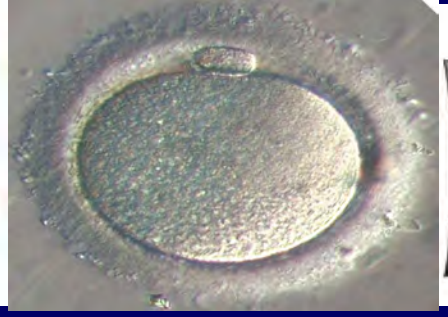

# Que faire chez une femme en insuffisance ovarienne qui désire une grossesse ?

Ph. MERVIEL, M.T. LE MARTELOT, S. ROCHE, C. LELIEVRE, S. BOUEE, J.J. CHABAUD, D. BEAUVILLARD, H. DRAPIER

*Centre d'AMP, CECOS Bretagne, Oncofertilité*

*CHRU BREST*

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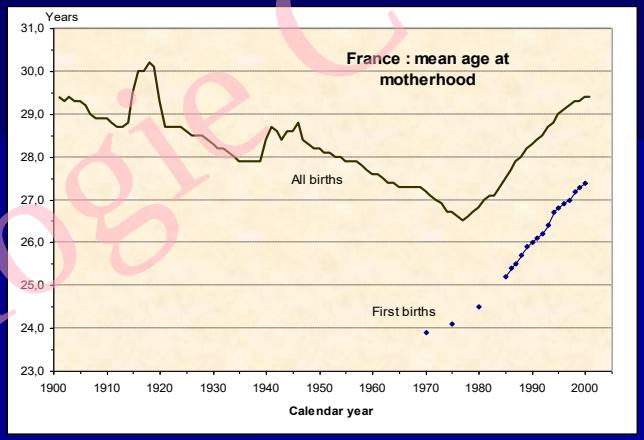
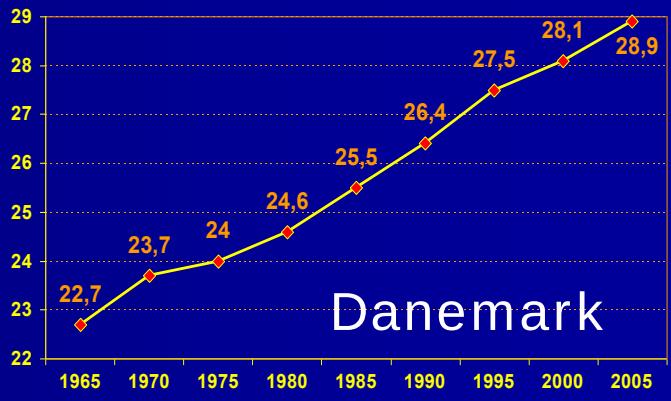
# Le désir tardif d'enfant est devenu un phénomène de société

- Maîtrise de la contraception
- Carrière, difficultés professionnelles
- Secondes unions
- Ignorance (ou déni) du déclin de la fertilité avec l'age
- 30,8 ans en France pour la 1ère G

France




- **25 ans → 24%/cycle (8% de FCS) → 60, 80 et 90%**
- **35 ans → 12%/cycle**, mais ~ **35% de FCS**
- **42 ans → 6%/cycle**, mais ~ **50% de FCS**

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# Causes IOP (1)

- Age: réduction quantitative du pool folliculaire + atteintes irréversibles de la qualité ovocytaire
  - Stress oxydatif intracelullaire
  - Microcirculation péri-folliculaire : réduction de la concentration O2 intra-folliculaire
  - Fonction des cellules de la granulosa
  - Non disjonctions méiotiques : aneuploïdies embryonnaires
- Génétiques : Turner, mosaïques, mutations X , autosomes
- Auto-immunité : anticorps anti-ovaire, autres auto-AC
- Iatrogènes : chirurgie ovarienne, chimio-, radiothérapie
- Pathologies pelviennes : infection, endométriose

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# Autres **causes d'IOP**

- Surpoids/Obésité
- Age des 1$^{ères}$ règles
- « Imprinting » in-utéro
- Environnement (OEM/ portable, Perturbateurs endocriniens, pesticides, Bisphénol A)
- Tabac: Augmentation chez les fumeuses du risque de non conception de 23% en 6 mois et de 54% en 1 an. TG cumulatif à 1 an diminué de 15%

**Table 4** Effects of obesity upon assisted reproductive technology (ART).

| Effects of obesity upon ART |
|---|
| Impaired USS image quality due to adipose tissue[a] |
| Increased duration of stimulation |
| Increased total gonadotrophin dose required (WMD 361.94, 95% CI: 156.47, 567.40; BMI <30 vs >30)[b] |
| Increased follicular asynchrony[c] |
| Increased cycle cancellation (OR 1.35, 95% CI: 0.99, 1.84; BMI >30 vs <30)[d] |
| Poor response to superovulation[e] |
| Reduced follicular hCG concentration on day of ovum pickup (inverse correlation with BMI ($r=-0.353$, $P<0.001$))[f] |
| Relative reduction in number of cumulus–oocyte complex recovered at ovum pickup[g] |
| Relative reduction in metaphase II oocytes recovered at ovum pickup[h] |
| Reduced number of surplus good quality embryos available for cryopreservation[i] |
| Reduced pregnancy rates (OR 1.47, 95% CI: 1.20, 1.80; BMI <30 vs >30)[j] |
| Increased miscarriage rates (OR=1.53, 95% CI: 1.27, 1.84; BMI >30 vs <30)[k] |

OR, odds ratio; WMD, weighted mean difference.
[a]Martinuzzi *et al.* (2008). [b]Homburg *et al.* (1996), Fulghesu *et al.* (1997), Dale *et al.* (1998), Fedorcsak *et al.* (2001), Mulders *et al.* (2003) and Maheshwari *et al.* (2007). [c]Mulders *et al.* (2003), van Swieten *et al.* (2005), Balen *et al.* (2006), Bellver *et al.* (2006), Maheshwari *et al.* (2007) and Esinler *et al.* (2008). [d]Mulders *et al.* (2003) and Maheshwari *et al.* (2007). [e]Al-Azemi *et al.* (2004). [f]Carrell *et al.* (2001). [g]Maheshwari *et al.* (2007) and Esinler *et al.* (2008). [h]Wittemer *et al.* (2000) and Dokras *et al.* (2006). [i]Carrell *et al.* (2001), Metwally *et al.* (2007a, 2007b) and Esinler *et al.* (2008). [j]Wang *et al.* (2000), Carrell *et al.* (2001), Loveland *et al.* (2001), Nichols *et al.* (2003), Fedorcsak *et al.* (2004), Maheshwari *et al.* (2007) and Bellver *et al.* (2010). [k]Bellver *et al.* (2006).

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# Prévision de la mauvaise réponse

- Critères cliniques :

- Âge, cycles courts, BMI, antécédents de FCS
- **Risques d'altération prématurée de la** réserve (X Fra)

- Critères biologiques :
  - indirects : FSH plasmatique à J3
  - directs : Sécrétions ovariennes : E2, AMH

- Echographie : follicules à J3 (CFA)

- Risque de mauvaise réponse malgré une réserve ovarienne normale :

. Anomalie de la réceptivité ovarienne ? (R-FSH)

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# Toner, Fertil Steril 2003

- AMH, CFA, (FSH): Quantité **d'ovocytes**
- Âge: Qualité des ovocytes

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Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

# The value of Anti-Müllerian hormone in low and extremely low ovarian reserve in relation to live birth after in vitro fertilization

Igna F. Reijnders [a], Willianne L.D.M. Nelen [a], Joanna IntHout [b], Antonius E. van Herwaarden [c], Didi D.M. Braat [a], Kathrin Fleischer [a,*]

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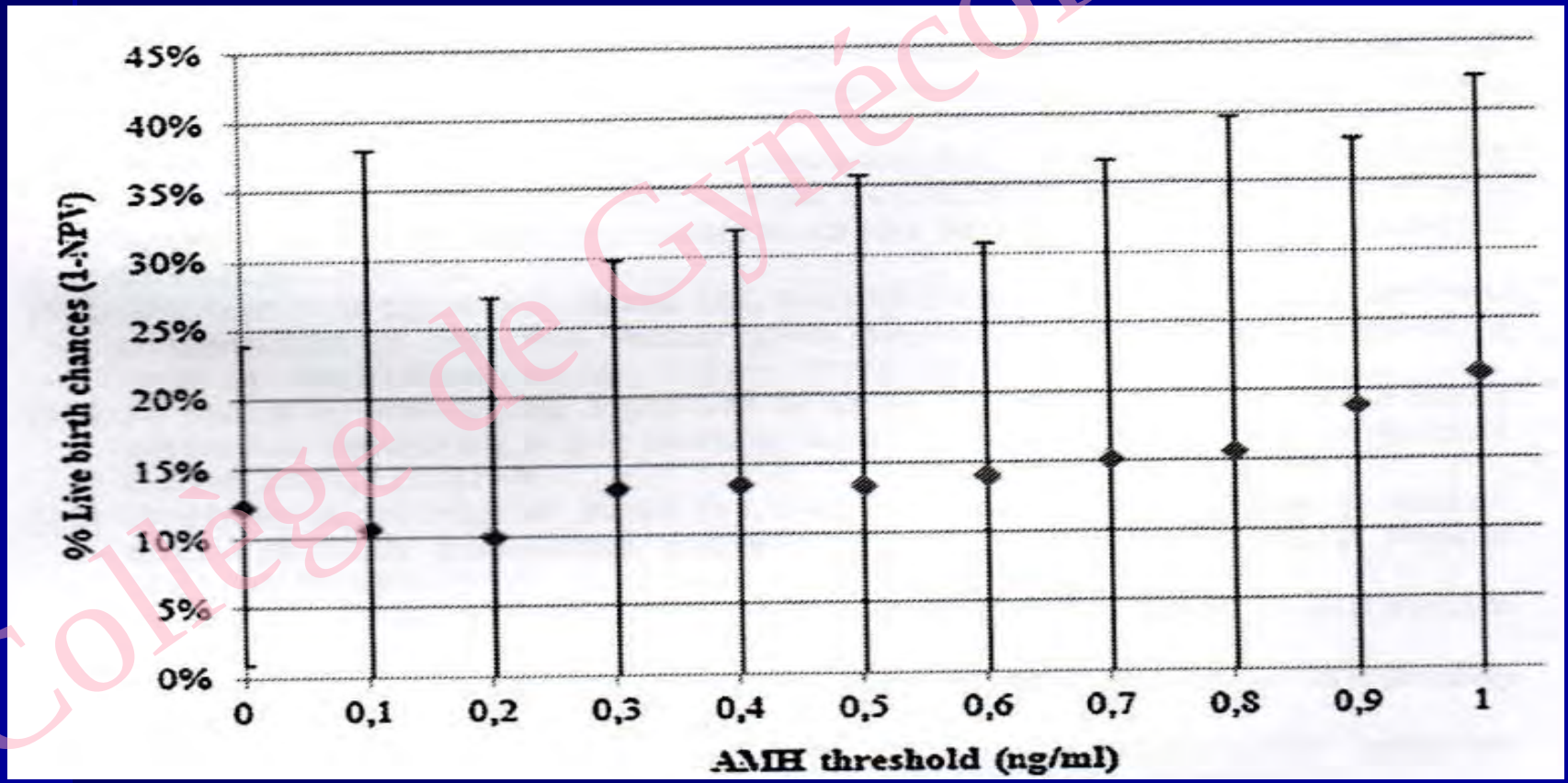
[b] Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands
[c] Department of Laboratory Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

**Femmes ≥ 36 ans**
156 / 577 femmes
**ont une AMH ≤ 1,05** ng/ml

→ TENTATIVE TEST

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# MAUVAISES REPONDEUSES

- Fonctionnement ovarien non optimal en réponse à la stimulation ovarienne
  - Augmentation du taux **d'annulations**
  - Réduction du taux **d'implantation**
  - Réduction du taux de grossesses cliniques
  - Augmentation du taux de fausses-couches
- Evaluée à 10-25% de la population en AMP (*Tarlatzis BC, Hum Reprod Update 2003)*
- Dépend largement de la stratégie de chaque centre: critères de **recrutement, d'acceptation des dossiers et d'annulations en cours de** traitement

- Nombre de follicules matures: < 2, 3, 4, 5
- FSH de base (UI/l): > 6,5, 9, 12, 15
- E2 à J5 (pg/ml): < 100, 300, 400, 500, 660
- E2 avant hCG: < 300, < 660
- Age > 40 ans
- Dose quotidienne de gonadotrophines > 300 UI
- Durée de la stimulation
- Annulation des cycles
- Nombre d'ovocytes récupérés: ≤ 3, 4, <6

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# Population hétérogène

- Fausses mauvaises répondeuses :
  - Erreur de prescription : stimulation insuffisante
  - **Erreur d'administration du traitement**

- Mauvaises répondeuses avérées :

  Notion rétrospective : femmes déjà stimulées, avec critères de mauvaise réponse patente

- Patientes à risque de mauvaise réponse :

  Notion prospective : femme non encore stimulée, avec seulement des facteurs de risque de réponse insuffisante

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# Critères de Bologne

(ESHRE consensus on poor ovarian response définition, Ferraretti AP et al., Hum Reprod 2011; 26: 1616-24)

- 2 des 3 critères doivent être présents:
  - **Age maternel avancé (≥ 40 ans) ou un autre facteur de** risque de POR
  - **Une POR préalable (≤ 3 ovocytes avec une stimulation** conventionnelle)
  - Un test de réserve ovarienne anormal (AFC < 5-7 follicules ou AMH < 0,5-1,1 ng/ml)
- 2 épisodes de faible réponse après une stimulation maximale suffit à définir une POR (sans âge maternel avancé ou tests de réserve ovarienne anormaux)
- Un cycle de stimulation est essentiel pour définir une POR (sinon expected POR)

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# Expérience équipe Bologne sur 1er cycle FIV (3825 cycles)

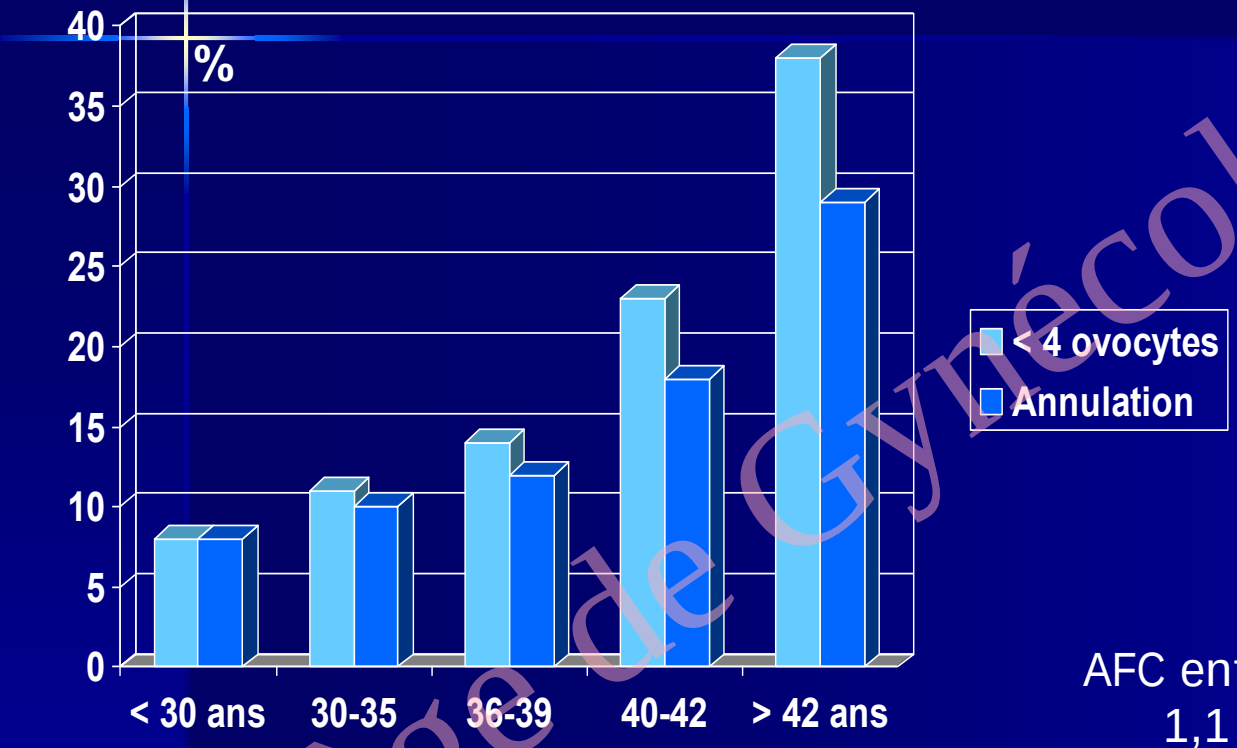


**TABLE 3** | Different patient categories generated by combining the parameters used to define the poor ovarian response patient according to Bologna criteria.

| Criteria | Combined with |
|---|---|
| ≥ 40 years | • One previous POR episode<br>• Abnormal ORT |
| Other risk factor | • One previous POR episode<br>• Abnormal ORT |
| One previous POR | • ≥40 years<br>• Other risk factor<br>• Abnormal ORT |
| Abnormal ORT | • ≥40 years<br>• Other risk factor<br>• Previous POR episode |
| 2 previous episodes of POR after maximal stimulation | • Alone<br>• Or with any other criteria |

*POR, poor ovarian response (cycles canceled or ≤3 oocytes with the use of conventional ovarian stimulation); ORT, ovarian reserve tests (AFC <5–7 follicles or AMH <0.5–1.1 ng/mL); Other risk factor: genetic or acquired conditions possibly linked to a reduced number of resting follicles.*

AFC entre 5 et 7 et AMH entre 0,5 et 1,1 ng/ml → Seuils trop larges

**Polyzos (RBM 2013)**: 485 p / 823 c; ≥ 300 UI/j; critères de Bologne: **Pas de différence +/- 40 ans sur le taux de naissance/cycle (5,2 vs 7,1%) ou /patiente (8,8 vs 11,6). Seul le nombre d'ovocytes recueillis est significativement lié au taux de naissance (OR 1,92 [1,03-3,55] entre > 3 et 1-3 ovocytes)**

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# Critères de Bologne: pronostics différents

**TABLE 4 |** Clinical studies evaluating IVF outcomes in different subgroups of poor ovarian responders according to the Bologna criteria.

| Study | Number of patients (IVF/ICSI cycles) included | Subgroups included | Live birth rate/cycle (number of cycles) | Ability of Bologna criteria to identify homogeneous patient populations with similar pregnancy outcomes |
|---|---|---|---|---|
| Busnelli et al. (58) | 362 (362) | Group 1: anamnestic risk factors for POR and one episode of POR; Group 2: one previous episode of POR and abnormal ORT; Group 3: anamnestic risk factors for POR and abnormal ORT; Group 4: anamnestic risk factors for POR, one previous POR cycle and abnormal ORT Group 5: two episodes of POR after maximal stimulation | Group 1: 10% (40)<br>Group 2: 4% (52)<br>Group 3: 6% (190)<br>Group 4: 8% (73)<br>Group 5: 0% (7)<br>*P*-values did not differ among subgroups (P=0.65) | Yes;<br>The study suffered from a type II error due to small patient cohort included in each subgroup. |
| La Marca et al. (66) | 210 (452) | Group 1: ≥ 40 years-old + previous POR;<br>Group 2: previous POR and abnormal ORT;<br>Group 3: ≥ 40 years-old + abnormal ORT;<br>Group 4: previous POR + ≥ 40 years-old + abnormal ORT;<br>Group 5: two previous POR episodes | Group 1: 7.4% (76)<br>Group 2: 6.6% (91)<br>Group 3: 5.9% (76)<br>Group 4: 6.7% (136)<br>Group 5: 5.5% (73)<br>*P*-values not provided | Yes;<br>The study suffered from a type II error due to small patient cohort included in each subgroup. |
| Bozdag et al. (67) | 821 (1257) | Group 1: ≥40 years-old + previous POR episode;<br>Group 2: ≥40 years-old + AFC<7;<br>Group 3: AFC<7 + previous POR episode;<br>Group 4: ≥40y + AFC <7 + previous POR episode | Group 1: 3.3% (123)<br>Group 2: 6.3% (253)<br>Group 3: 8.7% (575) ($P = 0.001$; statistically different from all other groups)<br>Group 4: 2.3% (306) ($P = 0.002$; statistically different from all other groups) | No;<br>The number of subjects in each group was adequate to avoid a type II error. |

*ORT, ovarian reserve test; Anamnestic risk factors: advanced maternal age (≥40years), evidence of ovarian endometrioma at the basal ultrasound, previous ovarian surgery, previous chemotherapy, genetic abnormalities, shortening of the menstrual cycle.*

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# Classification POSEIDON

(Patient Oriented Strategies Encompassing IndividualizeD Oocyte Number)

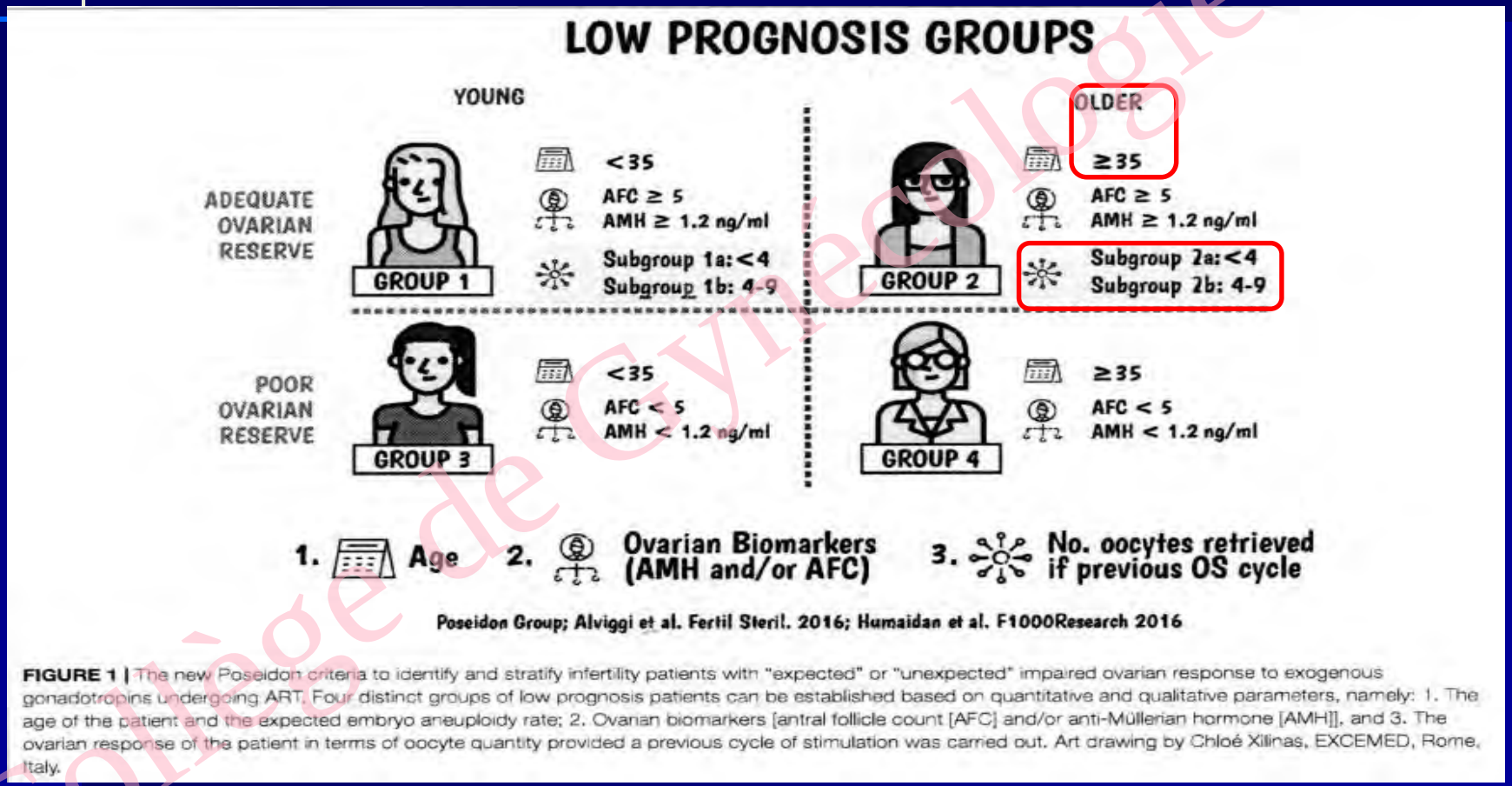


**FIGURE 1 |** The new Poseidon criteria to identify and stratify infertility patients with "expected" or "unexpected" impaired ovarian response to exogenous gonadotropins undergoing ART. Four distinct groups of low prognosis patients can be established based on quantitative and qualitative parameters, namely: 1. The age of the patient and the expected embryo aneuploidy rate; 2. Ovarian biomarkers [antral follicle count [AFC] and/or anti-Müllerian hormone [AMH]], and 3. The ovarian response of the patient in terms of oocyte quantity provided a previous cycle of stimulation was carried out. Art drawing by Chloé Xilinas, EXCEMED, Rome, Italy.

**L'importance de la cohorte ovocytaire permet d'augmenter la probabilité d'avoir un blastocyste euploïde**

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*Que faire chez une femme en insuffisance ovarienne qui désire une grossesse ?*

# Prise en charge en FIV

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# Protocoles Mauvaises Répondeuses

- Mini puis microdoses d'agonistes de la GnRH
- Protocole agoniste GnRH stop
- Augmentation doses de FSH
- Protocole agoniste step-down
- Protocole agoniste court microdoses
- Protocole antagoniste GnRH
- Flushing folliculaire
- Double stimulation
- Corifollitropine α
- Mild stimulation, cycle spontané, cycle naturel modifié

Antagonist
Microdose flare
Long protocol
LH added
Letrozole + FSH ± antagonist
DHEA
Short protocol
Transdermal testosterone
Growth hormone
HCG added at stimulation
Increase of FSH dose
Clomiphene citrate + FSH/HMG + -antagonist
Luteal FSH start
Estrogen for luteal support
Follicular flushing
Long-stop protocol
FSH/HMG only (no agonist or antagonist)
FSH dose 300 IU
Late FSH start
Metformin
Ultrashort agonist-antagonist
Modified flare
Low-dose aspirin
Natural cycle
Mini-long protocol
Step-down of FSH dose
Luteal phase antagonist
Gamete intrauterine transfer
Day of embryo transfer
Early (Day 1) FSH start
FSH dose 450 IU
FSH dose 600 IU
Clomiphene citrate only

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# Historique

- 1/ Mini ou microdoses **d'agonistes de la GNRH** (1994 – Feldberg): diminution du blocage hypophyso-ovarien (P long)
- 2/ Protocole « Stop » (1998 – Faber): stopper le blocage au début de la stimulation (P long)
- 3/ Augmentation des doses de FSH (Land: 600 UI/j): Khalaf 450, Freour 300 UI

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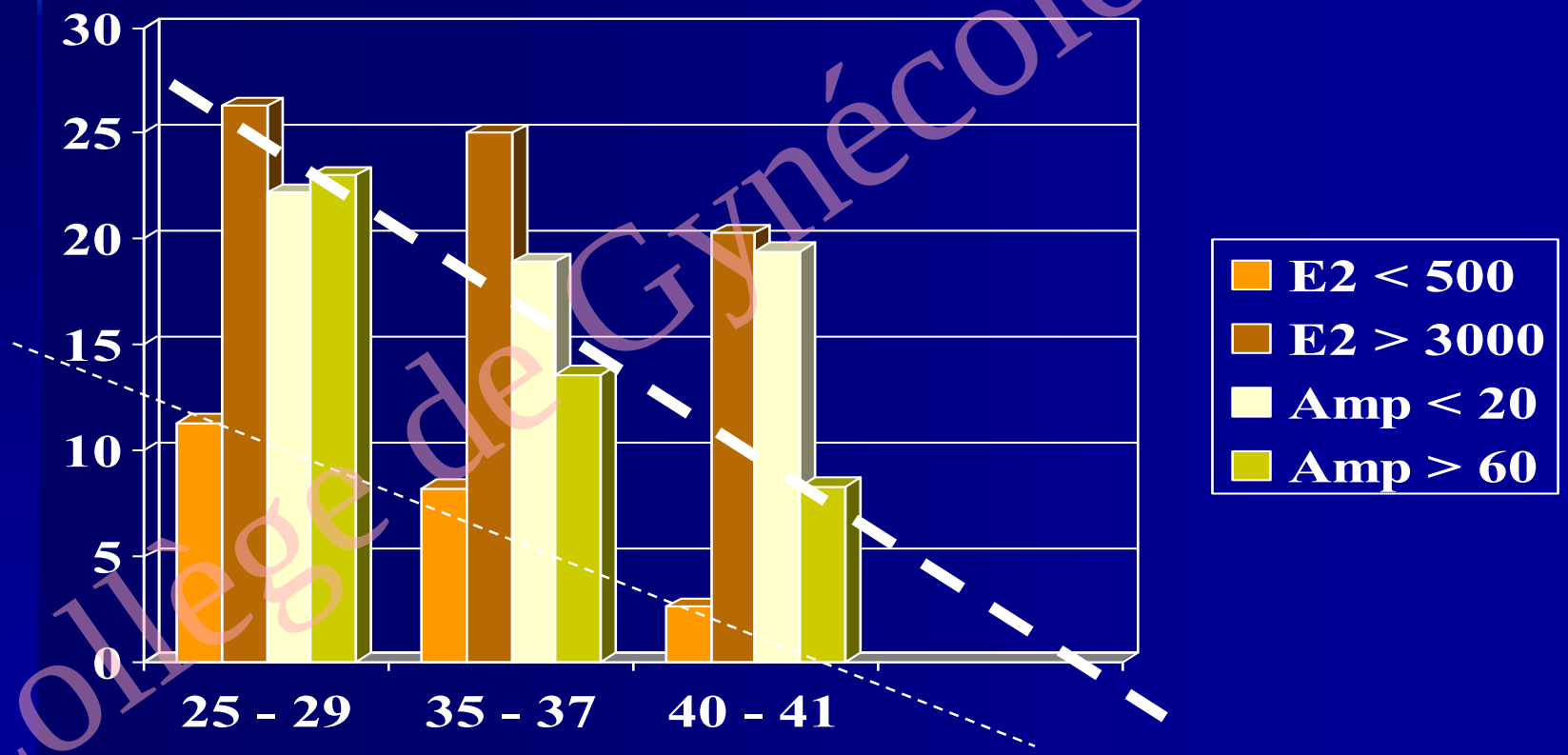
# Taux de grossesses cliniques par **ponction selon l'âge et la réponse à la stimulation et le nombre d'ampoules** consommées: Max 450 UI/j

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# Historique (2)

- 4/ Protocole Step-Down (Agonistes 0,1-0,025 / FSH 450 UI vs 450 – 300 (> 200 pg/ml) – 150 UI (> 2 foll > 12 mm), (Cedrin Durnerin - 2000): Idem
- 5/ Protocole Agoniste court flare-up (Surrey - 1998): combiner l'effet flare-up avec la FSH +/- COP avant (effet rebond à l'arrêt)
- 6/ Antagoniste (Akman – 2001): pas de blocage initial

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# Agonistes ou Antagonistes ?

| | Agoniste | Antagoniste |
|---|---|---|
| Akman, 2001, 48 | | Idem / Ag C |
| Fasouliotis, 2003, 53 | | Sup / Ag C |
| Copperman, 2003, 1773 | | Idem / Ag C |
| | | Sup / Ag L |
| Malmusi, 2005, 55 | Ag C > Ant | |
| Mohamed, 2005, 134 | | Idem / Ag C |
| Cheung, 2005, 66 | | Idem / Ag L |
| Marci,2005, 60 | | Sup / Ag L |
| Brook, 2006, 31 | | Idem / Ag L |

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Merviel et al. Reproductive Health (2015) 12:52
DOI 10.1186/s12978-015-0039-2

REPRODUCTIVE HEALTH

RESEARCH Open Access

# Comparative prospective study of 2 ovarian stimulation protocols in poor responders: effect on implantation rate and ongoing pregnancy

Philippe Merviel[1,3*], Rosalie Cabry-Goubet[2,3], Emmanuelle Lourdel[1], Aviva Devaux[2,3], Naima Belhadri-Mansouri[2,3], Henri Copin[2,3] and Moncef Benkhalifa[2,3]

462 femmes avec protocole agoniste long + 375 UI/j: 22 naissances (4,7%)
Reprise pour 2ème cycle, randomisée entre:
- COP + GnRHa 0,025/j + FSH 375 UI/j
- FSH 375 UI/j + antagoniste
→ Même taux de GE/t (14,5%)

**Table 4** Prognostic factors in the P2 and P3 protocols correlated with occurrence of clinical pregnancy (in a multivariate analysis)

| Factors | OR | 95 % CIs | *p* |
|---|---|---|---|
| Female age < 36 | 2.39 | 1.45-3.34 | <0.01 |
| No woman tobacco use | 3.05 | 1.62-4.48 | < 0.02 |
| Total dose of FSH/hMG < 5000 IU | 1.77 | 1.11-2.93 | < 0.05 |
| Endometrial thickness > 10 mm | 2.48 | 1.57-3.39 | < 0.01 |

**Table 3** Ovarian stimulation results in the P2 and P3 COH protocols

| | P2 | P3 |
|---|---|---|
| Number of cycles | 220 | 220 |
| Total FSH/hMG dose (IU) | 4664 ± 605 | 4680 ± 641 |
| Duration of stimulation (days) | 11.8 ± 2.3 | 11.6 ± 2.7 |
| Estradiol levels on hCG day (pg/ml) | 1215 ± 350[a] | 712 ± 251[b] |
| Progesterone levels on hCG day (ng/ml) | 0.8 ± 0.2 | 0.7 ± 0.3 |
| Endometrial thickness (mm) | 8.7 ± 1.3 | 8.4 ± 1.2 |
| No of oocyte pick-ups | 204 | 196 |
| No of oocytes retrieved (per pick-up) | 1224 (6.0 ± 4.1) | 1218 (6.2 ± 4.9) |
| No of M2 oocytes retrieved | 894 (4.3 ± 3.7) | 913 (4.6 ± 4.1) |
| No of oocytes fertilized | 721 | 694 |
| No of embryos obtained | 487 (2.3 ± 0.5)[a] | 426 (2.1 ± 0.3)[b] |
| Grade I/II embryos (%) | 35.9 | 36.8 |
| No of overall cancelled cycles (%) | 42 (19.0) | 51 (23.1) |
| No of embryos transfer | 178 | 169 |
| Embryos per transfer | 2.1 ± 0.2[c] | 1.9 ± 0.4[d] |
| Clinical pregnancy rate per transfer (%) | 17.9 | 15.9 |
| Ongoing pregnancy rate per transfer (%) | 14.6 | 14.2 |
| Implantation rate per embryo transferred (%) | 8.9 | 8.4 |
| No of cycles with cryopreservation (%) | 15.7 | 9.4 |
| No of cryopreserved embryos | 69 | 43 |

[a-b]: significant difference at p < 0.001
[c-d]: $p < 0.01$

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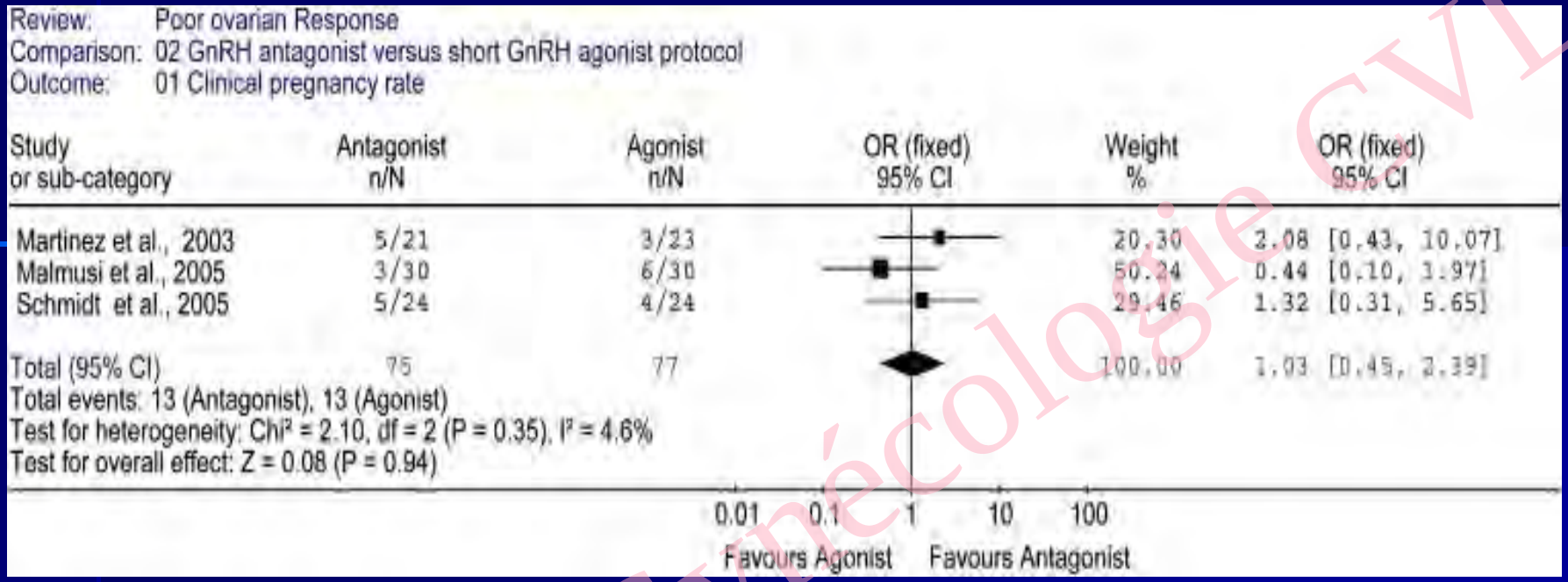
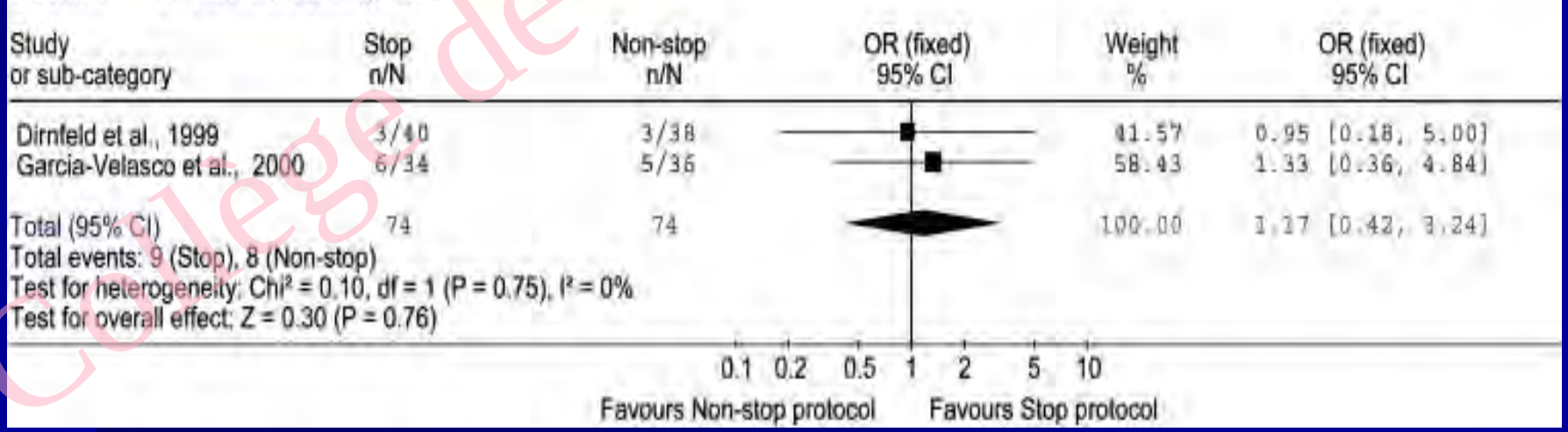
Review: Poor ovarian Response
Comparison: 02 GnRH antagonist versus short GnRH agonist protocol
Outcome: 01 Clinical pregnancy rate




Review: Poor ovarian Response
Comparison: 03 Stop vs. Non-stop long GnRH agonist protocol
Outcome: 01 Clinical pregnancy rate

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# Historique (3)

- 7: Protocoles MILD (Antagoniste + FSH 150, débuté à J5): Les protocoles classiques avec fortes doses recrûtent des follicules destinés à l'apoptose. Baart: moins d'aneuploïdies
- 8/ Duostim, Cumul ovocytaire
- 9/ Corrifollitropine α (step-up puis step-down: séquentiel ?)

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# Cycles naturel modifié
## [Lainas, Hum Reprod 2015]

- NMC: dès qu'un foll ≥ 14 mm, FSH 150 UI/j et antagoniste
- HDFSH: FSH 300 UI/j J2 et antagoniste

→ Ovo: 1,1 vs 2,4; OF: 0,7 vs 1,4, Top ET: 0,5 vs 0,8 ($p < 0,001$)

→ Taux identique de cycles avec au moins 1 Top ET (62%)

→ OR LBR NMC/HDFSH: 4 [1,1-14]

**Table IV Baseline characteristics in cycles that did or did not result in live birth after treatment by either MNC or HDFSH antagonist protocol.**

| | No live birth, $N = 308$ | Live birth, $N = 17$ | $P$ |
|---|---|---|---|
| | Mean ± RSE 95% CI[a] | | |
| Age (years) | 41.2 ± 0.3<br>40.6–41.7 | 37.6 ± 0.5<br>36.5–38.7 | <0.001 |
| Body mass index (kg/m$^2$) | 23.1 ± 0.3<br>22.6–23.7 | 22.3 ± 0.6<br>21.1–23.5 | 0.202 |
| Duration of infertility (years) | 3.5 ± 0.2<br>3.0–3.9 | 3.2 ± 0.4<br>2.4–4.1 | 0.647 |
| Number of previous attempts | 3.3 ± 0.1<br>3.1–3.5 | 3.9 ± 0.4<br>3.2–4.7 | 0.114 |
| Basal FSH (IU/l) | 22.7 ± 0.8<br>21.0–24.4 | 17.4 ± 1.0<br>15.5–19.3 | <0.001 |
| Basal LH (IU/l) | 9.9 ± 0.5<br>9.0–10.7 | 8.3 ± 0.8<br>6.8–9.8 | 0.088 |
| Basal estradiol (pg/ml) | 34.0 ± 1.4<br>31.4–36.7 | 33.9 ± 3.3<br>27.4–40.4 | 0.968 |
| Basal progesterone (ng/ml) | 0.6 ± 0.0<br>0.5–0.7 | 0.5 ± 0.1<br>0.4–0.7 | 0.320 |
| Antral follicle count | 2.7 ± 0.1<br>2.6–2.9 | 2.9 ± 0.3<br>2.4–3.5 | 0.394 |
| Cause of infertility[b] | % (95% CI)[b] | | |
| Poor ovarian reserve only | 6.5 (3.5–9.5) | 47.1 (22.1–72.1) | <0.001 |
| Poor ovarian reserve + male factor | 15.3 (10.7–19.8) | 23.5 (4.6–42.5) | |
| Poor ovarian reserve + endometriosis | 6.8 (3.7–9.9) | 11.8 (0–26.2) | |
| Poor ovarian reserve + advanced maternal age (≥40 years) | 60.1 (53.4–66.7) | 11.8 (0.0–27.2) | |
| Poor ovarian reserve + tubal factor | 11.4 (7.4–15.3) | 5.9 (0–17.1) | |
| Fertilization method | | | |
| IVF | 34.9 (27.7–42.1) | 35.3 (11.8–58.8) | 0.974 |
| ICSI | 65.1 (57.9–72.4) | 64.7 (41.2–88.2) | |
| Day of embryo transfer | | | |
| Day 2 | 23.7 (17.1–30.3) | 6.7 (0–18.5) | 0.135 |
| Day 3 | 76.3 (69.8–82.8) | 93.3 (81.5–100.0) | |

FSH, follicle stimulating hormone; LH, luteinizing hormone; MNC, modified natural cycle; HDFSH, high-dose FSH; hCG, human chorionic gonadotrophin; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.
[a]Simple linear regression with clustered robust standard error (RSE) adjusted for multiple observations.
[b]Univariable logistic regression with clustered RSE adjusted for multiple observations.

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# Double stimulation (DuoStim) [Vaiarelli A, Fr Endoc 2018]

- Groupe 3 et 4 de la classif POSEIDON
- FPS: 4 mg E2 à partir de J21 → 2-3è j des règles, puis FSH 300 + 75 LH et antagoniste. Déclenchement par Buséréline 0,5
- 5 jours après la ponction, protocole identique pour LPS
- Freeze all blastocyste → TEC 1 B (CNM ou CA)

→ OPR: 39,5 et 49,4 %

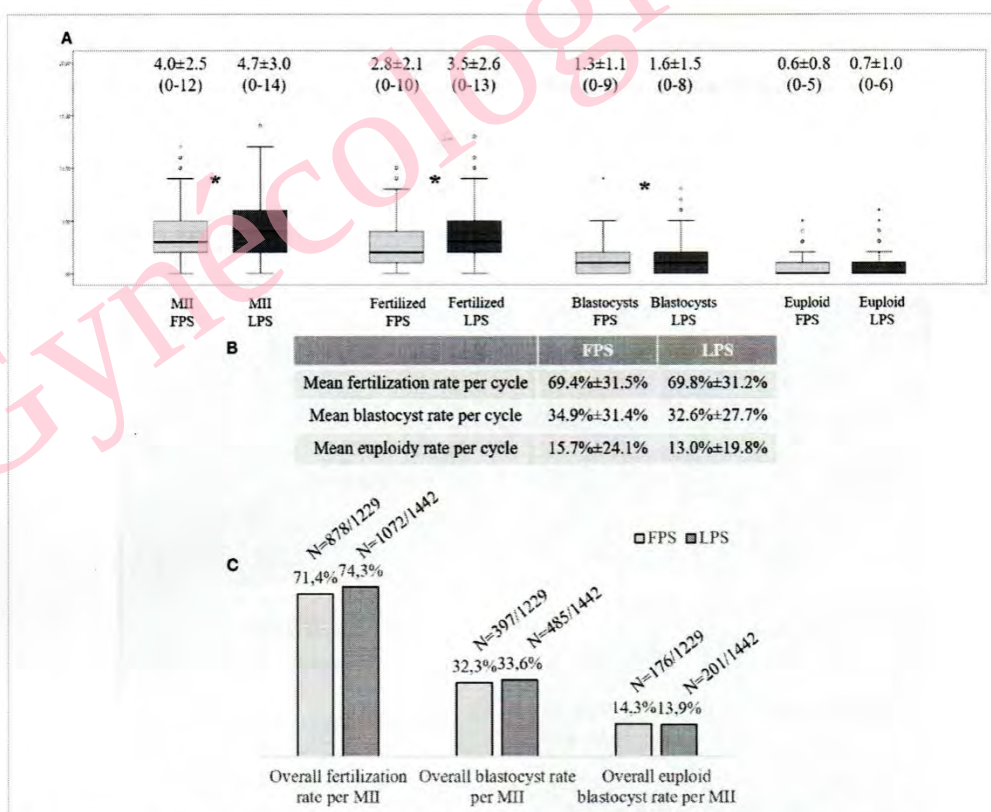


**FIGURE 1** | Multicenter clinical experience at the G.EN.E.R.A. centers for reproductive medicine (Rome, Naples, Marostica, and Umbertide) with the application of a DuoStim approach. **(A)** Mean number of metaphase (MII) oocytes, fertilized embryos, blastocysts, and euploid blastocysts obtained per cycle after follicular phase stimulation (FPS) and luteal phase one (LPS); **(B)** Mean embryological results calculated per MII oocyte retrieved and inseminated in FPS- and LPS-derived cycles; **(C)** Overall embryological results of the MII oocytes collected after FPS and LPS, respectively. The stars identify statistically significant differences. The non-Gaussian distribution of the data was assessed through the Shapiro–Wilk test. Wilcoxon signed-rank test and Fisher's exact test were used to test for significant differences between FPS- and LPS-derived data.

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# Corifollitropine alpha (Comport)
## [Drakopoulos, Hum Reprod 2017]

- 152 femmes < 40 ans, Bologne (1 à 2 cycles antérieurs avec faible réponse, AMH < 1,1 et AFC < 7)
- Corifollitropine 150 µg J2 (S1) → S8 puis HMG 300 UI/j, vs FSHr 300/j + antagoniste. hCGu, transfert J3

→ Aucune différence en terme de grossesse

**Table II ICSI outcomes of the two treatment groups in the whole study population.**

| | Group A corifollitropin alfa and hp-HMG (*n* = 77) | Group B:rec-FSH (*n* = 70) | Difference % (95% CI) MH[1] odds ratios (95% CI) | *P*-value |
|---|---|---|---|---|
| Number of oocytes retrieved, mean (SD) | 3.6 (3.1) | 3.6 (2.7) | (−0.9 to 0.9)* | 0.7[a] |
| Number of MIIs, mean (SD) | 2.9 (2.8) | 2.7 (2) | (−0.6 to 1)* | 0.8[a] |
| Cycle cancellation, *n* (%) | 12 (15.6%) | 7 (10%) | +5.6 (−5.1 to 16.3) | 0.3[b] |
| | | | 1.6 (0.6–4.5) | |
| Cycles with ET, *n* (%) | 54 (70.1%) | 55 (78.6%) | −8.5 (−22.5 to 5.5) | 0.2[b] |
| | | | 0.6 (0.3–1.4) | |
| Top quality embryos among patients with ET**, *n* (%) | 33 (67.3%) | 30 (61.2%) | +6.1 (−9.3 to 21.6) | 0.5[b] |
| | | | 1.2 (0.5–2.8) | |
| Number of embryos transferred, mean (SD) | 1.3 (1.01) | 1.4 (0.9) | (−0.4 to 0.2)* | 0.7[c] |
| Patients with supernumerary cryopreserved embryos, *n* (%) | 22 (28.6%) | 10 (14.3%) | +14.3 (13–27.3) | 0.04[b] |
| | | | 2.4 (1.01–5.5) | |
| Number of embryos cryopreserved, mean (SD) | 0.6 (1.3) | 0.3 (0.8) | (−0.05 to 0.6)* | 0.04[a] |
| Positive hCG, *n* (%) | 13 (16.9%) | 16 (21.3%) | −4.4 (−17.1 to 8.3) | 0.3[b] |
| | | | 0.7 (0.3–1.6) | |
| Clinical pregnancy, *n* (%) | 11 (14.3%) | 12 (17.1%) | −2.8 (−14.5 to 8.9) | 0.6[b] |
| | | | 0.8 (0.3–2) | |
| Ongoing pregnancy, *n* (%) per-protocol | 11 (14.3%) | 11 (15.7%) | −1.5 (−13 to 10) | 0.8[b] |
| | | | 0.9 (0.4–2.3) | |
| Pregnancy > 12 weeks, *n* (%) per-protocol | 11 (14.3%) | 11 (15.7%) | −1.5 (−13 to 10) | 0.8[b] |
| | | | 0.9 (0.4–2.3) | |
| Live birth, *n* (%) per-protocol | 10 (12.9%) | 10 (14.3%) | −1.3 (−12.3 to 9.7) | 0.8[b] |
| | | | 0.9 (0.3–2.3) | |
| Ongoing pregnancy, *n* (%) in patients with ET** | 11 (20.3%) | 11 (20%) | +0.3 (−14.7 to 15.3) | 0.9[b] |
| | | | 1.03 (0.4–2.6) | |
| Ongoing pregnancy, *n* (%) intention-to treat*** | 11 (14.3%) | 11 (14.7%) | −0.4 (−11.5 to 10.8) | 0.9[b] |
| | | | 0.9 (0.4–2.4) | |

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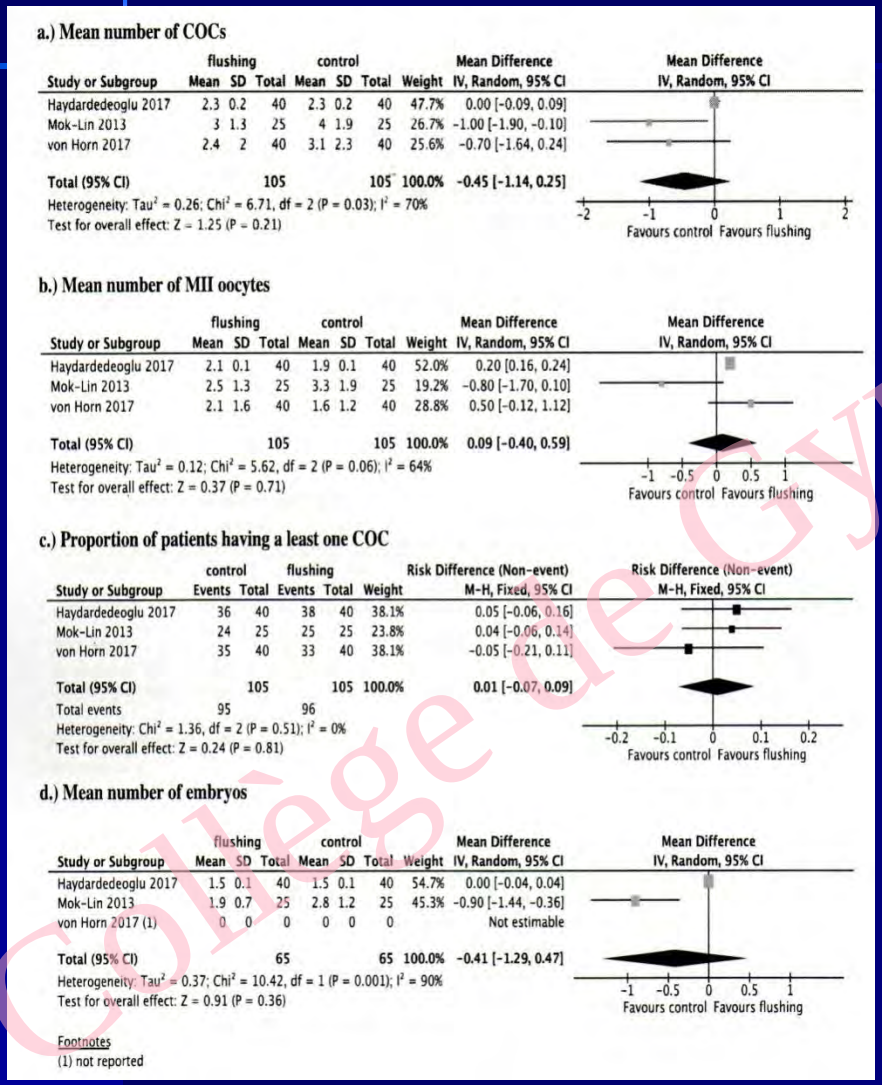
# Flushing folliculaire

## [Neumann K, RBM 2017]



a.) Mean number of COCs

| Study or Subgroup | flushing Mean | SD | Total | control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 2.3 | 0.2 | 40 | 2.3 | 0.2 | 40 | 47.7% | 0.00 [-0.09, 0.09] |
| Mok-Lin 2013 | 3 | 1.3 | 25 | 4 | 1.9 | 25 | 26.7% | -1.00 [-1.90, -0.10] |
| von Horn 2017 | 2.4 | 2 | 40 | 3.1 | 2.3 | 40 | 25.6% | -0.70 [-1.64, 0.24] |
| **Total (95% CI)** | | | **105** | | | **105** | **100.0%** | **-0.45 [-1.14, 0.25]** |

Heterogeneity: Tau² = 0.26; Chi² = 6.71, df = 2 (P = 0.03); I² = 70%
Test for overall effect: Z = 1.25 (P = 0.21)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Favours control Favours flushing

b.) Mean number of MII oocytes

| Study or Subgroup | flushing Mean | SD | Total | control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 2.1 | 0.1 | 40 | 1.9 | 0.1 | 40 | 52.0% | 0.20 [0.16, 0.24] |
| Mok-Lin 2013 | 2.5 | 1.3 | 25 | 3.3 | 1.9 | 25 | 19.2% | -0.80 [-1.70, 0.10] |
| von Horn 2017 | 2.1 | 1.6 | 40 | 1.6 | 1.2 | 40 | 28.8% | 0.50 [-0.12, 1.12] |
| **Total (95% CI)** | | | **105** | | | **105** | **100.0%** | **0.09 [-0.40, 0.59]** |

Heterogeneity: Tau² = 0.12; Chi² = 5.62, df = 2 (P = 0.06); I² = 64%
Test for overall effect: Z = 0.37 (P = 0.71)

Mean Difference IV, Random, 95% CI
-1 -0.5 0 0.5 1
Favours control Favours flushing

c.) Proportion of patients having a least one COC

| Study or Subgroup | control Events | Total | flushing Events | Total | Weight | Risk Difference (Non-event) M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 36 | 40 | 38 | 40 | 38.1% | 0.05 [-0.06, 0.16] |
| Mok-Lin 2013 | 24 | 25 | 25 | 25 | 23.8% | 0.04 [-0.06, 0.14] |
| von Horn 2017 | 35 | 40 | 33 | 40 | 38.1% | -0.05 [-0.21, 0.11] |
| **Total (95% CI)** | | **105** | | **105** | **100.0%** | **0.01 [-0.07, 0.09]** |
| Total events | 95 | | 96 | | | |

Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

Risk Difference (Non-event) M-H, Fixed, 95% CI
-0.2 -0.1 0 0.1 0.2
Favours control Favours flushing

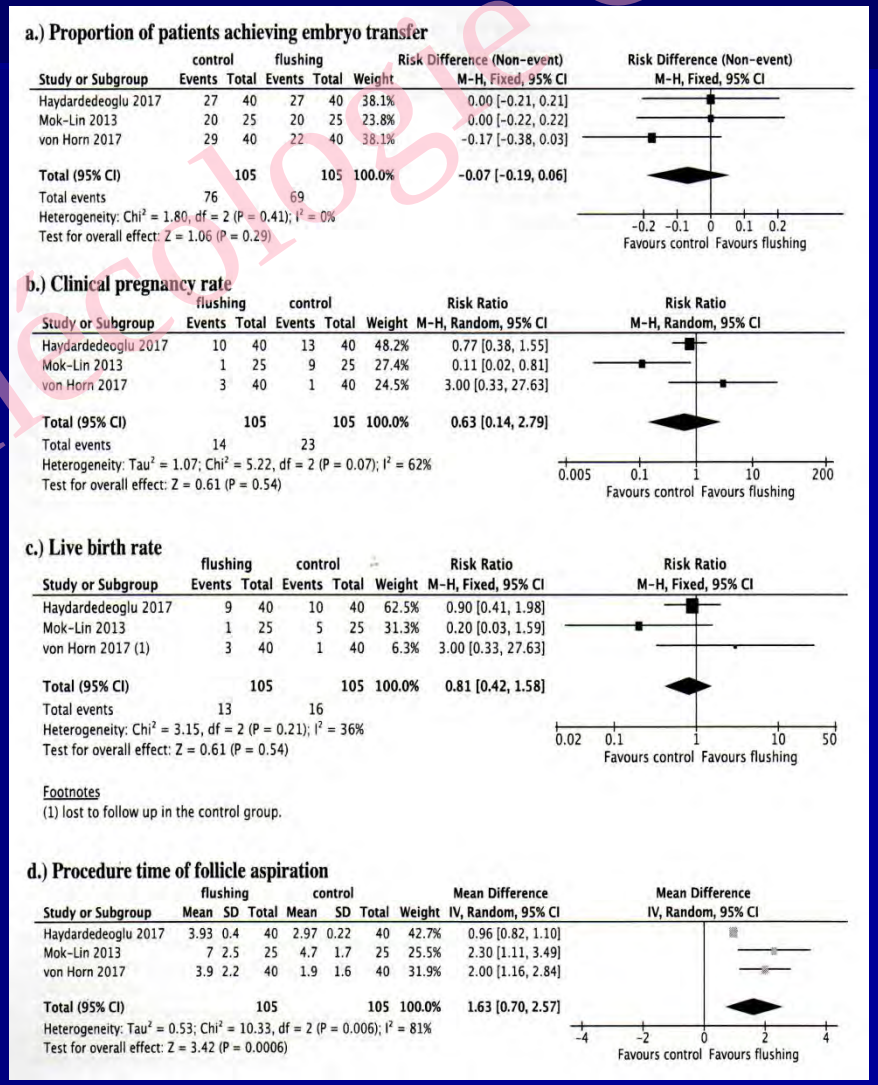
d.) Mean number of embryos

| Study or Subgroup | flushing Mean | SD | Total | control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 1.5 | 0.1 | 40 | 1.5 | 0.1 | 40 | 54.7% | 0.00 [-0.04, 0.04] |
| Mok-Lin 2013 | 1.9 | 0.7 | 25 | 2.8 | 1.2 | 25 | 45.3% | -0.90 [-1.44, -0.36] |
| von Horn 2017 (1) | 0 | 0 | 0 | 0 | 0 | 0 | | Not estimable |
| **Total (95% CI)** | | | **65** | | | **65** | **100.0%** | **-0.41 [-1.29, 0.47]** |

Heterogeneity: Tau² = 0.37; Chi² = 10.42, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 0.91 (P = 0.36)

Footnotes
(1) not reported

Mean Difference IV, Random, 95% CI
-1 -0.5 0 0.5 1
Favours control Favours flushing



a.) Proportion of patients achieving embryo transfer

| Study or Subgroup | control Events | Total | flushing Events | Total | Weight | Risk Difference (Non-event) M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 27 | 40 | 27 | 40 | 38.1% | 0.00 [-0.21, 0.21] |
| Mok-Lin 2013 | 20 | 25 | 20 | 25 | 23.8% | 0.00 [-0.22, 0.22] |
| von Horn 2017 | 29 | 40 | 22 | 40 | 38.1% | -0.17 [-0.38, 0.03] |
| **Total (95% CI)** | | **105** | | **105** | **100.0%** | **-0.07 [-0.19, 0.06]** |
| Total events | 76 | | 69 | | | |

Heterogeneity: Chi² = 1.80, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

Risk Difference (Non-event) M-H, Fixed, 95% CI
-0.2 -0.1 0 0.1 0.2
Favours control Favours flushing

b.) Clinical pregnancy rate

| Study or Subgroup | flushing Events | Total | control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 10 | 40 | 13 | 40 | 48.2% | 0.77 [0.38, 1.55] |
| Mok-Lin 2013 | 1 | 25 | 9 | 25 | 27.4% | 0.11 [0.02, 0.81] |
| von Horn 2017 | 3 | 40 | 1 | 40 | 24.5% | 3.00 [0.33, 27.63] |
| **Total (95% CI)** | | **105** | | **105** | **100.0%** | **0.63 [0.14, 2.79]** |
| Total events | 14 | | 23 | | | |

Heterogeneity: Tau² = 1.07; Chi² = 5.22, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.61 (P = 0.54)

Risk Ratio M-H, Random, 95% CI
0.005 0.1 1 10 200
Favours control Favours flushing

c.) Live birth rate

| Study or Subgroup | flushing Events | Total | control Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 9 | 40 | 10 | 40 | 62.5% | 0.90 [0.41, 1.98] |
| Mok-Lin 2013 | 1 | 25 | 5 | 25 | 31.3% | 0.20 [0.03, 1.59] |
| von Horn 2017 (1) | 3 | 40 | 1 | 40 | 6.3% | 3.00 [0.33, 27.63] |
| **Total (95% CI)** | | **105** | | **105** | **100.0%** | **0.81 [0.42, 1.58]** |
| Total events | 13 | | 16 | | | |

Heterogeneity: Chi² = 3.15, df = 2 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.61 (P = 0.54)

Footnotes
(1) lost to follow up in the control group.

Risk Ratio M-H, Fixed, 95% CI
0.02 0.1 1 10 50
Favours control Favours flushing

d.) Procedure time of follicle aspiration

| Study or Subgroup | flushing Mean | SD | Total | control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Haydardedeoglu 2017 | 3.93 | 0.4 | 40 | 2.97 | 0.22 | 40 | 42.7% | 0.96 [0.82, 1.10] |
| Mok-Lin 2013 | 7 | 2.5 | 25 | 4.7 | 1.7 | 25 | 25.5% | 2.30 [1.11, 3.49] |
| von Horn 2017 | 3.9 | 2.2 | 40 | 1.9 | 1.6 | 40 | 31.9% | 2.00 [1.16, 2.84] |
| **Total (95% CI)** | | | **105** | | | **105** | **100.0%** | **1.63 [0.70, 2.57]** |

Heterogeneity: Tau² = 0.53; Chi² = 10.33, df = 2 (P = 0.006); I² = 81%
Test for overall effect: Z = 3.42 (P = 0.0006)

Mean Difference IV, Random, 95% CI
-4 -2 0 2 4
Favours control Favours flushing

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# Résultats

- < 37-38 ans: entre 10 et 20 % de TGE
- > 38-40 ans: entre 5 et 10 % de TGE

*Attention aux publications « optimistes ! »*

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*Que faire chez une femme en insuffisance ovarienne qui désire une grossesse ?*

# Traitements adjuvants en FIV

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# ESPART (LHr) [Humaidan P, Hum Reprod 2017]

- FSH 300 +/- LH 150 UI/j avec protocole long agoniste de la GnRH
- Aucune différence significative sur les taux de G
- Plus de FCS dans le groupe FSH seule (12,4 vs 6,7 %; OR: 0,52; p: 0,005

**Table III Primary efficacy outcome (number of oocytes retrieved) for patients randomized to receive either r-hFSH/r-hLH or r-hFSH monotherapy.**

| | r-hFSH/r-hLH | | | r-hFSH | | | Unadjusted | | Adjusted for over-dispersion (Poisson regression model) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Mean (SD) | Median (range) | *n* | Mean (SD) | Median (range) | Between-group difference (95% CI) | *P*-value | Between-group difference (95% CI) | *P*-value |
| ITT | | | | | | | | | | |
| Overall | 462 | 3.3 (2.71) | 3.0 (0–15) | 477 | 3.6 (2.82) | 3.0 (0–16) | −0.24 (−0.47, 0.00) | 0.054 | −0.24 (−0.74, 0.27) | 0.182 |
| Age <35 years | 57 | 3.5 (2.96) | 3.0 (0–12) | 61 | 3.3 (2.50) | 3.0 (0–13) | −* | 0.229 | −* | 0.407 |
| Age ≥35 years | 405 | 3.3 (2.67) | 3.0 (0–15) | 416 | 3.6 (2.86) | 3.0 (0–16) | −0.32 (−0.64, −0.01) | 0.013 | −0.32 (−0.78, 0.18) | 0.085 |
| PP | | | | | | | | | | |
| Overall | 377 | 3.8 (2.67) | 3.0 (0–15) | 395 | 4.0 (2.74) | 3.0 (0–16) | −0.17 (−0.44, 0.09) | 0.202 | −0.17 (−0.72, 0.37) | 0.340 |

*Negative of Hessian not positive definite.
ITT, intention-to-treat; PP, per-protocol; r-hFSH, recombinant human FSH; r-hLH, recombinant human LH.

**Table IV Secondary and other efficacy endpoints (ITT population)**

| | r-hFSH/r-hLH (*n* = 462) | r-hFSH (*n* = 477) | Odds ratio* (95% CI) unless otherwise indicated | *P*-value |
|---|---|---|---|---|
| Cancelled cycles,† *n* (%) | 35 (7.6) | 32 (6.7) | 1.12 (0.68, 1.85) | 0.654 |
| Biochemical pregnancy, *n* (%) | 80 (17.3) | 114 (23.9) | 0.68 (0.49, 0.94) | 0.020 |
| Clinical pregnancy, *n* (%) | 65 (14.1) | 80 (16.8) | 0.83 (0.58, 1.20) | 0.320 |
| Ongoing pregnancy, *n* (%) | 51 (11.0) | 59 (12.4) | 0.90 (0.60, 1.35) | 0.599 |
| Implantation rate, *n*/*N* (%)‡ | 79/538 (14.7) | 93/597 (15.6) | 0.93 (0.67, 1.29)§ | 0.675 |
| Live birth, *n* (%) | 49 (10.6) | 56 (11.7) | 0.91 (0.60, 1.38) | 0.663 |
| Total FSH dose administered (IU), mean (SD) | 3997.7 (1188.33)‖ | 4113.6 (1193.93) | −119.3 (−269.9, 31.3)§ | 0.120 |
| Number of MII oocytes in ICSI patients, mean (SD) | 2.9 (2.07)¶ | 3.1 (2.14)** | *Unadjusted:* −0.24 (−0.64, 0.15)<br>*Adjusted for over-dispersion:* −0.24 (−0.72, 0.23) | *Unadjusted:* 0.063<br>*Adjusted for over-dispersion:* 0.124 |

*r-hFSH/r-hLH versus r-hFSH.
†All cycle cancellations were due to lack of ovarian response.
‡*n* is the number of foetal sacs identified by transvaginal ultrasound and *N* is the total number of embryos transferred.
§Data are mean difference between groups (95% CI).
¶381 patients receiving r-hFSH underwent ICSI and data were not available for 15 of these patients.
‖Data missing for 10 patients.
**360 patients receiving r-hFSH plus r-hLH underwent ICSI, and data are not available for 13 of these patients.
ITT, intention-to-treat; MII, metaphase II; r-hFSH, recombinant human FSH; r-hLH, recombinant human LH.

**Table VI Observed (unadjusted) live birth rates according to BSC and treatment group.**

| BSC | Patients with a previous ART cycle | Patients with no previous ART cycle | r-hFSH/r-hLH (*N* = 462) | | r-hFSH (*N* = 477) | |
|---|---|---|---|---|---|---|
| | | | *n* (%*) | Live birth rate, *n* (%†) | *n* (%*) | Live birth rate, *n* (%†) |
| 0 (mild) | <40 years old **AND** previous ART cycle with ≥2 oocytes retrieved | <40 years old **AND** AMH > 0.5 ng/ml | 170 (36.8) | 18 (10.6) | 156 (32.7) | 34 (21.8) |
| 1 (moderate) | ≥40 years old **OR** previous ART cycle with <2 oocytes retrieved | ≥40 years old **OR** AMH ≤ 0.5 ng/ml | 209 (45.2) | 23 (11.0) | 254 (53.3) | 19 (7.5) |
| 2 (severe) | ≥40 years old **AND** previous ART cycle with <2 oocytes retrieved | ≥40 years old **AND** AMH ≤ 0.5 ng/ml | 83 (18.0) | 8 (9.6) | 67 (14.0) | 3 (4.5) |
| Overall | | | 462 (100.0) | 49 (10.6) | 477 (100.0) | 56 (11.7) |

*Percentage of total population receiving each treatment.
†Percentage of population with BSC score for each treatment.
BSC, baseline severity score; r-hFSH, recombinant human FSH; r-hLH, recombinant human LH.

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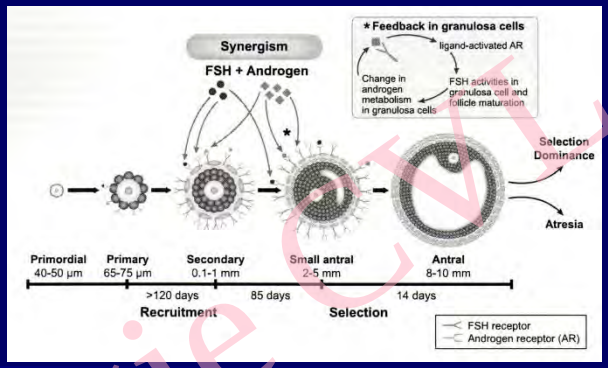
# Testostérone
## [Bosdou JK, Hum Reprod 2016]




- Critères de Bologne
- Gel de testostérone 10 mg/j pendant 21 jours (désensibilisation)
- Protocole DT long + FSH 225 UI/j, transfert J2

→ Pas de différence du nbre **d'ovocytes (3,5** vs 3), ni du taux de fécondation (66%)

→ Pas de différence LBR

**Table IV Clinical outcome between the testosterone pretreatment group and the no pretreatment group.**

| | Testosterone pretreatment (*n* = 26) | No pretreatment (*n* = 24) | Difference % 95% CI *P*-value |
|---|---|---|---|
| | % (*n*) | | |
| Proportion of patients with at least one top quality embryos | 20.0 (4) | 23.8 (5) | −3.8 −28.2 to +21.5 0.72 |
| Patients with embryo transfer | 83.3 (20) | 91.3 (21) | −8.0 −28.2 to +12.7 0.47 |
| Cancelation rate | 7.7 (2) | 4.2 (1) | +3.5 −13.5 to +20.3 1.00 |
| Positive hCG (intention to treat [ITT] analysis) | 7.7 (2) | 8.3 (2) | −0.6 −19.0 to +16.9 1.00 |
| Positive hCG per embryo transfer | 10.0 (2) | 9.5 (2) | −0.5 −20.2 to +21.7 1.00 |
| Clinical pregnancy (ITT analysis) | 7.7 (2) | 8.3 (2) | −0.6 −19.0 to +16.9 1.00 |
| Clinical pregnancy per embryo transfer | 10.0 (2) | 9.5 (2) | −0.5 −20.2 to +21.7 1.00 |
| Live birth rate (ITT analysis) | 7.7 (2) | 8.3 (2) | −0.6 −19.0 to +16.9 1.00 |
| Live birth per embryo transfer | 10.0 (2) | 9.5 (2) | −0.5 −20.2 to +21.7 1.00 |

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# DHEA, GH [Gonda KJ, RBM 2017]

Table 1 – Reported outcomes of DHEA and HGH supplementation for fertility.

| DHEA | HGH |
|---|---|
| *Positive outcomes* | |
| Improved hormone levels (Barad and Gleicher, 2005, 2006; Casson et al., 2000; Gleicher et al., 2010b) | Greater number of overall and MII oocytes (Bassiouny et al., 2016; Eftekhar et al., 2013; Lattes et al., 2015) |
| Greater egg and embryo numbers (Barad and Gleicher, 2005, 2006) | Higher fertilization rates (Bassiouny et al., 2016; Bergh et al., 1994) |
| Higher fertilization rates (Barad and Gleicher, 2006) | Increased number of embryos (Eftekhar et al., 2013; Lattes et al., 2015) |
| Improved embryo quality (Barad and Gleicher, 2006; Gleicher et al., 2010a) | Increased number of top-quality embryos (Lattes et al., 2015) |
| Lower rate of cycle cancellations (Barad and Gleicher, 2006; Barad et al., 2007) | May improve embryo quality (Bosch et al., 2016) |
| Lower rate of miscarriage (Gleicher et al., 2009) | Increased number of cryopreserved embryos (Lattes et al., 2015) |
| Higher clinical and cumulative pregnancy rates (Barad et al., 2007; Wiser et al., 2010) | |
| *Neutral outcomes* | |
| No improvement in ovarian response to stimulation (Sciard et al., 2016; Vlahos et al., 2015; Yeung et al., 2014) | No difference in the number of overall and MII oocytes (Dunne et al., 2015; Norman et al., 2016; Tesarik et al., 2005) |
| No increase in the number of embryos available (Sciard et al., 2016; Vlahos et al., 2015; Xu et al., 2014) | No improvement in embryo quality (Norman et al., 2016; Tesarik et al., 2005) |
| No increase in fertilization rates (Xu et al., 2014) | No difference in clinical pregnancy rates (Bassiouny et al., 2016; Dunne et al., 2015; Eftekhar et al., 2013; Kucuk et al., 2008; Norman et al., 2016) |
| No reduction in miscarriage rates (Sciard et al., 2016; Yeung et al., 2014) | No difference in live birth outcomes (Bassiouny et al., 2016; Norman et al., 2016) |
| No difference in clinical or ongoing pregnancy rates (Kara et al., 2014; Vlahos et al., 2015; Yeung et al., 2014) | |
| No difference in live birth outcomes (Vlahos et al., 2015; Yeung et al., 2014) | |

DHEA, dehydroepiandrosterone; HGH, human growth hormone; MII, metaphase II.

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# Coenzyme Q10
## [Xu Y, Reprod Biol Endoc 22018]

- Groupe 3 Poseidon (< 35 ans, AMH < 1,2 et AFC < 5)
- Stress oxydatif (ROS) et dysfonctions mitochondriales → altérations ADN
- Coenzyme Q10 impliqué dans la chaine respiratoire mitochondrilae et la production d'ATP (anti-oxydant, augmente le clivage embryonnaire et l'obtention de blastocyste)
- CoQ10 200 mg x 3/j – 60j (n: 76)
- FSH 225 + HMG 225/j + antagoniste (76/93). Transfert J3

→ Amélioration de la FSH J3 après CoQ10 (12,25 vs 10,5, p: 0,006); AMH et AFC inchangés

**Table 3** ART cycle stimulation parameters and embryology outcomes

| Variable | Study group ($n = 76$) | Control group ($n = 93$) | $p$- value |
|---|---|---|---|
| Cycle stimulation | | | |
| Total dose of Gn (IU), median (IQR) | 2000 (1200, 4275) | 3075 (1900, 4275) | 0.03 |
| Duration of stimulation (days), median (IQR) | 10 (9, 11) | 11 (9, 12) | 0.08 |
| Peak E2 concentration (pmol/l), median (IQR) | 2349 (892, 4784) | 1685 (1125, 3042) | 0.02 |
| Endometrial thickness on the day of hCG trigger (mm), mean ± SD | 10.12 ± 1.93 | 10.34 ± 1.50 | 0.13 |
| Patients who had oocyte retrieval | 72/76 (94.74) | 83/93 (89.25) | 0.82 |
| Cancelled cycles [a], n (%) | 4/76 (5.23) | 10/93 (10.75) | 0.27 |
| Embryology outcomes | | | |
| Retrieved oocytes, median (IQR) | 4 (2, 5) | 2 (1, 4) | 0.002 |
| ICSI cycles, n (%) | 24/76 (31.58) | 19/93 (20.43) | 0.20 |
| Fertilized oocytes (2PN), median (IQR) | 0.80 (0.50, 0.93) | 0.50 (0.33, 1.0) | 0.01 |
| Fertilization rate [b], n (%) | 191/253 (67.49) | 191/283 (45.06) | 0.001 |
| Number of high quality embryos, median (IQR) | 1 (0, 2) | 0 (0, 1.75) | 0.03 |

[a]Included women in who did not respond to stimulation and did not have oocyte retrieval
[b]Calculated as following: the number of total 2PN embryos divided by the number of total inseminated oocytes
*E2* – estradiol; *Gn* – gonadotrophin; *hCG* – human chorionic gonadotrophin; *IQR* – interquartile range; *LH* - luteinizing hormone; *P* - progesterone, *2PN* – two pronuclear, *SD* - standard deviation

**Table 4** Clinical reproductive outcomes

| Variable | Study group ($n = 76$) | Control group ($n = 93$) | $p$-value |
|---|---|---|---|
| Number of fresh ET cycles[a], n (%) | 66/76 (86.84) | 64/93 (68.82) | 0.35 |
| Patients who had oocyte retrieval but no ET [b], n (%) | 6/72 (8.33) | 19/83 (22.89) | 0.04 |
| Number of FET cycles, n (%) | 12/76 (15.79) | 3/93 (3.23) | 0.01 |
| Patients with cryopreserved embryos, n (%) | 14/76 (18.42)[c] | 4/93 (4.30)[d] | 0.012 |
| Number of embryos per ET[e], median (IQR) | 2 (1,2) | 1 (1,2) | 0.04 |
| Clinical pregnancy rate per fresh ET[f], n (%) | 23/66 (34.85) | 16/64 (25.00) | 0.24 |
| Cumulative clinical pregnancy rate[g], n (%) | 24/76 (31.58) | 16/93 (17.20) | 0.11 |
| Multiple pregnancy, n (%) | 4/76 (5.26) | 3/93 (3.23) | 0.70 |
| Spontaneous miscarriage, n (%) | 2/23 (8.67) | 2/16 (12.50) | 0.73 |
| Live birth rate per fresh ET[f], n (%) | 21/66 (31.82) | 14/64 (21.88) | 0.33 |
| Cumulative live birth rate[G], n (%) | 22/76 (28.95) | 14/93 (15.54) | 0.08 |

[a]All patients with available embryos had fresh ET
[b]Included women who had hCG andoocyte retrieval but did not have oocytes or useable embryos
[c]Embryos for 2women from this group did not survive the thawing (2/14, 14.29%)
[d]Embryos for 1 woman from this group did not survive the thawing (1/4, 25%)
[e]All the transferred embryos were day-3 cleavage stage embryos
[f]Calculated as follows: the number of clinical pregnancies/ live births originated from fresh ET divided by the number of women with transferred embryos
[g]Calculated as follows: the number of clinical pregnancies/ live births originated from one completed ART cycle including fresh and frozen-thaw ETs divided by the number of women treated
*ET* – embryo transfer; *FET* – frozen-thaw embryo transfer; *IQR* – interquartile range

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# Résultats des protocoles et traitements adjuvants

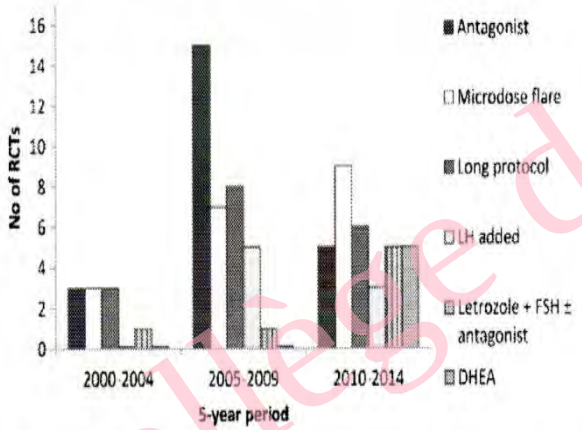


**Figure 4** Most popular interventions in 'poor responder' randomized trials (presented in three 5-year intervals to display trends). DHEA, dehydroepiandrosterone.

**Table III Interventions with at least one RCT indicating benefit in reproductive outcomes.**

| Intervention | Significant outcome | Number of RCTs showing benefit | Number of RCTs showing no benefit |
|---|---|---|---|
| Estrogen add-back for luteal support | Live birth | **1 RCT** Kutlusoy *et al.* (2014) | **1 RCT** Aghahosseini *et al.* (2011) |
| rLH 4-day treatment followed by rFSH treatment during long protocol | Live birth | **1 RCT** Ferraretti *et al.* (2014) | **None** |
| DHEA supplementation | Ongoing pregnancy | **1 RCT** Moawad and Shaeer (2012) | **4 RCTs** Wiser *et al.* (2010) Artini *et al.* (2012) Kara *et al.* (2014) Yeung *et al.* (2014) |
| Antagonist flexible protocol (compared with microdose flare protocol) | Ongoing pregnancy | **1 RCT** Lainas *et al.* (2008) | **8 RCTs** Akman *et al.* (2001) Martinez *et al.* (2003) Malmusi *et al.* (2005) Schmidt *et al.* (2005) De Placido *et al.* (2006) Demirol and Gurgan (2009) Kahraman *et al.* (2009) Davar *et al.* (2013) |
| Day 2 embryo transfer (compared with Day 3) | Ongoing pregnancy | **1 RCT** Bahceci *et al.* (2006) | **None** |
| Long protocol (compared with antagonist protocol) | Clinical pregnancy | **1 RCT** Prapas *et al.* (2013) | **7 RCTs** Cheung *et al.* (2005) Marci *et al.* (2005) Tazegul *et al.* (2008) Kim *et al.* (2009) Shahrokh Tehrani Nejad *et al.* (2008) Kim *et al.* (2011) Sunkara *et al.* (2014) |
| Follicular flushing | Clinical pregnancy | **1 RCT** Mok-Lin *et al.* (2013) | **1 RCT** Levens *et al.* (2009) |
| Day 4 FSH start (compared with Day 1 FSH start) during antagonist protocol | Clinical pregnancy | **1RCT** Baerwald *et al.* (2012) | **None** |
| Transdermal testosterone | Clinical pregnancy | **1 RCT** Kim *et al.* (2011) | **2 RCTs** Massin *et al.* (2006) Fabregues *et al.* (2009) |
| Luteal phase FSH start | Clinical pregnancy | **1 RCT** Kucuk *et al.* (2008) | **2 RCTs** Kucuk and Sozen (2007) Kansal Kalra *et al.* (2008) |
| Addition of rLH mid-stimulation (compared with FSH dose increase) | Clinical pregnancy | **1 RCT** Ruvolo *et al.* (2007) | **2 RCTs** De Placido *et al.* (2001) De Placido *et al.* (2005) |
| High FSH dose (300 IU/day) (compared with 150 IU/day) | Clinical pregnancy | **1 RCT** Klinkert *et al.* (2005) | **None** |

rLH/rFSH, recombinant LH/FSH.

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*Que faire chez une femme en insuffisance ovarienne qui désire une grossesse ?*

# Prise en charge hors FIV

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# Conversion en IAC d'une FIV
## en cas de mauvaise réponse

**IVF and IUI cycle outcomes according to follicular response.**

| Outcome | IVF (n = 184) | IUI (n = 141) |
|---|---|---|
| 1 follicle ≥16 mm | | |
| Early pregnancy | 9.5% (6/63) | 10.2% (8/78) |
| Ultrasound pregnancy | 7.9% (5/63) | 10.2% (8/78) |
| Live birth | 4.8% (3/63) | 5.1% (4/78) |
| 2 follicles ≥16 mm | | |
| Early pregnancy | 20.6% (25/121) | 11.1% (7/63) |
| Ultrasound pregnancy | 16.5% (20/121) | 7.9% (5/63) |
| Live birth | 11.6% (14/121) | 1.6% (1/63) * |

*Note:* CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

*Quinquin. Bologna poor responders: IVF or IUI? Fertil Steril 2014.*

Quinquin, Fertil Steril 2014

**Pregnancy outcomes according to whether IVF or IUI was performed.**

| | IVF | IUI | Age-adjusted RR (95% CI) | *P* value |
|---|---|---|---|---|
| 1 Follicle | | | | |
| n | 104 | 267 | | |
| Biochemical | 11.5% | 6.7% | 1.7 (0.8–3.6) | .183 |
| Clinical pregnancy | 7.7% | 3.7% | 2.0 (0.8–5.3) | .162 |
| Live birth | 2.9% | 2.6% | 0.9 (0.2–3.8) | .930 |
| 2 Follicles | | | | |
| n | 208 | 146 | | |
| Biochemical | 20.2% | 7.5% | 2.7 (1.5–5.1) | <.001 |
| Clinical pregnancy | 14.4% | 4.8% | 3.2 (1.4–7.2) | .002 |
| Live birth | 8.7% | 3.4% | 2.9 (1.1–7.8) | .030 |
| 3 Follicles | | | | |
| n | 312 | 61 | | |
| Biochemical | 26.0% | 9.8% | 2.7 (1.2–5.7) | .006 |
| Clinical pregnancy | 15.8% | 8.2% | 2.1 (0.9–4.8) | .081 |
| Live birth | 11.9% | 6.6% | 2.1 (0.8–5.4) | .122 |

*Note:* CI = confidence interval; RR = relative risk; other abbreviations as in Table 1.

*Reichman. IVF vs. IUI in the setting of ≤3 follicles. Fertil Steril 2013.*

Reichman, Fertil Steril 2013

Intérêt de la FIV / IAC avec 2 follicules ?

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# FIV ou IIU ? [Fujii DT, EJOGRB 2018]

**Table 1**
Characteristics of studies meeting inclusion criteria for the systematic review. (*) Used definition of poor responder as defined by Bologna criteria. (^) IVF includes standard microdrop insemination and ICSI. RCT = randomized controlled trial.

| Study | Year | Study Type | Country | Cycle Type | Ovarian Stimulation | Definition of Poor Response | Number of Patients (IUI / IVF^) | Failure to Retrieve Oocytes |
|---|---|---|---|---|---|---|---|---|
| Wood et al. | 2003 | Retrospective | UK | Fresh, autologous IVF | GnRH agonist with hMG | ≤3 follicles | 48 IUI / 79 IVF | NR |
| Freour et al. | 2009 | Retrospective | France | Fresh, autologous IVF | GnRH agonist or antagonist with FSH | ≤4 follicles | 47 IUI / 44 IVF | NR |
| Norian et al. | 2010 | Retrospective | USA | Fresh, autologous IVF | GnRH agonist or antagonist with combination FSH and hMG | ≤4 follicles ≥14 mm, E2 < 1000 pg/mL at time of hCG administration | 269 IUI / 167 IVF | 2.4% |
| Nicopoullos et al. | 2011 | Retrospective | UK | Fresh, autologous IVF | GnRH agonist or antagonist with recombinant FSH, urinary FSH, or hMG, | ≤2 follicles ≥12 mm, at time of hCG administration | 247 IUI / 800 IVF | 9.8–16.5% |
| Shohieb et al. | 2012 | Retrospective | Egypt, Saudi Arabia | Fresh, autologous IVF | GnRH agonist or antagonist with FSH and hMG | ≤4 follicles ≥14 mm, E2 < 1000 pg/mL at time of hCG administration | 68 IUI / 152 IVF | NR |
| Reichman et al. | 2013 | Retrospective | USA | Fresh, autologous IVF | GnRH agonist or antagonist with combination FSH and hMG | ≤3 follicles ≥14 mm, at time of hCG administration | 474 IUI / 624 IVF | 0.9–8.6% |
| Elzeiny et al. | 2014 | RCT | Australia | Fresh, autologous IVF | GnRH antagonist with recombinant FSH | 2 or 3 follicles ≥16 mm at time of hCG administration | 33 IUI / 10 IVF | NR |
| Quinquin et al | 2014 | Retrospective | France | Fresh, autologous IVF | GnRH agonist or antagonist with combination FSH and hMG | ≤2 follicles ≥16 mm, at time of hCG administration* | 141 IUI / 184 IVF | 16% |

**Table 2**
Average age and overall outcome data of studies meeting inclusion criteria for the systematic review. (*) Denotes statistically significant difference ($P < 0.05$). (^) Denotes percentages computed from source data. (–) Denotes no data.

| Study | Age | | Clinical Pregnancy | | Live Birth | |
|---|---|---|---|---|---|---|
| | IUI | IVF | IUI | IVF | IUI | IVF |
| Wood et al. | 36.1±3.4 | 37.4±3.7* | 12.5% | 7.7% | – | – |
| Freour et al. | 34.7±3.34 | 33.43±3.53 | 14.9% | 7% | – | – |
| Norian et al. | 37.0±3.8 | 36.9±4.1 | 5.2% | 25.7%* | 4.1% | 19.8%* |
| Nicopoullos et al. | 39.3±3.9 | 39.6±3.9* | 3.6% | 8.1%* | – | – |
| Shohieb et al. | 36.4±2.7 | 36.3±3.2 | 10.3% | 17.1% | 7.4% | 11.2% |
| Reichman et al. | 40.3±3.4* | 38.1±4.8 | 3.4%^ | 13.9%^ | 2.5%^ | 9.3%^ |
| Elzeiny et al. | 33±4.2 | 34±3.5 | 12% | 40%* | 6% | 40%* |
| Quinquin et al (one follicle) | 36.9±3.5 | 36.9±3.7 | 9.2%^ | 13.6%^ | 3.5%^ | 9.2%^ |
| (two follicles) | 36.2±3.6 | 36.7±3.4 | | | | |

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# FIV ou IIU ?

**Table 3**

Outcome data stratified by number of follicles. – = not reported. (*) Denotes statistically significant difference ($P < 0.05$). (–) Denotes no data. (#) IVF includes standard microdrop insemination and ICSI.

| Study | Clinical Pregnancy per Number of Follicles (IUI vs. IVF#) | | | | | | | | Live Birth per Number of Follicles (IUI vs. IVF#) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | | 2 | | 3 | | 4 | | 1 | | 2 | | 3 | | 4 | |
| | IUI | IVF | IUI | IVF | IUI | IVF | IUI | IVF | IUI | IVF | IUI | IVF | IUI | IVF | IUI | IVF |
| Wood et al. | 22% | 0% | 9% | 5% | 0% | 11% | – | – | – | – | – | – | – | – | – | – |
| Freour et al. | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Norian et al. | – | – | – | – | – | – | – | – | 0% | 0% | 2% | 6% | 7% | 20% | 12% | 22% |
| Nicopoullos et al. | 5.0% | 5.4% | 2.4% | 9.2%* | – | – | – | – | – | – | – | – | – | – | – | – |
| Shohieb et al. | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Reichman et al. | 3.7% | 7.7% | 4.8% | 14.4%* | 8.2% | 15.8% | – | – | 2.6% | 2.9% | 3.4% | 8.7%* | 6.6% | 11.9% | – | – |
| Elzeiny et al. | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Quinquin et al. | 10.2% | 7.9% | 7.9% | 16.5% | – | – | – | – | 5.1% | 4.8% | 1.6% | 11.6%* | – | – | – | – |

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# Chirurgie de l'endométriose

- Place du traitement coelio-chirurgical après échecs de FIV: Littman, Fertil Steril 2005

| | Coelio-chir | Pas de Tt | |
|---|---|---|---|
| N patientes | 29 | 35 | |
| Age | 34 | 37 | NS |
| Echecs FIV | 2 | 2 | |
| Stades | 4 I, 6 II, 6 III et 13 IV (dt 7 KO) | | |
| TG (spontanée) | 75,8 (44,8) | 37,1% (5,7) | < 0,01 |
| St I | 100 (75) | | |
| St II | 83 (33) | | |
| St III | 83 (50) | | |
| St IV | 61 (30) | | |
| KO | 28 (14) | | |

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# Soriano D, Fertil Steril 2016

**Comparison of operative and postoperative variables between women who delivered after surgery and women who failed to deliver after surgery.**

| Characteristic | Delivered after surgery (n = 33) | Failed to deliver after surgery (n = 45) | *P* value |
|---|---|---|---|
| Salpingectomy performed at surgery (%) | 23/33 (70) | 23/45 (51) | .09 |
| Ovarian endometrioma surgical cystectomy/ablation/ drainage (%) | 19/33 (58) | 25/45 (56) | ns |
| Rectovaginal nodule resection (%) | 6/33 (18) | 14/45 (31) | ns |
| Normal uterus appearance (at surgery) (%) | 15/33 (45.5) | 9/45 (20) | .02 |
| Endometriosis fertility index, median (range) | 3 (0–7) | 4 (0–7) | ns |
| Follow-up after surgery (mo) | 67.8 (30.3) | 58.7 (30.6) | ns |
| Interval (mo) between surgery and pregnancy (with delivery), median (IQR) | 6 (4–13) | NA | |
| No. of IVF cycles after surgery until delivery, median (IQR) | 2 (2–5) | NA | |
| Previous IVF cycles (m, range) | 4 (2-7) | 6 (3-9) | |

*Note:* IQR = interquartile range; NA = not available; ns = not significant.

*Soriano. Endometriosis radical surgery and fertility outcome. Fertil Steril 2016.*

42 % de G après échecs de 4,6 tentatives, dont 9 % spontanées

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# L'AVENIR

- Prévention des risques « in-utéro » et « ex-utéro »
- Inciter à faire des enfants tôt (< risque de cancer du sein [une première G avant 30 ans diminue le risque de 25%], d'endométriose)
- Préservation de la fertilité en cas de traitements gonadotoxiques
- Anti-oxydants (vit C et E) ?
- Cryoconservation ovocytaire pour toutes les femmes ?


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# CONCLUSIONS


- Evaluation de la réserve ovarienne par la FSH + oestradiol, mais surtout AMH et/ou CFA
- Déterminer la dose de départ des gonadotrophines
- Protocoles antagoniste de la GnRH ou court agoniste de la GnRH microdoses
- Pas d'intérêt pour Testostérone, LH, +/- DHEA, +/- GH
- **Prévenir les risques d'altération** de la fonction ovarienne
- Place pour une « tentative test » même si RO basse

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# Merci de votre attention

CENTRE D'ASSISTANCE MÉDICALE À LA PROCRÉATION
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