Place pour traitement renforcé par faible dose HCG après déclenchement par agoniste ?
- Cycle différé
  - Recherche du meilleur protocole tjs en cours
  - Optimisation du cycle artificiel par dosage de la progestérone avant transfert embryon

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Take home message: what have we learnt today ? Antonio Pellicer

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