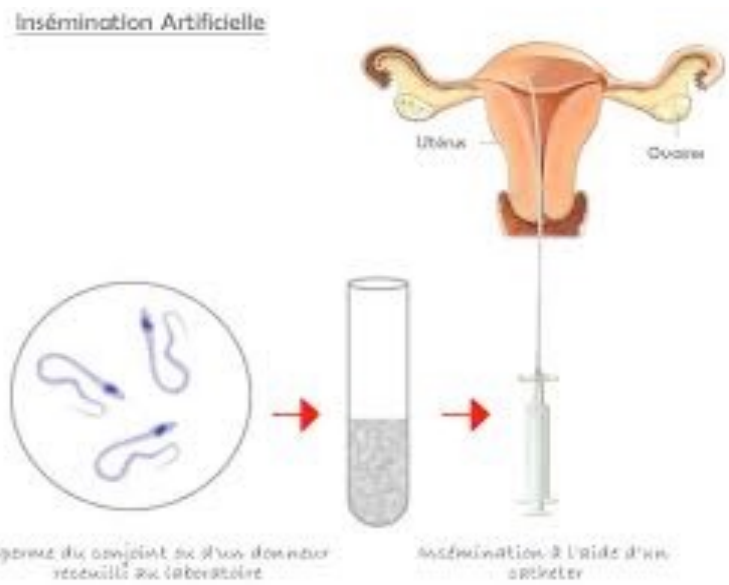

Optimisation des résultats en IAC

Anne Guivarc'h-Levêque
Clinique Mutualiste La Sagesse
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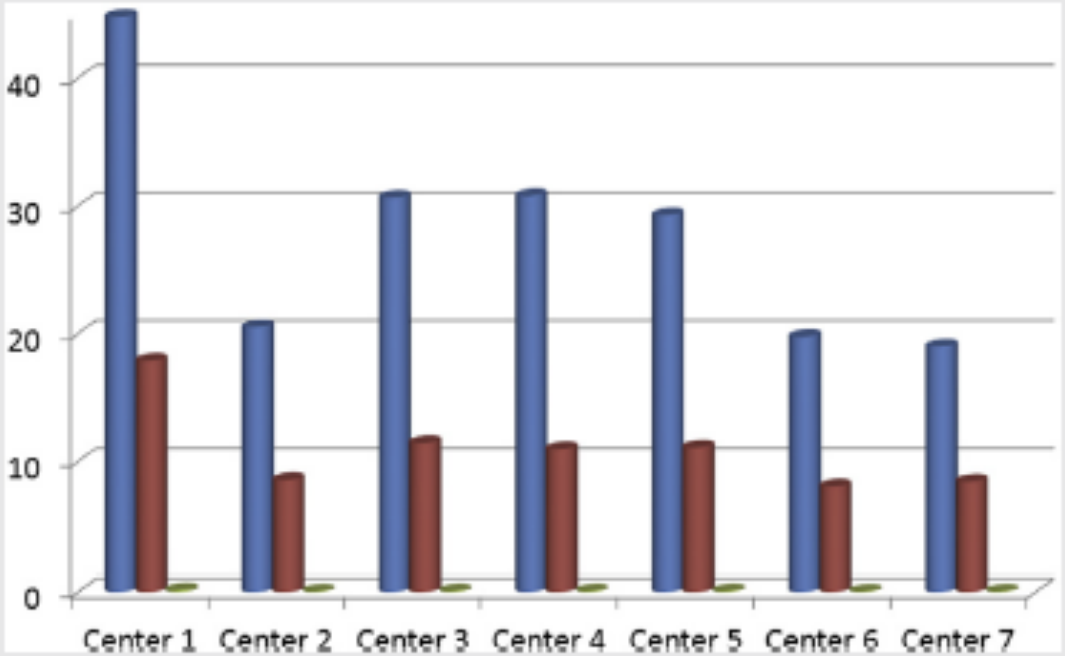
Introduction

- Résultats des IIU
- Indications des IIU
- Optimisation des protocoles de stimulations
- Facteurs pronostics succès

Résultats 7 centres français

FIGURE 1



Delivery rate per couple and per attempt as a function of ART centers. *P*<.001.

Monraisin. Practices of intrauterine insemination. Fertil Steril 2016.

1827 cycles sur 1 an
2,6±1,3 nb tent
33±4,8 Age

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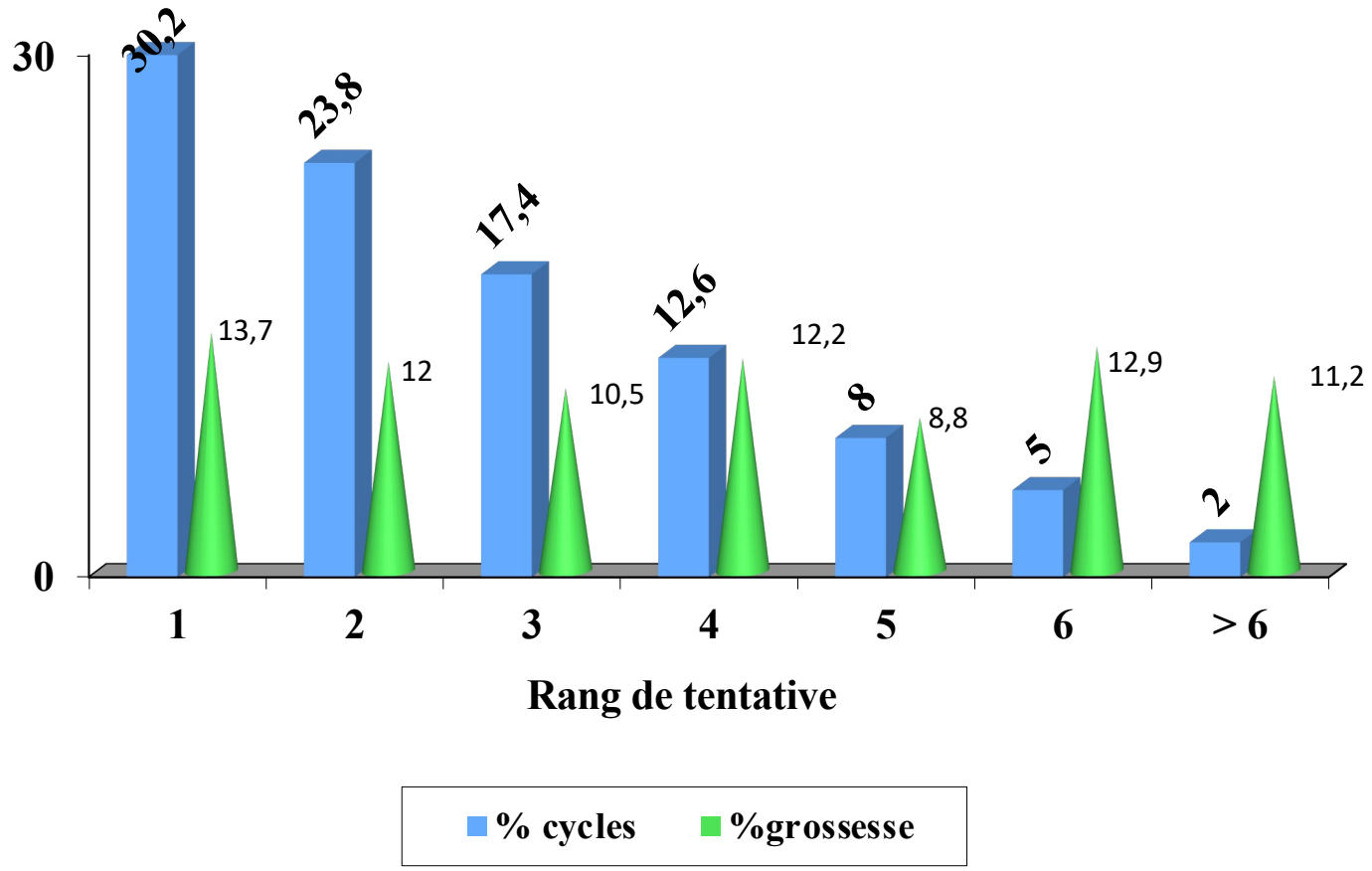
Monraisin Fertil Steril 2016

Résultats Sagesse sur 3987 cycles



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A Guivarc'h données personnelles

Indication IIU (1)

- Anomalie de glaire cervicale
  - Qualitative
  - Quantitative
  - Y at'il encore un interêt test Huhner?
    - ✓NON

	Non fait	Positif	Déficient	Négatif	P
N	416	95	86	110	
Taux de grossesse	31 %	32 %	37 %	30 %	NS

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Indications IIU (2)

- Anomalie masculine modérée

Table I. Rate of clinical pregnancies/cycle depending on the NMSI

	Group					Total
	1	2	3	4	5	
NMSI ($\times 10^6$)	$n < 1$	$1 \leq n < 2$	$2 \leq n < 5$	$5 \leq n < 10$	$n \geq 10$	
Cycles	96	173	471	1119	705	2564
Pregnancies	3	15	56	165	92	331
% pregnancies/cycle	3.13%	8.67%	11.89%	14.75%	13.05%	12.91%

Global $\chi^2 = 14.74$; df $= 4$; $P = 0.005$. In the 2×2 comparison: group 1 was significantly different from group 3 ($\chi^2 = 6.57$; $P = 0.01$); group 1 was significantly different from group 4 ($\chi^2 = 10.02$; $P = 0.002$); group 1 was significantly different from group 5 ($\chi^2 = 7.96$; $P = 0.005$); and group 2 was significantly different from group 4 ($\chi^2 = 4.61$; $P = 0.03$).

Au moins 1 Million de spermatozoides mobiles inseminés

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Wainer R Human Reprod 2004

Indication IIU (3)

- Endométriose modérée

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates (Tummon, et al., 1997).	**C**

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of intrauterine insemination alone, as it increases pregnancy rates (Nulsen, et al., 1993).	**C**

Indication IIU (4)

- Infertilité inexpliquée

1.8 Unexplained infertility

1.8.1 Ovarian stimulation for unexplained infertility

1.8.1.1 Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**

1.8.1.2 Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**

1.8.1.3 Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**

1.8.1.4 Offer IVF treatment (see recommendations 1.11.1.3–4) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**

1.9.1.3 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse:

- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)
- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[2016]**

NICE guideline 2013

TUI study :RCT
intrauterine insemination with clomiphene citrate stimulation compared with expectant management

- 201 couples with unexplained infertility
- 3 cycles comparing :
  - IUI –Clomiphene Citrate
  - Expecting management

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C.M. Farquhar Lancet 2018

Results

- IUI-C was associated with an increase in CLBR compared to EM group [31%] vs.[9%]P = 0.0003;
- 3 fold increase after IUI !
- IUI should be proposed to couples with unexplained infertility

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C.M. Farquhar Lancet 2018

CC compared to FSH in IIU for unexplained infertility Super study

- 24 centers in Nederland
- 369 cycles randomised for CC treatment
- 369 for FSH

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Danhof Human Reprod 2018

Results

- Ongoing pregnancy
  - 113 (31%)after FSH-IUI
  - 97 (26%) after CC-IUI (ns)
- Multiple pregnancy
  - 5 (1%) FSH-IUI
  - 8 (2%) CC-IUI (ns)
- Should prefer for unexplained infertility
  - CC-IUI
- Less expensive
- As effective as FSH

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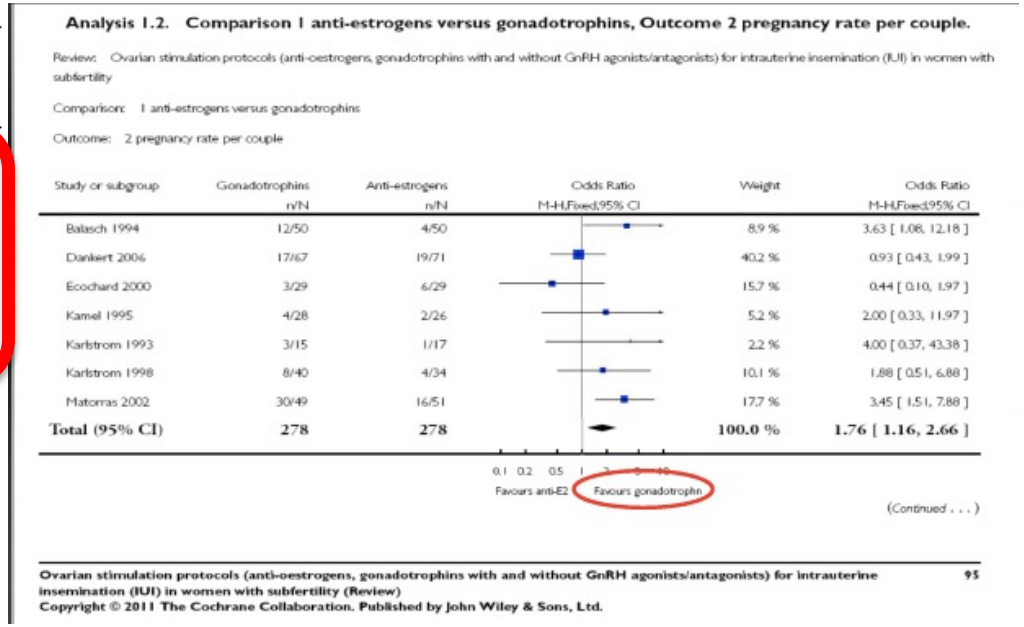
Danhof Human Reprod 2018

Controverse sur Traitement CC/FSH

Table 3
Clinical pregnancy and live birth rates in unexplained and mild male infertility subgroups.

	rFSH protocol $n = 109$	CC protocol $n = 110$	p value
Unexplained infertility			
Clinical pregnancy per patient (%)	43/94 (60.6%)	28/87 (32.2%)	<0.01*
Live birth rate per patient (%)	38/94 (40.4%)	19/87 (21.8%)	<0.01*
Live birth rate per patient[a] (%)	42/94 (44.7%)	25/87 (28.7%)	<0.05*
Mild male infertility			
Clinical Pregnancy per patient (%)	4/15 (26.7%)	3/22 (13.6%)	NS
Live birth rate per patient (%)	3/15 (20%)	3/22 (13.6%)	NS
Live birth rate per patient[a] (%)	5/15 (33.3%)	3/22 (13.6%)	NS

[a] Live births resulting from spontaneous pregnancy are
* Shows significant difference.



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Erdem EJGO 2015 Cochrane 2011

IIU/IVF unexplained infertility :RCT

- Unexplained infertility 1 year
- 23-37 years
- 101 couples
  - 1 to 3 cycles IIU with FSH
- 106 couples
  - 1 IVF cycle long agonist protocol

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Nani A Fertil Steril 2017

Résults

- IUI group
  - 11 spontaneous pregnancies
  - 24,7 % live birth
- IVF group
  - 25 spontaneous pregnancies
  - 31,1 % live birth
  - 3 OHSS
- 147 000 £ for IIU
  - 8166 £ for newborn
- 316 000 £ for IVF
  - 10560 £ for newborn

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Comments

- IVF shoudn't be first line for unexplained infertility
- Regarding the number of spontaneous pregnancies
  - One more year expecting management for the women < 35 should be considered

Reaction of the NICE

The NICE guidelines of 2013 advised that first-line treatment for unexplained infertility should be expectant management for two years followed by IVF. IUI was not recommended. UK journalists covering ESHRE's Annual Meeting this year followed up data presented by Farquhar et al (that LBRs were three times higher with IUI than with expectant management) and were told by the NICE press office that NICE planned to update their guidance in light of this latest research. 'This new paper will be considered as part of that update,' NICE told the Daily Telegraph (above).

Indication IIU (6)

- Anovulation
- Dysovulation

Anovulatory women not conceiving after 6 ovulatory cycles withCC. Should we switch to FSH and or add IUI ? RCT

- 666 women randomized
  - 173 CC
  - 162 CC+IUI
  - 165 FSH
  - 166 FSH+IUI

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Weiss N Lancet 2018

Results (1)

- Overall CC pregnancy
  - 42%
- Overall FSH pregnancy
  - 53%
  - RR 0,79 (0,68-0,92)
- IUI
  - 49%
- No IUI
  - 45%
  - RR 1,08 (0,93-1,26)

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Weiss N Lancet 2018

Results (2)et commentaire

- Time to pregnancy
  - 4,6 month CC
  - 4,2 month FSH
  - 4,3 month IUI
  - 4,5 month without IUI
- Advantage to switch for FSH
- No need to add IUI

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Weiss N Lancet 2018

Indications IIU (7)
Mauvaise réponse à la FIV?

Mise au point

Réponse insuffisante à la stimulation en vue de FIV : maintenir la ponction ou choisir l' insémination ?☆

In vitro fertilization versus conversion to intrauterine insemination in patients with poor response to controlled ovarian hyperstimulation

P.-E. Bouet *, G. Legendre, L. Delbos, C. Dreux, P. Jeanneteau, V. Ferré-L'Hotellier, L. Boucret, P. Descamps, P. May-Panloup

Service de médecine de la reproduction, CHU d'Angers, 4, rue Larrey, 49000 Angers, France

Etude CONFIRM en cours

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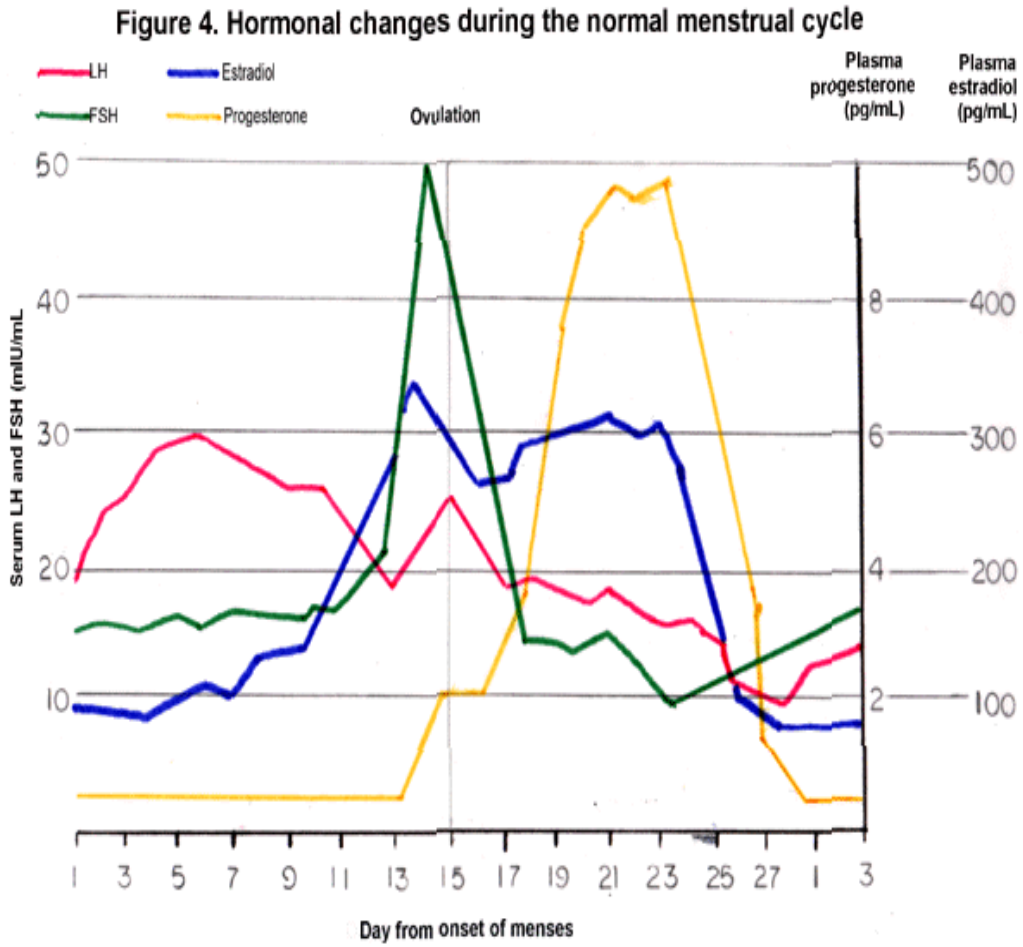
Monitorage ovulation



Y a t'il un intérêt à doser la progestérone en fin phase folliculaire en IIU ?

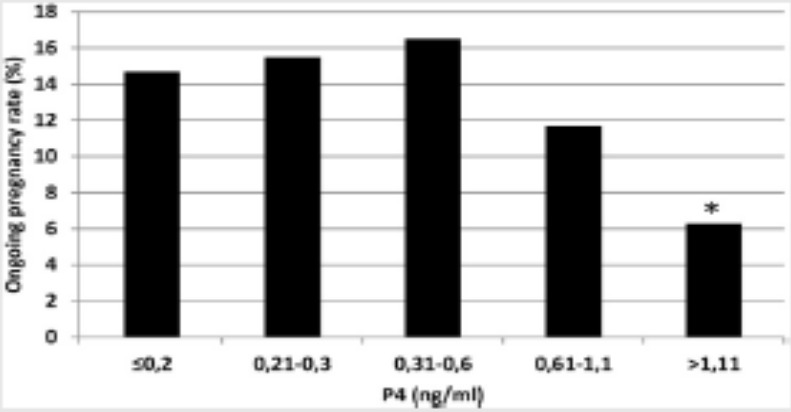
TABLE 1

Clinical characteristics of the study population, according to P level.

Characteristic	<0.20 ng/mL (n = 619)	0.21–0.30 ng/mL (n = 474)	0.31–0.60 ng/mL (n = 681)	0.61–1.10 ng/mL (n = 430)	>1.11 ng/mL (n = 254)	*P* value
Age (y)	35.0 (34.7–35.3)	35.3 (35.0–35.6)	35.1 (34.8–35.4)	35.3 (34.9–35.7)	35.4 (34.9–35.9)	.720
BMI (kg/m^2)	22.5 (22.2–22.8)	23.0 (22.8–23.2)	22.8 (22.7–22.9)	23.2 (22.8–23.6)	23.5 (23.0–24.0)	.524
Endometrial thickness (mm)	9.4 (9.3–9.5)	9.3 ± (9.2–9.4)	9.3 (9.1–9.5)	9.2 (9.1–9.3)	9.4 (9.2–9.6)	.628
Length of stimulation (d)	10.1 (9.8–10.4)	10.0 (9.7–10.3)	10.4 (10.1–10.7)	10.4 (10.1–10.7)	10.0 (9.4–10.4)	.069
Doses of FSH (IU)	525 (507–543)[a]	541 (509–573)[b]	601 (576–626)[a,b]	598 (568–628)[a]	644 (607–681)[a,b]	< .001

Note: Data are shown as mean (range). BMI = body mass index.
[a,b] $P < .05$.

FIGURE 1



Significant differences in ongoing pregnancy rates, depending on P (P4) concentration. *$P < .05$.

Requena. Progesterone affects outcomes in IUI. Fertil Steril 2015.

Requena M Fertil Steril 2015

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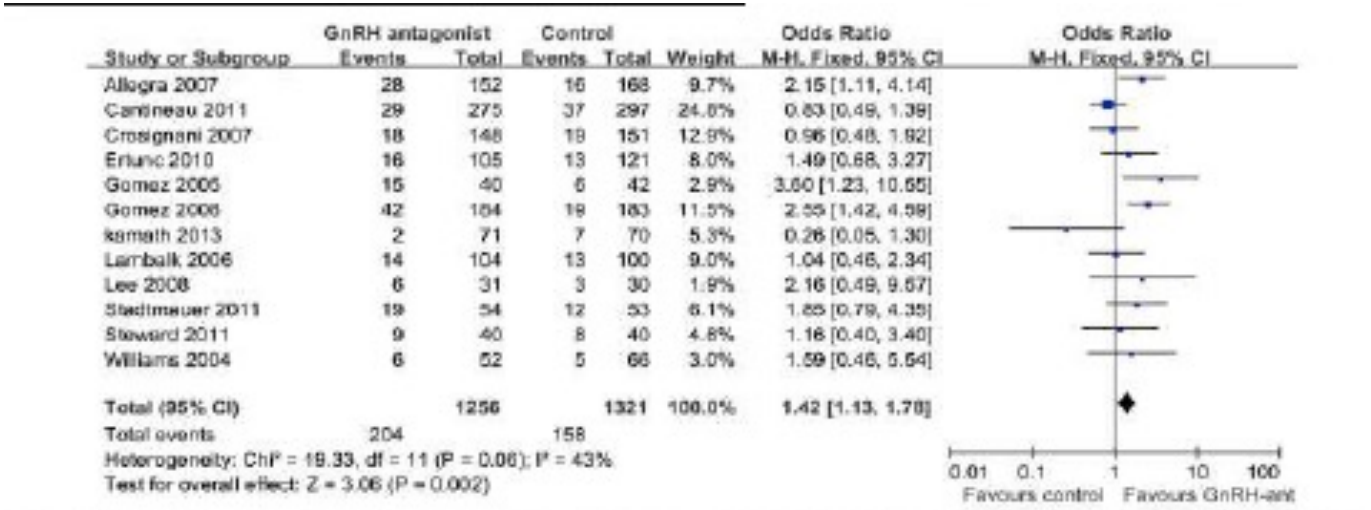
Y a’t’il un intérêt à utiliser les antagonistes dans les IIU



Study or Subgroup	GnRH antagonist Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Allegra 2007	28	152	16	168	9.7%	2.15 [1.11, 4.14]
Cantineau 2011	29	275	37	297	24.8%	0.83 [0.49, 1.39]
Crosignani 2007	18	148	19	151	12.9%	0.96 [0.48, 1.92]
Erlunc 2010	16	105	13	121	8.0%	1.49 [0.68, 3.27]
Gomez 2005	15	40	6	42	2.9%	3.60 [1.23, 10.55]
Gomez 2006	42	184	19	183	11.5%	2.55 [1.42, 4.58]
kamath 2013	2	71	7	70	5.3%	0.26 [0.05, 1.30]
Lambalk 2006	14	104	13	100	9.0%	1.04 [0.46, 2.34]
Lee 2008	6	31	3	30	1.9%	2.16 [0.49, 9.67]
Stadtmauer 2011	19	54	12	53	6.1%	1.85 [0.79, 4.35]
Steward 2011	9	40	8	40	4.8%	1.16 [0.40, 3.40]
Williams 2004	6	52	5	66	3.0%	1.59 [0.46, 5.54]
Total (95% CI)		1256		1321	100.0%	1.42 [1.13, 1.78]
Total events	204		158			

Heterogeneity: Chi² = 19.33, df = 11 (P = 0.06); I² = 43%
Test for overall effect: Z = 3.06 (P = 0.002)

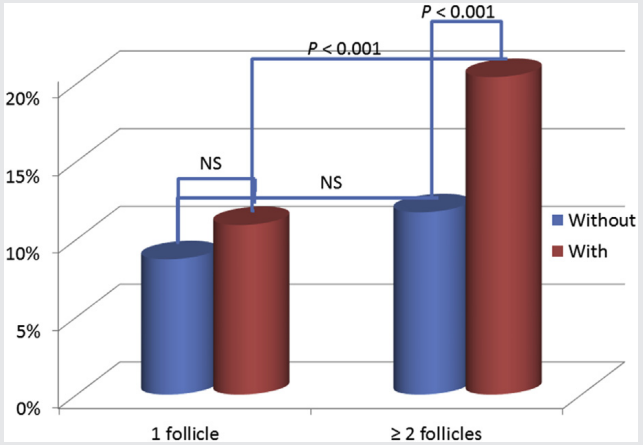
Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours control Favours GnRH-ant

Figure 2. Forest plot of odds ratios (ORs) and 95% confidence interval (CI) of pooled trials comparing GnRH antagonist and control for clinical pregnancy rate.

2014
12 RCT

Luo et al, PlosOne, 2014

FIGURE 3



Delivery rate per attempt as a function of the number of mature follicles and with or without the use of a gonadotropin-releasing hormone (GnRH) antagonist.

Monraisin. Practices of intrauterine insemination. Fertil Steril 2016.

Pas si un foll
Oui si 2 foll

Quid des G X ?

Monraisin Fertil Steril 2015

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Prognostic factors influencing IUI success (1)RCT

- Female age is the most important
  - Sharp decline after 40 years
  - Still acceptable up to 42 for sperm donors
- Pregnancies decrease with one patent tube
- Weight
- Smoking women /men
- Male age

Stillcontroversial

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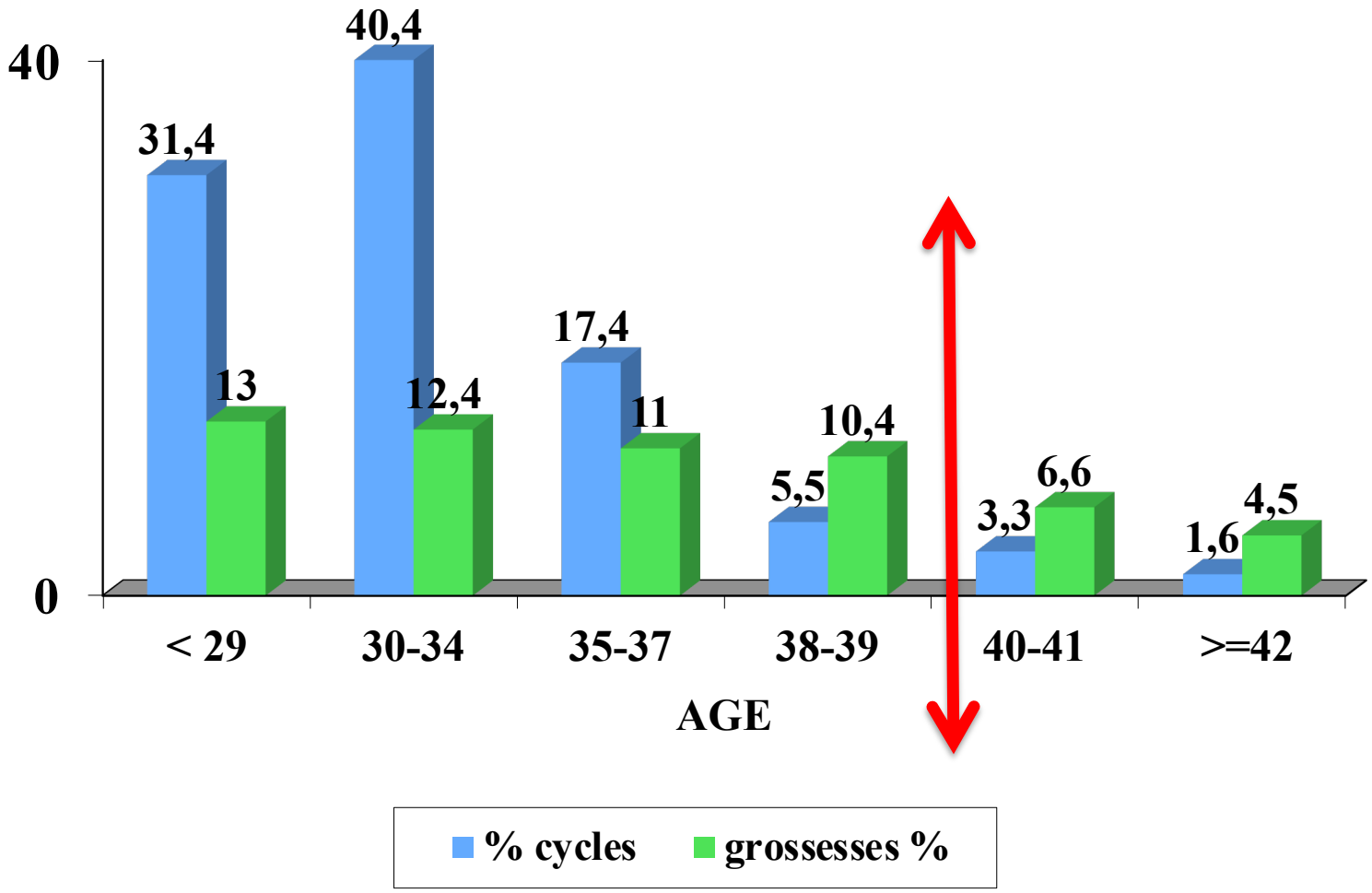
Thijssen A RBMO 2017

Résultats IIU selon âge



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Anne Guivarc'h personnel data

Prognostic factors influencing IUI success (2)

- Sperm quality is the most important male factor
  - IMC (inseminated motile count) > 1-2 million
- Benefit of ovarian stimulation for
  - Unexplained infertility
  - Moderate mild endometriosis
  - Mild male factor

Thijssen A RBMO 2017

Prognostic factors influencing IUI success (3)

- IUI should be performed after 12-36h after HCG injection
- Bed rest still controversial
- Interest of progesterone luteal support with ovarian stimulation+IUI

Thijssen A RBMO 2017

Conclusion

- Regain d'intérêt pour IIU/FIV dans l'infertilité inexpliquée
- Baisse d'intérêt dans trouble isolé de l'ovulation/ rapport programmé
- Place dans les situations de mauvaise réponse en cours d'évaluation

Smr Société de Médecine de la Reproduction

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

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