Quels traitements préalables aux stimulations en FIV ?

Anne Guivarc'h-Levêque
Rennes

Paris 11/2012

E2 et OP

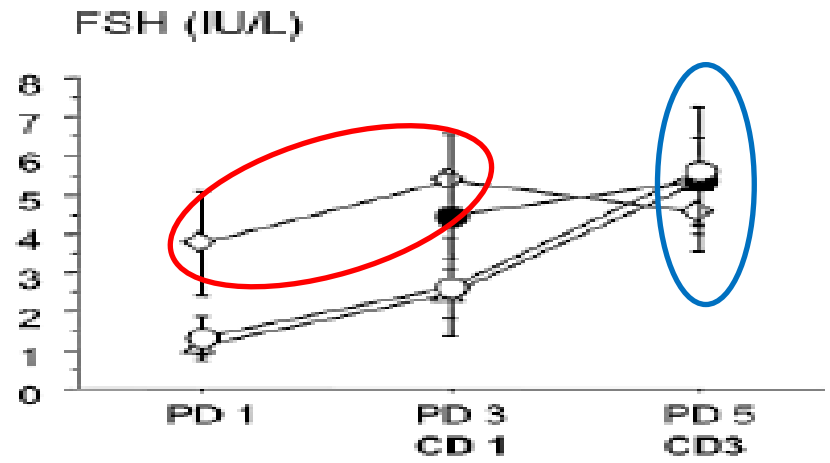
- Pourquoi un prétraitement?
- Comment l' utiliser ?
- Impact sur résultats
- Place dans l'organisation d'un centre

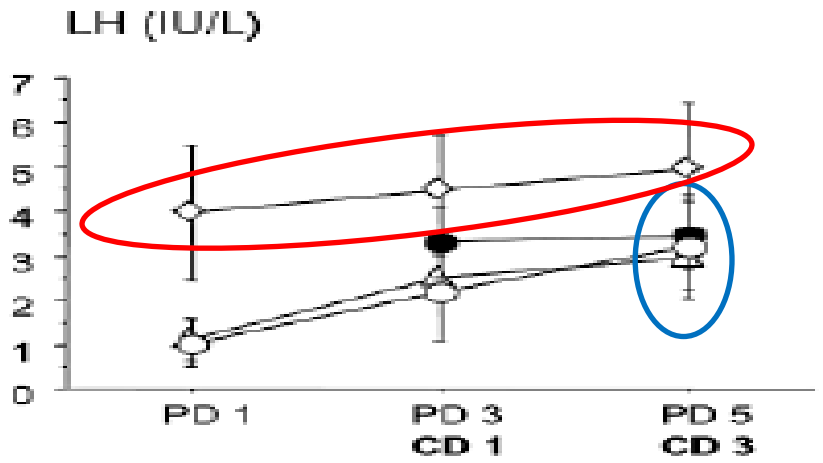
Pourquoi un prétraitement?

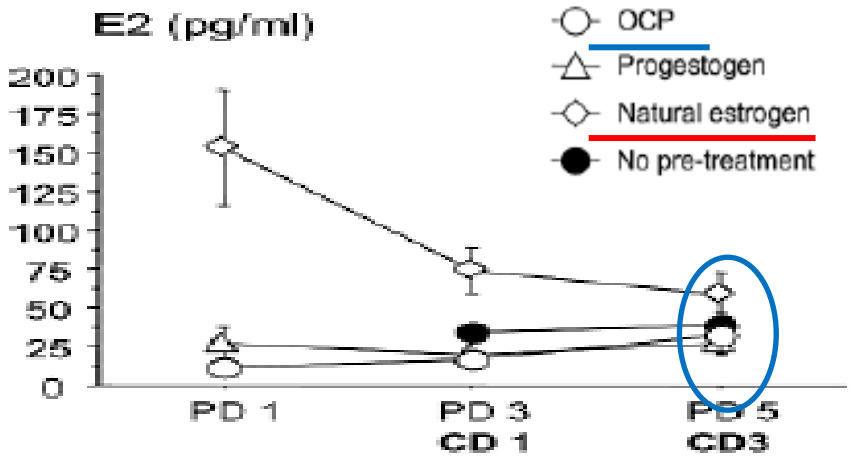
- Transition folliculo-lutéale
  - ↗ FSH 3j avant règle (Mais V JCEM 1987)
  - Inhiber par administration d'E2 (Le Nestour E JCEM 1993)
- Inhomogénéité cohorte folliculaire induite par ↗ FSH femme + agée
  - (Klein NA JCEM 1996)
- Supériorité ago long/ago court
  - (Tan SL fertil Steril 1992)
- Souplesse dans l'organisation

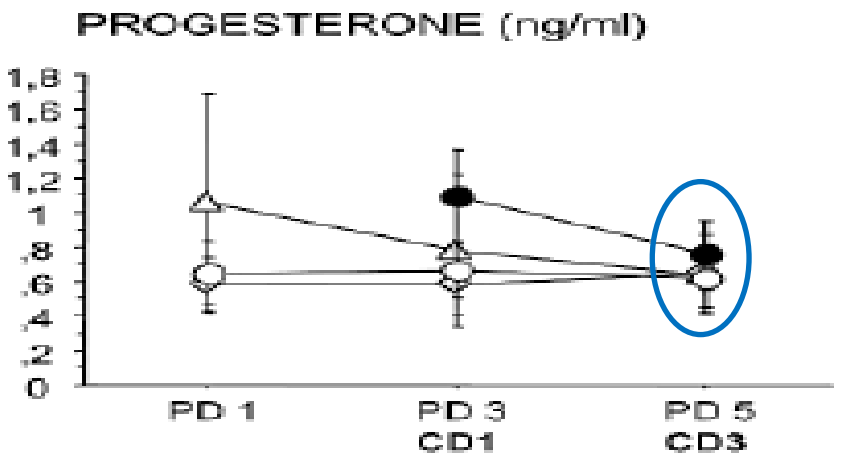
COMMENT L'UTILISER?

Profil hormonal à l'arrêt du prétraitement



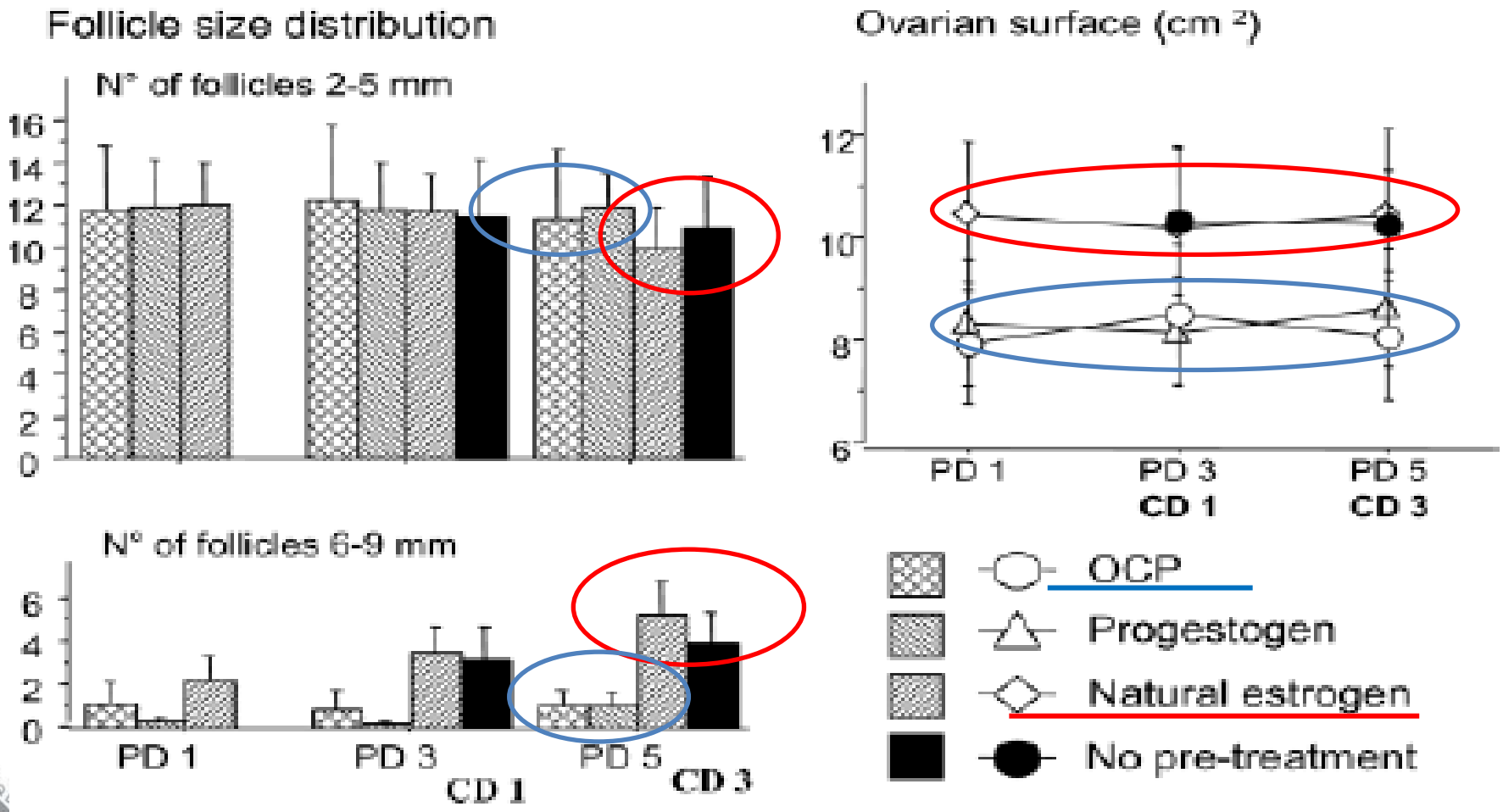






Cédrin I Human Reprod 2007

Ovaire arrêt prétraitement



Cédrin I Human Reprod 2007

Synthèse prétraitement

- Op et progestatif après 5j de wash out
  - Hormonologie = J3 cycle naturel
  - Taille foll antraux < cycle naturel
- Oestrogènes naturels
  - Rebond FSH lendemain arrêt
  - LH reste >
  - Taille foll antraux = cycle naturel

RÉSULTATS OP

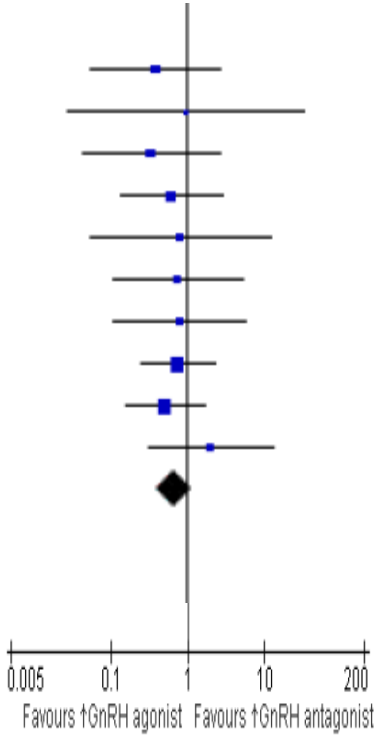
Grossesse clinique évolutive Ago long/OP+Antag

Figure 4. Forest plot of comparison: 1 GnRH antagonist versus long course GnRH agonist, outcome: 1.2 Ongoing pregnancy rate per women randomised.

1.2.4 Women receiving GnRH antagonist plus OCP						
Barmat 2005	13	40	17	40	8.9%	0.65 [0.26, 1.62]
Cheung 2005	3	33	3	33	2.1%	1.00 [0.19, 5.36]
Engmann 2008 a	16	34	19	32	8.0%	0.61 [0.23, 1.61]
Hurine 2006	17	91	20	91	12.5%	0.82 [0.40, 1.68]
Kim 2004	7	21	7	20	3.7%	0.93 [0.26, 3.38]
Kurzawa 2008	20	37	21	37	7.4%	0.90 [0.36, 2.24]
Lainas 2007	12	26	25	52	6.9%	0.93 [0.36, 2.38]
Lainas 2010	47	110	50	110	22.1%	0.90 [0.53, 1.52]
Rombauts 2006	41	234	26	117	22.1%	0.74 [0.43, 1.29]
Tehraninejad 2010	16	45	13	47	6.3%	1.44 [0.60, 3.49]
Subtotal (95% CI)		**671**		**579**	**100.0%**	**0.85 [0.66, 1.09]**
Total events	192		201			

Heterogeneity: $Chi^2 = 2.53$, $df = 9$ ($P = 0.98$); $I^2 = 0\%$

Test for overall effect: $Z = 1.28$ ($P = 0.20$)



Al-Inany HG Cochrane Review 2011

Programmation Op Antag/long

TABLE 2

Cycle outcome.

	OCP, n (%)	No OCP, n (%)	*P* value	Odds ratio (95% CI)
Biochemical PR	61/115 (53.0)	67/113 (59.3)	.17	0.7 (0.4, 1.3)
Clinical PR	56/115 (48.7)	64/113 (56.6)	.12	0.7 (0.4, 1.2)
Ongoing PR	55/115 (47.8)	61/113 (53.9)	.18	0.8 (0.5, 1.3)
Multiple PR	15/56 (26.7)	18/64 (28.1)	.43	0.9 (0.4, 2.1)
Implantation rate	75/207 (36.2)	80/204 (39.2)	.26	0.9 (0.6, 1.3)
Miscarriage rate	5/56 (8.9)	11/64 (17)	.09	0.5 (0.1, 1.4)
Live birth rate	51/115 (44.3)	53/113 (47)	.35	0.9 (0.5, 1.5)

Wash out 5J

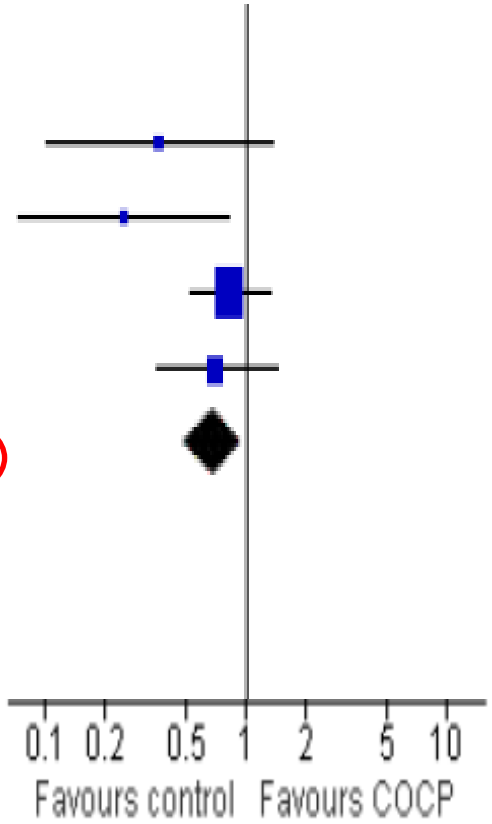
Garcia-Velasquo fertil Steril 2011

Grossesse clinique/évolutive
Op Antag/Antag

1.3.2 COCP + Ant vs Ant						
Cédrin-Durnerin 2007 (2)	5	21	11	24	7.2%	0.39 [0.12, 1.31]
Huirne 2006b	4	32	12	32	8.3%	0.27 [0.09, 0.83]
Kolibianakis 2006 (3)	51	250	60	254	59.2%	0.83 [0.54, 1.26]
Rombauts 2006 (4)	20	117	26	117	25.3%	0.72 [0.38, 1.38]
Subtotal (95% CI)		**420**		**427**	**100.0%**	**0.69 [0.50, 0.96]**
Total events	80		109			

Heterogeneity: Chi² = 4.30, df = 3 (P = 0.23); I² = 30%

Test for overall effect: Z = 2.23 (P = 0.03)



Smulders cochrane 2010

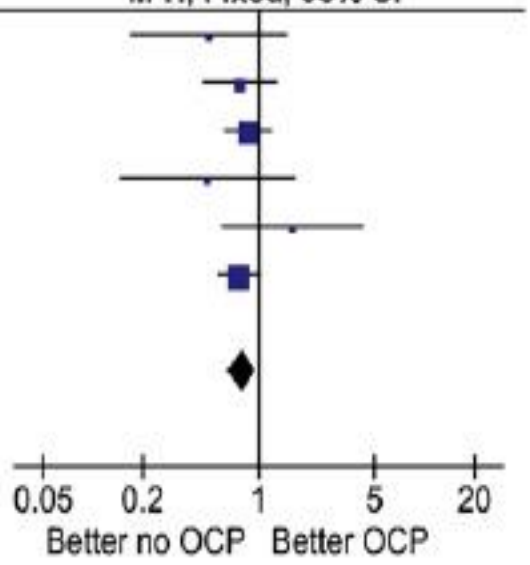
Oral contraceptive pretreatment significantly reduces ongoing pregnancy likelihood in gonadotropin-releasing hormone antagonist cycles: an updated meta-analysis

A

Study or Subgroup	OCP Events	OCP Total	no OCP Events	no OCP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Huirne	4	32	8	32	4.5%	0.50 [0.17, 1.50]	2006
Rombauts	20	117	26	117	14.7%	0.77 [0.46, 1.30]	2006
Kolibianakis	51	250	60	254	33.7%	0.86 [0.62, 1.20]	2006
Cedrin	3	21	7	24	3.7%	0.49 [0.14, 1.66]	2007
Kim	8	27	5	27	2.8%	1.60 [0.60, 4.27]	2009
Tavmergen	55	223	71	219	40.5%	0.76 [0.56, 1.03]	2009
Total (95% CI)		**670**		**673**	**100.0%**	**0.80 [0.66, 0.97]**	
Total events	141		177				

Heterogeneity: Chi² = 3.58, df = 5 (P = 0.61); I² = 0%

Test for overall effect: Z = 2.28 (P = 0.02)



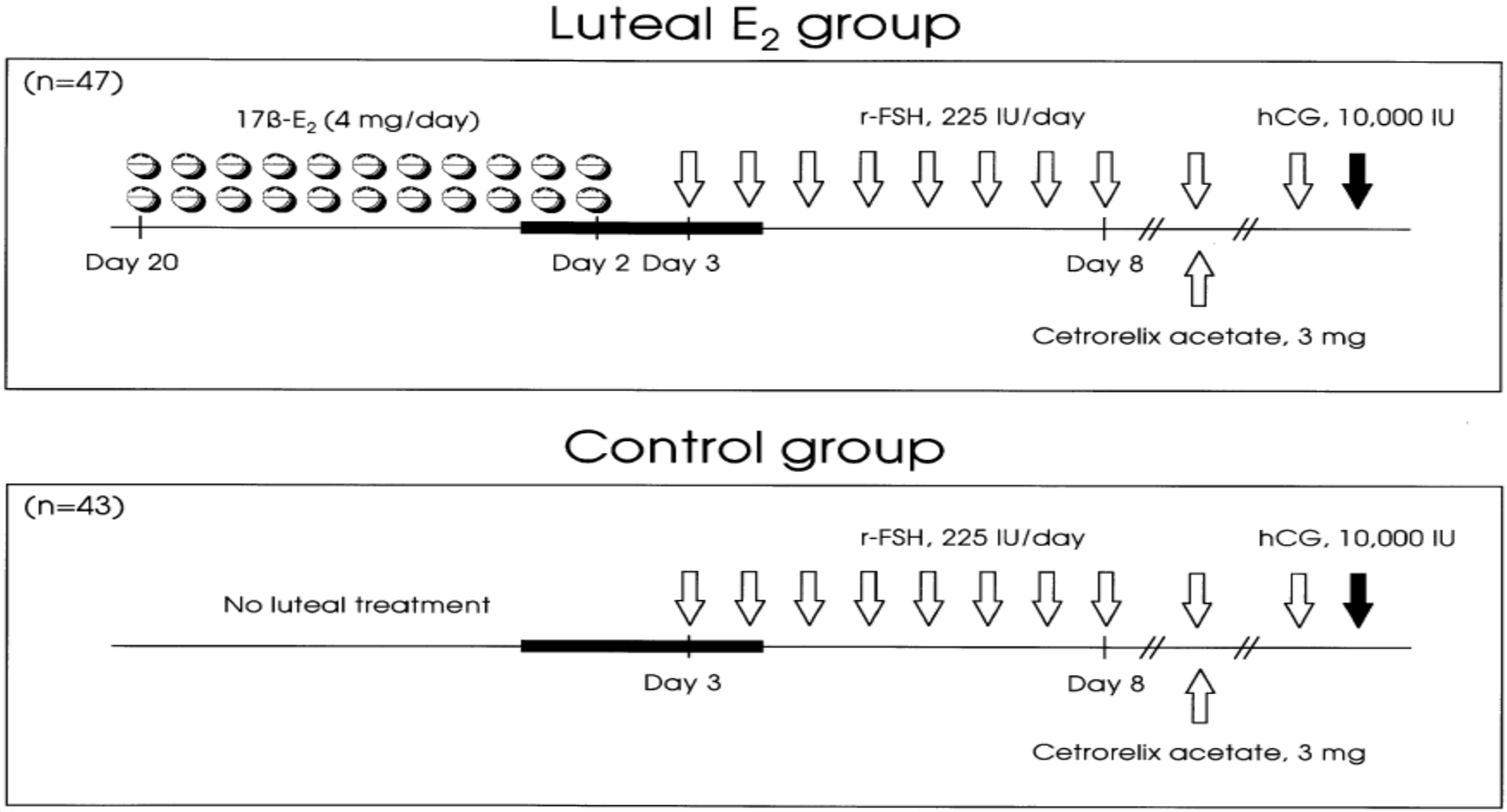
Durée de wash out variable 2 à 5j

Perte de 1 grossesse / 20 femmes traitées

Griesinger Fertil Steril 2010

RÉSULTATS E2

Prétraitement par E2



Fanchin R Human Reprod 2003

Luteal estradiol pre-treatment coordinates follicular growth during controlled ovarian hyperstimulation with GnRH antagonists

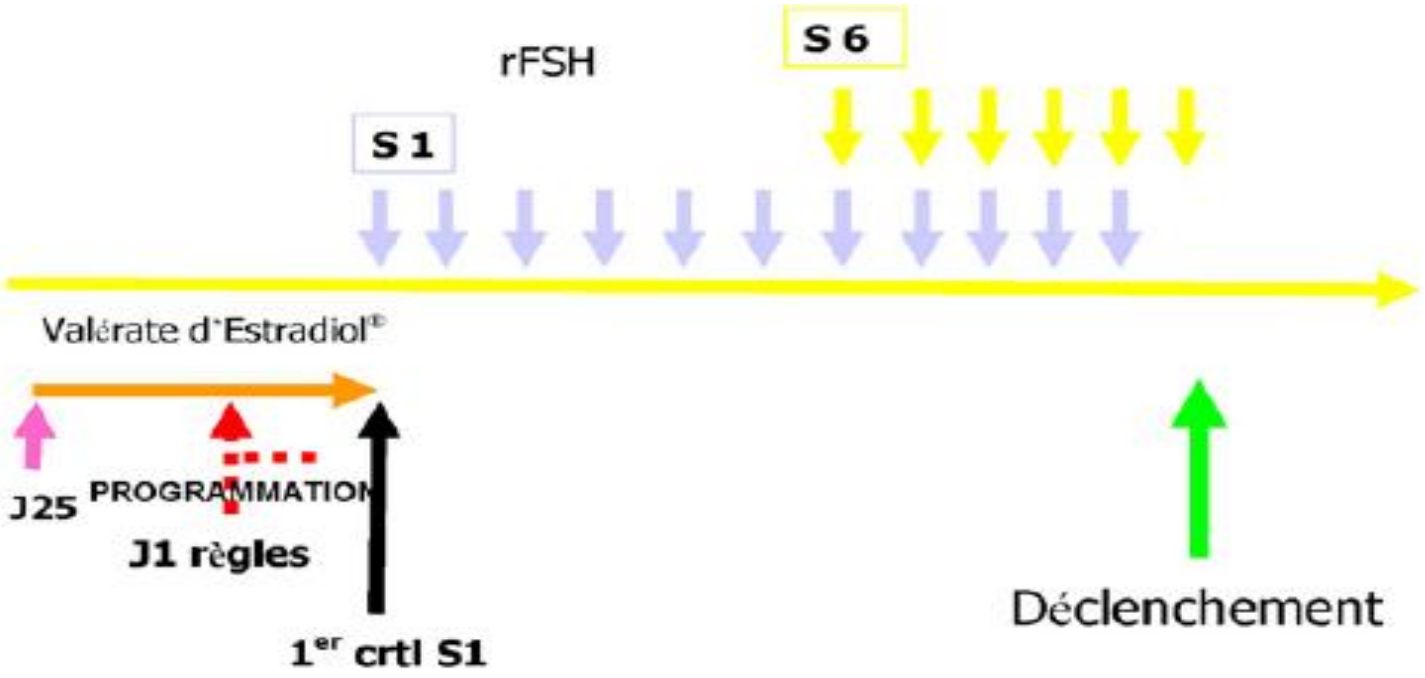
Renato Fanchin[1,3], Laurent Salomon[1], Altina Castelo-Branco[1], François Olivennes[1], Nelly Frydman[2] and René Frydman[1]

Table I. Follicular development and embryological results in women pre-treated or not with E_2 during the luteal phase

	Luteal E_2 group	Control group	*P*
No. of follicles >10 mm on day 8	16.4 ± 1.0	16.8 ± 0.9	NS
Mean follicular size on day 8 (mm)	9.9 ± 0.2	11.1 ± 0.3	<0.001
CV of follicular sizes on day 8	0.22	0.26	<0.02
Day of GnRH antagonist administration	9.1 ± 0.2	8.5 ± 0.2	<0.01
Day of HCG administration	11.9 ± 0.2	10.8 ± 0.2	<0.001
No. of follicles ⩾16 mm on day of HCG	9.9 ± 0.5	7.9 ± 0.5	<0.01
No. of mature follicles	9.3 ± 0.7	7.3 ± 0.5	<0.03
No. of available embryos	6.4 ± 0.6	4.6 ± 0.3	<0.01
No. of embryos transferred	2.6 ± 0.1	2.7 ± 0.1	NS
Clinical pregnancy rates/cycle	34%	25%	NS

Human reprod 2003

Programmation par E2



E2 Antag/ago long

Comparaison des populations traitées par Antagonistes et Agonistes de GnRH.

	Antagonistes $n = 436$	Agonistes $n = 412$	Significativité Test de Khi^2
Âge patientes	32,5 ± 5,9	33,1 ± 4,7	NS
Rang tentative	2,7 ± 1,4	2,2 ± 1,5	NS
Nombre de cycles	426	412	–
Taux d'annulation	12,4 %	12,1 %	NS
Taux de ponctions	87,6 %	87,9 %	NS
Taux de transferts	77,9 %	78,4 %	NS
Nombre moyen d'ovocytes inséminés	6,8 ± 5,3	7,6 ± 5,7	$p < 0{,}001$
Nombre moyen d'embryons	3,7 ± 3,2	4,1 ± 3,6	$p < 0{,}001$
Nombre d'embryons transférés	1,6 ± 1,03	1,6 ± 0,9	NS
Taux de grossesse/transfert (si transfert d'au moins 1 embryon « 411 »)	37,0 %	34,8 %	NS
Taux de grossesse/transfert – ICSI	32,2 %	33,3 %	NS
Taux de grossesse/transfert – FIV	22,8 %	21,1 %	NS
Taux de grossesse/transfert – Total	28,6 %	27,9 %	NS

Pretreatment with estrogen does not affect IVF-ICSI cycle outcome compared with no pretreatment in GnRH antagonist protocol: a prospective randomized trial

Isabelle Cédrin-Durnerin, M.D.,[a] Anne Guivarc'h-Levêque, M.D.,[b] and Jean-Noël Hugues, M.D., Ph.D.,[a] on behalf of the Groupe d'Etude en Médecine et Endocrinologie de la Reproduction

Parameter	Estrogen (n = 233)	No pretreatment (n = 220)	*P* value
Total FSH dose (IU)	1,557 ± 408	1,389 ± 347	<.0001
Daily FSH dose (IU)	162 ± 31	158 ± 30	NS
hCG administration (d)	10.8 ± 1.4	10.0 ± 1.5	<.0001
Oocytes	10.9 ± 5.7	10.2 ± 5.6	NS
M2 oocytes	8.0 ± 4.6	7.6 ± 4.7	NS
Delivery rate/cycle	26.6%	30%	NS
Delivery rate/retrieval	28.6%	32.3%	NS
Delivery rate/transfer	31.5%	34.3%	NS

Fertil Steril 2012

Oestradiol valerate pretreatment in GnRH-antagonist cycles: a randomized controlled trial

Christophe Blockeel [a,*], Sara Engels [a], Michel De Vos [a], Patrick Haentjens [b], Nikolaos P Polyzos [a], Dominic Stoop [a], Michel Camus [a], Paul Devroey [a]

	Control group (n = 39)	*Pretreatment group (n = 37)*	*Between-group difference*	*P-value*
Days of rFSH stimulation	8.6 ± 1.5	9.6 ± 1.4	1.0 (0.4 to 1.7)	0.004
Total rFSH (IU)	1295.0 ± 254.2	1485.1 ± 248.7	190.1 (75.1 to 305.1)	0.002
COC	12.2 ± 8.7	12.2 ± 6.2	0 (−3.5 to 3.5)	NS
MII oocytes	9.9 ± 7.8	10.0 ± 4.7	0.1 (−2.9 to 3.1)	NS
2PN oocytes	7.8 ± 6.5	8.4 ± 3.7	0.6 (−1.8 to 3.1)	NS

	Control group	*Pretreatment group*	*Between-group difference (%)*
Clinical pregnancy rate			
Per started cycle	16/42 (38.1)	17/44 (38.6)	0.5 (−20.0 to 21.1)
Per retrieval	16/39 (41.0)	17/37 (45.9)	4.9 (−17.4 to 27.2)
Per embryo transfer	16/37 (43.2)	17/35 (48.6)	5.4 (−17.7 to 28.3)

PRETRAITEMENT ET MAUVAISE REPONDEUSE

Op antag/antag/ago long
Mauvaise répondeuse

	Group A (MDP with OCP)	Group B (MDP without OCP)	Group C (GnRH agonist low-dose LP)	P[a]
No. of patients	27	27	28	
No. of cycles initiated	27	27	28	
No. of cycles completed	27	27	28	
Total dose of rhFSH (IU)	2963.9 ± 433.1	2931.5 ± 464.0	3390.2 ± 443.2	<.001
Days of rhFSH administration	10.0 ± 1.4	9.7 ± 1.4	11.6 ± 1.7	<.001
No. of follicles ≥14 mm on hCG day	4.9 ± 2.1	4.8 ± 2.1	4.9 ± 2.2	NS
Endometrial thickness on hCG day (mm)	10.3 ± 1.8	10.7 ± 2.2	10 6 ± 2.0	NS
No. of cycle with premature LH surge	0	0	0	NS
No. of cycles with ICSI	12 (44.4%)	10 (37.0%)	10 (35.7%)	NS
No. of oocytes retrieved	4.8 ± 2.0	4.4 ± 1.8	4.7 ± 2.1	NS
No. of mature oocytes	3.9 ± 1.5	3.0 ± 1.2	3.9 ± 1.8	.04
No. of fertilized oocytes	3.8 ± 1.6	2.9 ± 1.2	3.8 ± 1.7	.03
No. of grade I, II embryos	2.2 ± 1.1	1.5 ± 0.9	2.3 ± 1.2	.02
No. of embryos frozen	0.3 ± 0.7	0.2 ± 0.5	0.5 ± 0.9	NS
No. of embryos transferred	3.1 ± 0.3	3.0 ± 0.2	3.1 ± 0.3	NS
Clinical pregnancy rate per cycle (%)	33.3 (9/27)	22.2 (6/27)	25.0 (7/28)	NS
Implantation rate (%)	13.1 (11/84)	8.6 (7/81)	9.2 (8/87)	NS
Miscarriage rate per clinical pregnancy (%)	11. 1 (1/9)	16.7 (1/6)	14.3 (1/7)	NS
Live birth rate per cycle (%)	29.6 (8/27)	18.5 (5/27)	21.4 (6/28)	NS
Twin pregnancy rate per clinical pregnancy (%)	22.2 (2/9)	16.7 (1/6)	14.3 (1/7)	NS

Kim CH Fertil Steril 2011

E2 Antag/Antag Mauvaise répondeuse

Variable	Luteal E_2 group (n=86)	Standard GnRH antagonist group (n=69)	P value
Total dose of gonadotropin (IU)	2356.3±824.8	1980.9±714.9	.004
Total length of stimulation (day)	10.8±2.0	10.1±2.7	.045
Peak E_2 level (pg/mL)	938.9±653.9	588.5±318.5	<.0001
Maximal endometrial thickness (mm)	10.2±3.6	9.8±2.3	.586
No. of oocytes retrieved	4.5±2.9	3.2±1.9	.001
No. of 2PN embryos	2.9±2.1	2.3±1.9	.043
Fertilization rate	65.6%	65.6%	1.00
Good quality embryo rate	51.2%	25.0%	.047
No. of embryos transferred	2.2±0.9	1.6±1.2	.014

Variable	Luteal E_2 group (n=86)	Standard GnRH antagonist group (n=69)	P value
Cancellation rate	15.1%	37.7%	.002
Implantation rate	19.3%	8.7%	.020
Pregnancy rate per ET	37.0%	16.3%	.021
Clinical pregnancy rate per ET	30.1%	11.6%	.024
Ongoing pregnancy rate per ET	24.7%	9.3%	.051

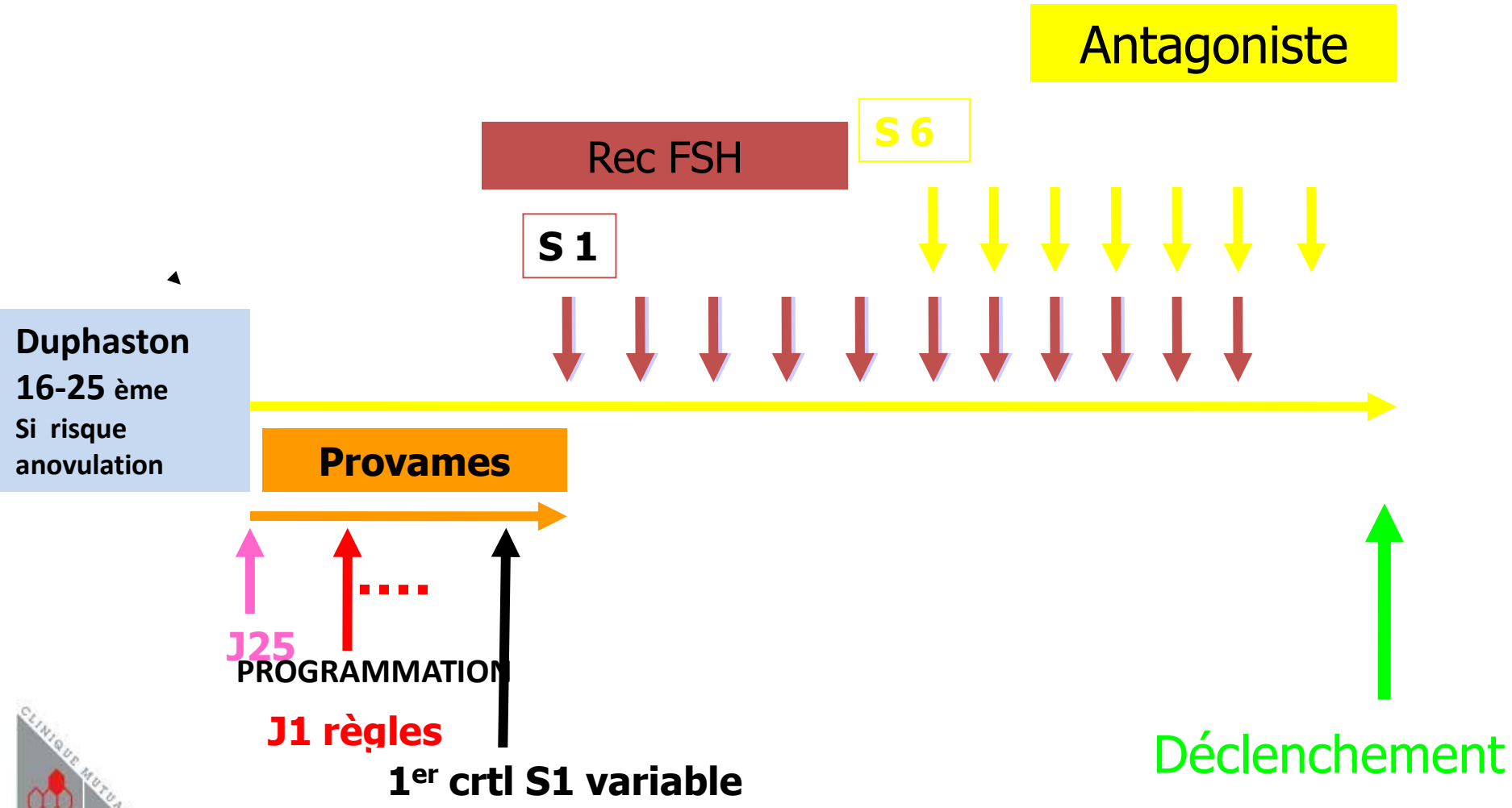
Chang J Assit reprod genet 2012

ORGANISATION DE L'ACTIVITÉ

Objectifs

- Alléger l'activité du week end
- Répartir l'activité sur la semaine

Programmation par Oestrogènes



Organisation pratique

Provames 2mg
1 cp matin et soir à débuter 3 à 5j avant date théoriques des règles
Appeler secrétariat de FIV en début de cycle qui vous indiquera le jour de votre début de stimulation
Poursuivre le Provames dans l'intervalle

ponction	Lundi (max 8) - - -	Mardi - - -	Mercredi - - -	Jeudi - - -	Vendredi - - -
Programmation début de stimulation	Jeudi (max 10) - - - - -	Vendredi - - - - -	Samedi - - - - -	Dimanche - - - - -	Semaine N° 20
Programmation début de stimulation					Semaine N° 21
Programmation début de stimulation					Semaine N° 22

Can oestradiol pretreatment be used to reliably avoid weekend oocyte retrievals?

G. Griesinger, E.M. Kolibianakis

OUI !!

Début de stimulation	1ère ponction	Dernière ponction
Jeudi	HCG S10	HCG S14
Vendredi	HCG S9	HCG S13
Samedi	HCG S8	HCG S12
Dimanche	HCG S7	HCG S11

OUI !!

	Control group (n = 39)	Pretreatment group (n = 37)	Between-group difference	P-value
Days of rFSH stimulation	8.6 ± 1.5	9.6 ± 1.4	1.0 (0.4 to 1.7)	0.004

Parameter	Estrogen (n = 233)	No pretreatment (n = 220)	*P* value
hCG administration (d)	10.8 ± 1.4	10.0 ± 1.5	<.0001

Avoidance of weekend oocyte retrievals during GnRH antagonist treatment by simple advancement or delay of hCG administration does not adversely affect IVF live birth outcomes

K.P. Tremellen [1,2,*] and M. Lane [1,2]

Human Reprod 2011

La durée de prise d'E2 au-delà des règles n'influence pas les résultats

TABLE 3

Comparison of hormonal and endometrial data between groups.

	1+2	3	4	5	6	7+8	*P* value[b]
E_2 at S1 (pg/mL)	134.9 ± 96.2	161.5 ± 106.9	174.7 ± 109.5	177.4 ± 119.5	188.2 ± 134.1	178.6 ± 101.3	<.0001[c]
LH at S1 (IU/L)	4.2 ± 2.9	4.5 ± 3.7	5.5 ± 4.0	6.2 ± 3.8	7.0 ± 4.0	7.9 ± 3.8	<.0001[c]
P at S1 (ng/mL)	0.57 ± 0.33	0.56 ± 0.29	0.53 ± 0.37	0.51 ± 0.36	0.49 ± 0.23	0.52 ± 0.37	NS
E_2 on the day of hCG (pg/mL)[a]	1,583 ± 788	1,720 ± 903	1,766 ± 876	1,867 ± 924	1,813 ± 909	1,964 ± 901	<.0001[c]
Endometrial thickness on the day of hCG (mm)[a]	10.1 ± 1.8	9.7 ± 1.8	10.1 ± 1.9	10.1 ± 2.0	10.0 ± 1.9	10.1 ± 2.0	NS
No. of oocytes retrieved	8.9 ± 7.0	8.9 ± 5.7	8.2 ± 4.9	8.4 ± 5.6	8.2 ± 5.2	8.1 ± 4.9	NS[b]
No. of obtained embryos	4.6 ± 3.9	4.9 ± 3.5	4.5 ± 3.1	4.8 ± 3.5	4.4 ± 3.1	4.7 ± 3.2	NS[b]
No. of transferred embryos	1.7 ± 0.9	1.7 ± 0.7	1.9 ± 0.8	1.9 ± 0.6	1.7 ± 0.7	1.9 ± 0.7	NS[b]
No. of cryopreserved embryos	0.9 ± 1.8	1.0 ± 2.0	0.8 ± 1.5	0.8 ± 1.7	0.7 ± 1.5	0.7 ± 1.7	NS[b]
Ongoing PR/transfer (%)	26.9	31.4	30.0	28.6	30.0	34.8	NS[d]
Delivery rate/transfer (%)	23.1	26.4	23.5	22.4	24.2	29.5	NS[d]

A Guivarc'h Fertil Steril 2011

Répartition activité ponction

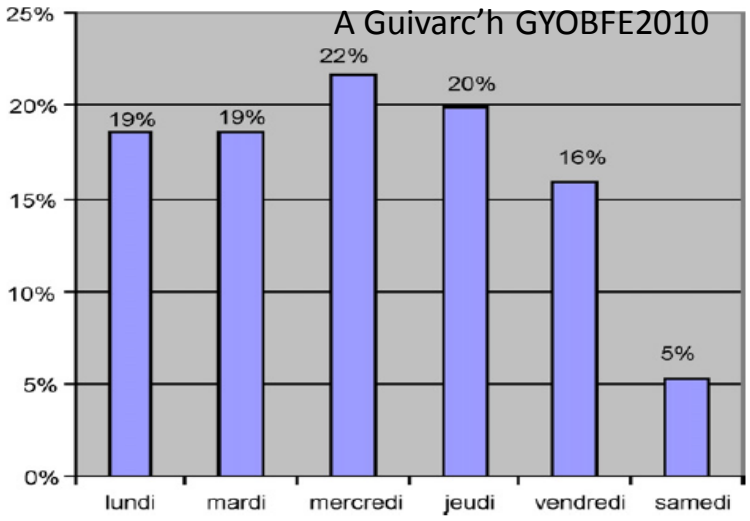
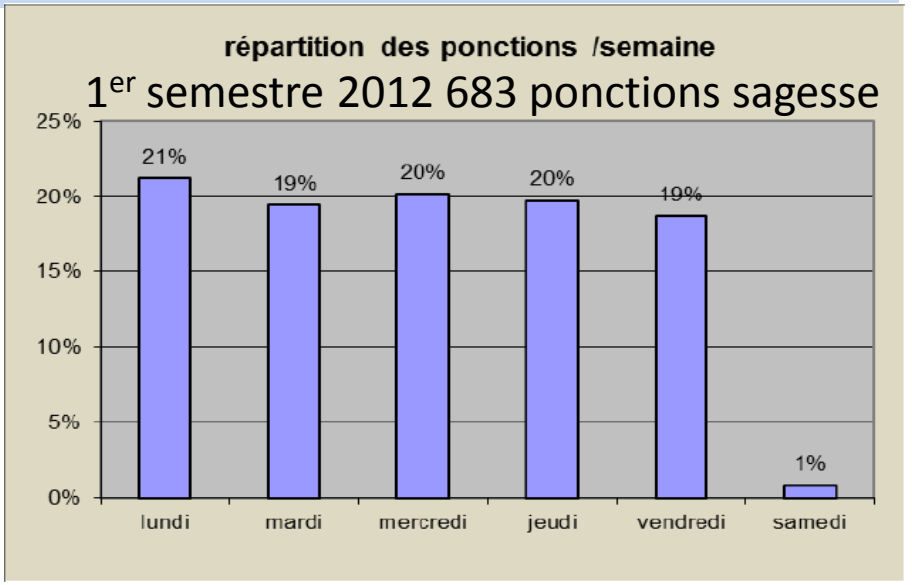
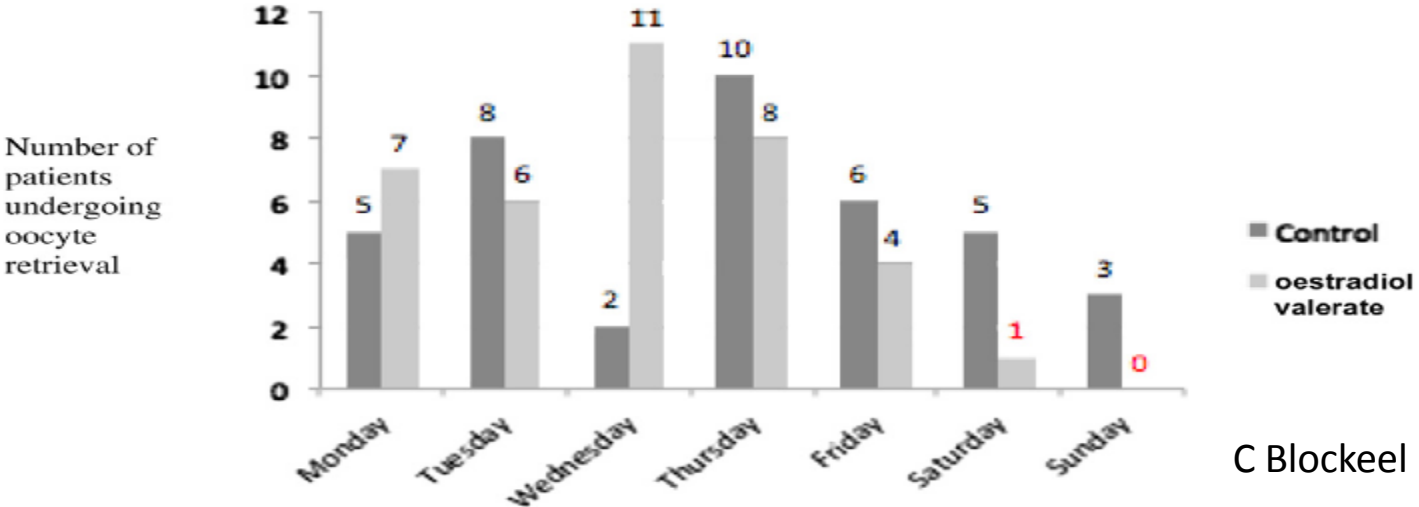


Fig. 3. Répartition de l'activité de ponction.





C Blockeel RBM 2012

Conclusion

- Prétraitement inhibe↗ FSH prémenstruelle et harmonise cohorte
  - Peu impact chez normo répondeuse
  - Bénéfice très probable
    - mauvaise répondeuse
    - Femme âgée
- Intérêt du prétraitement pour organiser les cycles antagonistes
- > E2/OP ? (la pilule est contraceptive!!)