

# Recommandations ESHRE pour la stimulation ovarienne FIV/ICSI



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# Introduction

La stimulation ovarienne pour FIV /  
ICSI

Pas de lignes directrices fondées sur des  
données probantes

Déterminer la prise en charge,  
recommandée, de la stimulation ovarienne  
sur la base des meilleurs preuves  
disponibles dans la littérature



# Questions clés

Quels sont les critères du choix du type d'induction d'ovulation ?

- Age
- Bilan hormonal
- Stratégie du type de transfert

Y'a t-il intérêt à un traitement préalable à l'induction de l'ovulation ?

Quel type de protocole ?

Quelles doses de FSH utiliser

# Autres questions

L'addition de LH a-t-elle intérêt ?

Quel type de déclenchement de l'ovulation ?

Stimulation maximale ou mild stimulation ?

Y'a t-il un chiffre optimal d'ovocytes pour l'obtention d'une grossesse ?

Y'a t-il une relation entre le nombre d'ovocytes et doses de FSH utilisées ?



# Objectifs

Fournir aux cliniciens des informations factuelles sur les différentes options de la stimulation ovarienne FIV/ICSI

- Réponse ovarienne optimale ?
- Taux de naissances vivantes ?
- L'observance des patientes ?
- Personnalisation ?
- La sécurité ?

Place du prétraitement et des adjuvants chez les mauvaises répondeuses

Prévention du OHSS chez les hyper-répondeuses

# Design de l'étude

Formulation des questions clés : 18

Articles publiés jusqu'à novembre 2018

Les critères de jugement des recommandations

Efficacité

- Taux de naissances vivantes par cycle initié
- Taux cumulé de naissances vivantes par cycle initié

Sécurité

- Risque de OHSS modéré ou sévère

# Les recommandations

Pré-stimulation : 7

Suppression du pic LH et la stimulation par les gonadotrophines : 40

Surveillance de la stimulation : 11

Déclenchement de l'ovulation et support de la phase lutéale : 18

Prévention du OOHS : 11

# Classement

Forte recommandation

Recommandation conditionnelle

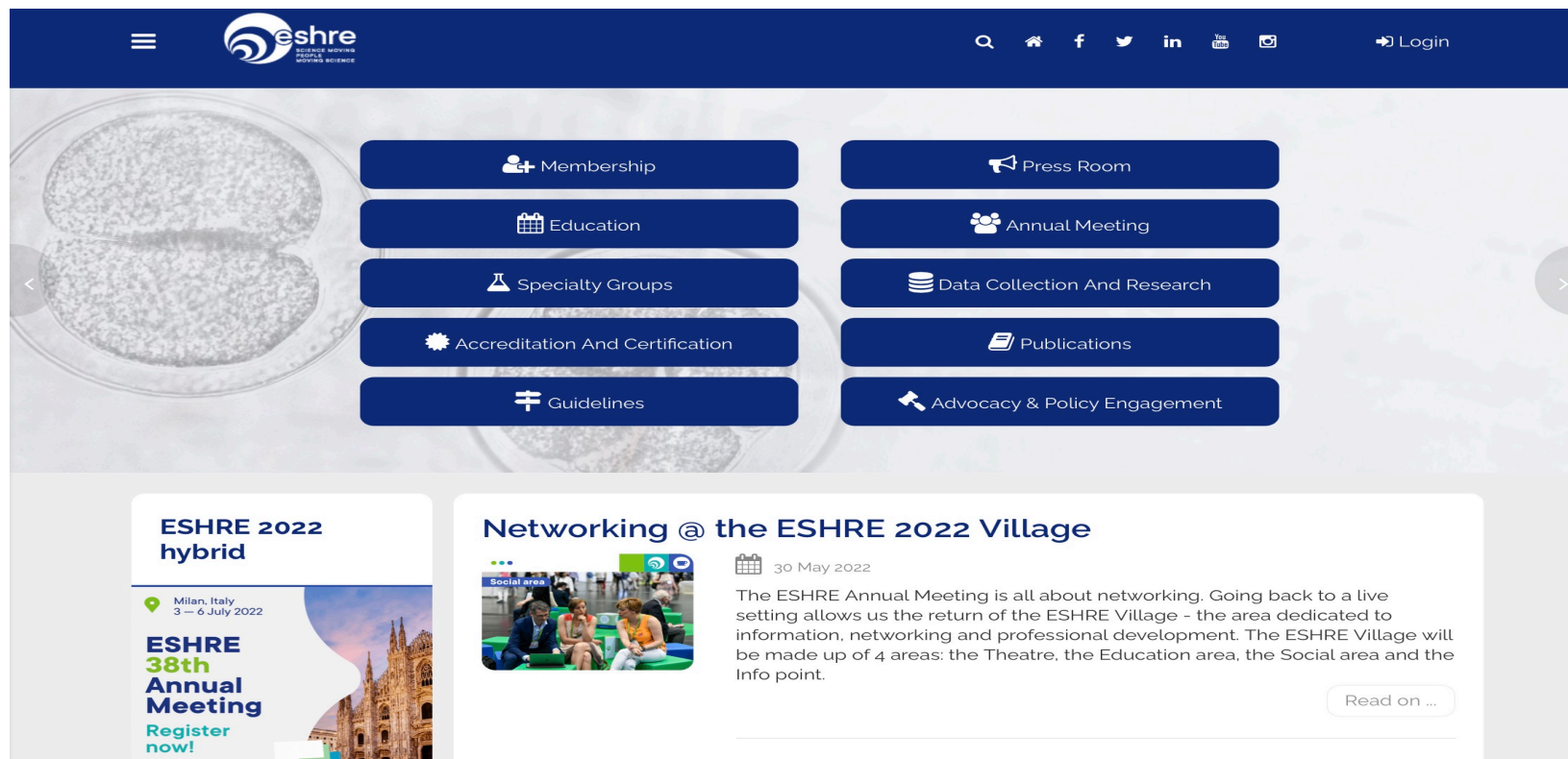
Avis expert : GPP

Note : forte, moyenne, faible ou très faible en fonction du niveau des preuves

For predicting high and low response to controlled ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests.

Strong ⊕○○○

# www.eshre.eu



The screenshot shows the ESHRE website homepage. The header is dark blue with the ESHRE logo on the left and navigation icons (search, home, Facebook, Twitter, LinkedIn, YouTube, Instagram) and a 'Login' button on the right. The main content area features a grid of ten blue buttons with white icons and text: Membership, Press Room, Education, Annual Meeting, Specialty Groups, Data Collection And Research, Accreditation And Certification, Publications, Guidelines, and Advocacy & Policy Engagement. Below this grid, there are two white boxes. The left box is for the 'ESHRE 2022 hybrid' meeting in Milan, Italy, from 3-6 July 2022, for the 38th Annual Meeting, with a 'Register now!' link. The right box is titled 'Networking @ the ESHRE 2022 Village' and dated 30 May 2022. It includes a photo of people in a social area and a paragraph about the ESHRE Annual Meeting and the ESHRE Village. A 'Read on ...' button is at the bottom right of the right box.

ESHRE 2022 hybrid  
Milan, Italy  
3 — 6 July 2022  
ESHRE 38th Annual Meeting  
Register now!

Networking @ the ESHRE 2022 Village  
30 May 2022  
The ESHRE Annual Meeting is all about networking. Going back to a live setting allows us the return of the ESHRE Village - the area dedicated to information, networking and professional development. The ESHRE Village will be made up of 4 areas: the Theatre, the Education area, the Social area and the Info point.  
Read on ...

# Pre-stimulation

|   |   |                                                                                                                                                                                                                                                                                                                                                                  |             |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                 |
|---|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 1 | 1 | For predicting high and poor response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests.<br><i>The clinical implications of these tests regarding change in management with the purpose of improving efficacy and safety have not been evaluated by the GDG.</i> | Strong      | ⊕○○○ | AFC and AMH both have a high accuracy in the prediction of an ovarian response. Basal FSH and inhibin B do have some predictive value for ovarian response, however for an accurate prediction very high cut-off levels need to be used. Age also has some predictive value, however assessment of expected ovarian response by age alone is not sufficiently reliable. Basal oestradiol and BMI alone are not predictors of ovarian response. |                 |
| 2 | 2 | Assessment of progesterone level on day 2 of the cycle at the start of ovarian stimulation is probably not recommended.                                                                                                                                                                                                                                          | Conditional | ⊕○○○ | Assessment of progesterone prior to initiation of stimulation on cycle day 2 appears to have some predictive value for the probability of pregnancy. The currently available evidence, however, is not solid, and the clinical value of this test was not assessed. The necessity of progesterone testing is dubious due to the very low incidence of abnormal test results.                                                                   |                 |
| 3 | 3 | Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is probably not recommended for improving efficacy and safety.                                                                                                                                                                                                        | Conditional | ⊕○○○ | Studies show no benefit on live birth rate/ongoing pregnancy rate using oestrogen as pre-treatment in antagonist protocols.                                                                                                                                                                                                                                                                                                                    | SoF table 1     |
| 3 | 4 | Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy and safety.                                                                                                                                                                                                                                        | Conditional | ⊕⊕○○ | Studies show no benefit on live birth rate/ongoing pregnancy rate using progesterone as pre-treatment in GnRH agonist nor GnRH antagonist protocols.                                                                                                                                                                                                                                                                                           | SoF table 2 a,b |
| 3 | 5 | The GDG acknowledges that oestrogen or progesterone are widely used for scheduling purposes. This is probably acceptable given the data on efficacy and safety.                                                                                                                                                                                                  | GPP         |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                |                 |
| 3 | 6 | COCP pre-treatment (12-28 days) is not recommended in the GnRH antagonist protocol because of reduced efficacy.                                                                                                                                                                                                                                                  | Strong      | ⊕⊕○○ | Evidence of lower live birth/ongoing pregnancy rate using 12 up to 28 days of COCP pre-treatment in the GnRH antagonist protocol. Even though the evidence for poor responders is less clear, the GDG recommends against (12-28 days) COCP pre-treatment in GnRH antagonist protocol.                                                                                                                                                          | SoF table 3 a,b |
| 3 | 7 | GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended.                                                                                                                                                                                                                                  | Conditional | ⊕○○○ | Current evidence shows no benefit for ongoing pregnancy rate per embryo transfer and number of oocytes in young normogonadotropic women. Evidence in poor responders is conflicting.                                                                                                                                                                                                                                                           | SoF table 4 a,b |

# Tests de la réponse ovarienne

|   |   |                                                                                                                                                                                                                                                                                                                                                                             |        |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | 1 | <p>For predicting high and poor response to ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests.</p> <p><i>The clinical implications of these tests regarding change in management with the purpose of improving efficacy and safety have not been evaluated by the GDG.</i></p> | Strong | ⊕○○○ | <p>AFC and AMH both have a high accuracy in the prediction of an ovarian response. Basal FSH and inhibin B do have some predictive value for ovarian response, however for an accurate prediction very high cut-off levels need to be used. Age also has some predictive value, however assessment of expected ovarian response by age alone is not sufficiently reliable. Basal oestradiol and BMI alone are not predictors of ovarian response.</p> |
|---|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Pour prédire la réponse ovarienne (mauvaise, normale ou hyper) à la stimulation, le compte des follicules antraux (AFC) ou le dosage de l'hormone anti-müllérienne (AMH) est recommandée par rapport aux autres tests de réserve ovarienne. Fort ⊕

# Progesterone J2

|   |   |                                                                                                                         |             |      |                                                                                                                                                                                                                                                                                                                                                                              |
|---|---|-------------------------------------------------------------------------------------------------------------------------|-------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2 | 2 | Assessment of progesterone level on day 2 of the cycle at the start of ovarian stimulation is probably not recommended. | Conditional | ⊕○○○ | Assessment of progesterone prior to initiation of stimulation on cycle day 2 appears to have some predictive value for the probability of pregnancy. The currently available evidence, however, is not solid, and the clinical value of this test was not assessed. The necessity of progesterone testing is dubious due to the very low incidence of abnormal test results. |
|---|---|-------------------------------------------------------------------------------------------------------------------------|-------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

L'évaluation du taux de progestérone au jour 2 du cycle au début de la stimulation n'est probablement pas recommandée. Conditionnel ⊕

Pas de preuves sur le rôle pronostique de la progestérone de base chez les femmes sous stimulation pour FIV/ICSI.



# Pré-traitement progestérone ou œstrogène

|   |   |                                                                                                                                                                 |             |      |                                                                                                                                                      |                 |
|---|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 3 | 3 | Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is probably not recommended for improving efficacy and safety.       | Conditional | ⊕○○○ | Studies show no benefit on live birth rate/ongoing pregnancy rate using oestrogen as pre-treatment in antagonist protocols.                          | SoF table 1     |
| 3 | 4 | Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy and safety.                                       | Conditional | ⊕⊕○○ | Studies show no benefit on live birth rate/ongoing pregnancy rate using progesterone as pre-treatment in GnRH agonist nor GnRH antagonist protocols. | SoF table 2 a,b |
| 3 | 5 | The GDG acknowledges that oestrogen or progesterone are widely used for scheduling purposes. This is probably acceptable given the data on efficacy and safety. | GPP         |      |                                                                                                                                                      |                 |

Un prétraitement à la progestérone ou aux œstrogènes avant la stimulation, dans un protocole antagoniste, n'est probablement pas recommandé pour améliorer l'efficacité et la sécurité . Conditionnel +

Le GDG reconnaît que l'œstrogène ou la progestérone sont largement utilisés à des fins de programmation. Ceci est probablement acceptable compte tenu des données sur l'efficacité et la sécurité.  
GPP

# Programmation

|   |   |                                                                                                                                 |             |      |                                                                                                                                                                                                                                                                                       |                 |
|---|---|---------------------------------------------------------------------------------------------------------------------------------|-------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 3 | 6 | COCP pre-treatment (12-28 days) is not recommended in the GnRH antagonist protocol because of reduced efficacy.                 | Strong      | ⊕⊕○○ | Evidence of lower live birth/ongoing pregnancy rate using 12 up to 28 days of COCP pre-treatment in the GnRH antagonist protocol. Even though the evidence for poor responders is less clear, the GDG recommends against (12-28 days) COCP pre-treatment in GnRH antagonist protocol. | SoF table 3 a,b |
| 3 | 7 | GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended. | Conditional | ⊕○○○ | Current evidence shows no benefit for ongoing pregnancy rate per embryo transfer and number of oocytes in young normogonadotropic women. Evidence in poor responders is conflicting.                                                                                                  | SoF table 4 a,b |

Le prétraitement par pilule contraceptive orale combinée (pilule OP) (12 à 28 jours) n'est pas recommandé dans le protocole antagoniste de la GnRH en raison d'une efficacité réduite. Fort ⊕⊕

Un prétraitement par antagoniste de la GnRH avant stimulation dans un protocole de gonadotrophine pour différer le démarrage, n'est probablement pas recommandé. Conditionnel ⊕

# Choix du protocole de stimulation

Suppression du pic LH

# PCOS et hyper-répondeuses

|    |   |                                                                                                                                |        |      |                                                                                                                                                                                                                 |             |
|----|---|--------------------------------------------------------------------------------------------------------------------------------|--------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 4A | 8 | The GnRH antagonist protocol is recommended for PCOS women, with regards to improved safety and equal efficacy.                | Strong | ⊕⊕○○ | Evidence indicates that GnRH antagonist protocol is as efficient as the GnRH agonist protocol, and significantly reduces the risk of OHSS in PCOS women.                                                        | SoF table 5 |
| 4A | 9 | The GnRH antagonist protocol is recommended for predicted high responders, with regards to improved safety and equal efficacy. | GPP    |      | Even though there is no specific evidence on expected non-PCOS high responders or PCOM patients, consensus of the guideline group is that GnRH antagonist protocol should be recommended in this patient group. |             |

Le protocole d'antagoniste de la GnRH est recommandé pour les femmes atteintes du syndrome des ovaires poly-kystiques (SOPK), en ce qui concerne une meilleure sécurité et une efficacité égale. Forte ⊕⊕

Le protocole d'antagoniste de la GnRH est recommandé pour les hyper-répondeuses, en ce qui concerne l'amélioration de la sécurité avec une efficacité égale. GPP

# PCOS et hyper-répondeuses

|    |    |                                                                                                                                                                                                           |             |      |                                                                                                                                                                                                                                                                                                                                                                                                                    |             |
|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 4A | 12 | The GnRH antagonist protocol is recommended for predicted high responders. However, if GnRH agonist protocols are used, a reduced gonadotropin dose is probably recommended to decrease the risk of OHSS. | Conditional | ⊕○○○ | The recommendation is extrapolated from a stratified group analysis of the RCT in which majority of the patients were treated with the long GnRH agonist protocol. Current evidence shows that lowering gonadotropin dosage may increase safety in GnRH agonist protocol. The guideline group would like to emphasize that clinicians are advised to use the GnRH antagonist protocol in expected high responders. | SoF table 6 |
|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|

Le protocole d'antagoniste de la GnRH est recommandé pour les hyper-répondeuses.

Si des protocoles agonistes de la GnRH sont utilisés, une dose réduite de gonadotrophines est probablement recommandée pour diminuer le risque de OHSS. Conditionnel ⊕

# PCOS et hyper-répondeuses

|    |    |                                                                                                                                                |             |      |                                                                                                                                                                                                                                                                                        |
|----|----|------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4A | 10 | The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted high responders.        | Conditional | ⊕○○○ | Clomiphene citrate, in addition to gonadotropin stimulation in OS has not been shown to improve outcomes in terms of efficacy and safety in cohort studies                                                                                                                             |
| 4A | 11 | There is insufficient evidence to recommend the addition of letrozole to gonadotropins in stimulation protocols for predicted high responders. | Conditional | ⊕○○○ | Current evidence indicates no benefit in terms of efficacy and safety of letrozole addition to gonadotropins for OS. Moreover, use of letrozole is off-label for ovarian stimulation and safety concerns have been raised regarding possible teratogenicity associated with letrozole. |
| 4A | /  | There is no evidence to justify the use of NC or MNC for OS in high responders.                                                                |             | /    | /                                                                                                                                                                                                                                                                                      |

L'ajout de citrate de clomifène aux gonadotrophines dans les protocoles de stimulation n'est probablement pas recommandé pour les hyper-répondeuse. Conditionnel ⊕

Il n'y a pas suffisamment de preuves pour recommander l'ajout de létrozole aux gonadotrophines dans les protocoles de stimulation pour hyper-répondeuse. Conditionnel ⊕

Il n'y a aucune preuve pour justifier l'utilisation du cycle naturel ou du cycle naturel modifié

# Les normo-répondeuses

|    |    |                                                                                                                                  |             |      |                                                                                                                                                                                                                                                                               |                 |
|----|----|----------------------------------------------------------------------------------------------------------------------------------|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 4B | 13 | The GnRH antagonist protocol is recommended for predicted normal responder women, with regards to improved safety.               | Strong      | ⊕⊕○○ | Owing to the comparable live birth rates between the GnRH antagonist and GnRH agonist protocols and the significant decrease in the risk of OHSS with the GnRH                                                                                                                | SoF table 7     |
| 4B | 15 | A reduced gonadotrophin dose is probably not recommended over a conventional gonadotrophin dose for predicted normal responders. | Conditional | ⊕⊕○○ | Although available studies suggest similar efficacy in terms of clinical pregnancy rate between reduced-dose and conventional dose stimulation, the lower number of oocytes retrieved could potentially compromise cumulative live birth rate in predicted normal responders. | SoF table 9 a,b |

Le protocole d'antagoniste de la GnRH est recommandé pour les femmes normo-répondeuses , en ce qui concerne l'amélioration de la sécurité. Forte ⊕⊕

Une dose réduite de gonadotrophine n'est probablement pas recommandée par rapport à une dose de gonadotrophine conventionnelle pour les normaux répondeuses . Conditionnel ⊕⊕

# Les normo-répondeuses

|    |    |                                                                                                                                                |             |      |                                                                                                                                                                                                                                                               |             |
|----|----|------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| 4B | /  | There is no evidence to support the recommendation for the use of Clomiphene Citrate in stimulation protocols for predicted normal responders. | /           | /    | The evidence was from studies performed in patients without predicted poor response. Thus, the included study population could include both normal and high responder patients, therefore, the conclusions from these studies could not be extrapolated.      | Conclusion  |
| 4B | 14 | The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders.               | Conditional | ⊕○○○ | Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of OS. The use of letrozole may reduce the risk of OHSS, however this was only shown in one small RCT. Moreover, use of letrozole is off-label for ovarian stimulation. | SoF table 8 |

Il n'existe aucune preuve permettant de recommander l'utilisation du citrate de clomifène dans les protocoles de stimulation.

L'ajout de létrozole aux gonadotrophines dans les protocoles de stimulation n'est probablement pas recommandé pour les prédits normo-répondeuses. Conditionnel ⊕



# Les mauvaises répondeuses

## Quel protocole ?

|    |    |                                                                                                                                    |             |      |                                                                                                                                                 |                  |
|----|----|------------------------------------------------------------------------------------------------------------------------------------|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 4C | 16 | GnRH antagonists and GnRH agonists are equally recommended for predicted poor responders.                                          | Conditional | ⊕⊕○○ | In women with poor ovarian response no differences exist in terms of safety and efficacy between the GnRH agonist and GnRH antagonist protocol. | SoF table 10 a,b |
| 4C | 21 | The use of modified natural cycle is probably not recommended over conventional ovarian stimulation for predicted poor responders. | Conditional | ⊕○○○ | There are no good quality, controlled studies available to support the use of Modified natural cycle or Natural cycle IVF in poor responders.   | SoF table 15     |

Les antagonistes de la GnRH et les agonistes de la GnRH sont également recommandés pour les mauvaises répondeuses . Conditionnel ⊕⊕

L'utilisation du cycle naturel modifié n'est probablement pas recommandée par rapport à la stimulation conventionnelle pour les mauvaises répondeuses. Conditionnel ⊕

# Les mauvaises répondeuses

|    |    |                                                                                                                                                           |             |      |                                                                                                                                                                                                                                                                |                  |
|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 4C | 17 | Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are equally recommended for predicted poor responders. | Strong      | ⊕⊕○○ | In women with poor ovarian response no differences exist in terms of safety and efficacy between CC alone, CC in combination with gonadotropins or gonadotropin stimulation alone.                                                                             | SoF table 11 a,b |
| 4C | 18 | The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted poor responders.                            | Conditional | ⊕⊕○○ | Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of OS. Moreover, use of letrozole is off-label for ovarian stimulation and safety concerns have been raised regarding possible teratogenicity associated with letrozole. | SoF table 12     |

Le citrate de clomifène seul ou en association avec les gonadotrophines et la stimulation par gonadotrophines seules sont également recommandé pour les mauvaises répondeuses . Fort ⊕⊕

L'ajout de létrozole aux gonadotrophines dans les protocoles de stimulation n'est probablement pas recommandé pour les mauvaises répondeuses . Conditionnel ⊕⊕

# Les mauvaises répondeuses

## Doses des Gonadotrophines

|    |    |                                                                                                            |             |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                  |
|----|----|------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 4C | 19 | It is unclear whether a higher gonadotropin dose is recommended over 150 IU for predicted poor responders. | Conditional | ⊕○○○ | There is evidence that a higher gonadotropin dose than 150 IU results in a higher number of oocytes in poor responders, and more chances of having an embryo for transfer. However, there was no difference in live birth/ongoing pregnancy rates. Furthermore, the sample sizes of the studies are small and therefore not sufficient to provide evidence for dose comparisons for live birth outcome. There is unlikely to be significant benefit with doses > 300 IU daily. | SoF table 13     |
| 4C | 20 | A gonadotropin dose higher than 300 IU is not recommended for predicted poor responders.                   | Strong      | ⊕○○○ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | SoF table 14 a,b |

Il n'est pas clair qu'une dose plus élevée de gonadotrophine est recommandée au-delà de 150 UI pour les mauvaises répondeuses. Conditionnel ⊕

Une dose de gonadotrophine supérieure à 300 UI n'est pas recommandée pour les mauvaises répondeuses. Forte ⊕

# Le protocole

|   |    |                                                                                                                                                                 |             |      |                                                                                                                                                                                                                                                  |                       |
|---|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| 5 | 22 | If GnRH agonists are used, the long GnRH agonist protocol is probably recommended over the short or ultrashort GnRH agonist protocol.                           | Conditional | ⊕⊕○○ | Compared to other GnRH agonist protocols, the long protocol provides better efficacy and is supported by a larger body of evidence.                                                                                                              | SoF table 16<br>a,b,c |
| 5 | 23 | The GnRH antagonist protocol is recommended over the GnRH agonist protocols given the comparable efficacy and higher safety in the general IVF/ICSI population. | Strong      | ⊕⊕⊕○ | Although the first studies reported slight but consistent lower pregnancy rates, which delayed the implementation of the GnRH antagonist protocol, several large meta-analyses published in the past 5-7 years support similar live birth rates. | SoF table 17<br>a,b   |
| 5 | 24 | The use of progestin for LH peak suppression is probably not recommended. If applied, progestin can only be used in the context of non-transfer cycles.         | Conditional | ⊕○○○ | Oral progestins are efficient in terms of LH suppression, with comparable oocyte yield and pregnancy outcomes as the GnRH short agonist protocol. This approach is easy, cheap and patient friendly. However, the available evidence is limited. |                       |

Si des agonistes de la GnRH sont utilisés, le protocole d'agoniste de la GnRH long est probablement recommandé par rapport au protocole d'agoniste de la GnRH court ou ultracourt. Conditionnel ⊕⊕

Le protocole d'antagoniste de la GnRH est recommandé par rapport aux protocoles d'agoniste de la GnRH compte tenu de l'efficacité comparable et de la sécurité supérieure dans la population générale de FIV/ICSI. Fort ⊕⊕⊕

L'utilisation d'un progestatif pour la suppression du pic de LH n'est probablement pas recommandée. S'il est utilisé, le progestatif ne peut être utilisé que dans le cadre de cycles sans transfert. Conditionnel ⊕

# Quelle Gonadotrophine ?

|   |    |                                                                                                                                                                         |             |      |                                                                                                                                                                                                                                                                                                          |              |
|---|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 6 | 25 | The use of recombinant FSH (rFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended.                                               | Strong      | ⊕⊕⊕○ | The results from the meta-analysis suggest a slightly higher efficacy (LBR/PR) with hMG compared to FSH in a GnRH agonist cycles, which was not considered clinically significant in the Cochrane review, and with no difference in safety, the GDG concluded that hMG is probably not superior to rFSH. | SoF table 18 |
| 6 | 26 | The use of recombinant FSH (rFSH) and purified FSH (p-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended.                                     | Strong      | ⊕⊕⊕○ | The use of rFSH is not preferable to p-FSH when downregulation is achieved with GnRH agonists, according to the Cochrane meta-analysis.                                                                                                                                                                  | SoF table 19 |
| 6 | 27 | The use of either recombinant FSH (rFSH) and highly purified FSH (hp-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended.                      | Strong      | ⊕⊕⊕○ | The use of rFSH is not preferable to hp-FSH, when downregulation is achieved by GnRH agonists according to the Cochrane meta-analysis and confirmed in subsequently published studies.                                                                                                                   | SoF table 20 |
| 6 | 28 | The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for ovarian stimulation in GnRH agonist protocols is equally recommended.               | Conditional | ⊕⊕⊕○ | In patients undergoing OS for IVF/ICSI, the use of hp-FSH does not appear to be preferable over hMG, if downregulation is achieved by GnRH agonists.                                                                                                                                                     | SoF table 21 |
| 6 | 29 | The use of recombinant LH (rLH) + recombinant FSH (rFSH) for ovarian stimulation is probably not recommended over hMG in GnRH agonist protocols with regards to safety. | Conditional | ⊕○○○ | HMG and rFSH+LH appear to result in an equal probability of pregnancy in GnRH agonist protocols. However, the risk of OHSS appears to be higher with the use of rFSH+rLH.                                                                                                                                | SoF table 22 |

L'utilisation de FSH recombinante (rFSH) et de hMG est recommandée de manière équivalente. Fort ⊕⊕⊕

L'utilisation de rFSH et de FSH purifiée (p-FSH) pour la stimulation dans le protocole d'agoniste de la GnRH est recommandée de manière équivalente. Forte ⊕⊕

L'utilisation de rFSH et de FSH hautement purifiée (hp-FSH) dans le protocole d'agoniste de la GnRH est recommandée de manière équivalente. Forte ⊕⊕

L'utilisation de hp-FSH et de hMG dans les protocoles d'agonistes de la GnRH est recommandée de manière équivalente. Conditionnel ⊕⊕

L'utilisation de LH recombinante (rLH) + rFSH n'est probablement pas recommandée par rapport à la hMG dans les protocoles d'agonistes de la GnRH en ce qui concerne la sécurité. Conditionnel ⊕

# Quelle gonadotrophine ?

|   |    |                                                                                                                                 |             |      |                                                                                                                                                                                                     |              |
|---|----|---------------------------------------------------------------------------------------------------------------------------------|-------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 6 | 30 | Letrozole is probably not recommended as a substitute for gonadotropins in poor responders.                                     | Conditional | ⊕○○○ | Due to the small number and size of RCTs available, no solid recommendation can be made. In addition, safety concerns have been raised regarding possible teratogenicity associated with letrozole. | SoF table 23 |
| 6 | /  | There is no evidence available to recommend the substitution of FSH by Clomiphene Citrate in ovarian stimulation.               | /           | /    | /                                                                                                                                                                                                   | Conclusion   |
| 6 | 31 | The use of long-acting and daily recombinant FSH (rFSH) is equally recommended in GnRH antagonist cycles for normal responders. | Strong      | ⊕⊕⊕○ | No differences have been observed in three large RCTs and in a small RCT in poor responders regarding the probability of pregnancy or the number of COCs retrieved and the incidence of OHSS.       | SoF table 24 |

Le létrozole n'est probablement pas recommandé comme substitut des gonadotrophines chez les mauvaises répondeuses. Conditionnel ⊕

Il n'y a aucune preuve disponible pour recommander la substitution de la FSH par le citrate de clomifène dans la stimulation ovarienne.

L'utilisation de rFSH à action prolongée est également recommandée, par rapport à la forme quotidienne dans les cycles d'antagonistes de la GnRH pour les répondeurs normaux. Forte ⊕⊕⊕

# L'ajustement du dosage des gonadotrophines

|   |    |                                                                                                                                                  |             |      |                                                                                                          |
|---|----|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------|
| 7 | 32 | Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended. | Conditional | ⊕○○○ | The current evidence does not support changing gonadotropin dose during OS in the mid-stimulation phase. |
|---|----|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------|

L'ajustement (augmentation ou diminution) de la dose de gonadotrophine lors de la phase intermédiaire de la stimulation n'est probablement pas recommandé. Conditionnel ⊕

# Les adjuvants

|   |    |                                                                                                                                                      |             |      |                                                                                                                                                                                                                                                                                                                                                                                                        |                  |
|---|----|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 8 | 33 | Routine use of adjuvant metformin before and/or during ovarian stimulation is not recommended with the GnRH antagonist protocol for women with PCOS. | Strong      | ⊕⊕○○ | As current evidence does not show beneficial effect of metformin in reducing OHSS when used with GnRH antagonist protocols and the inconsistent evidence for live birth outcome, metformin is not recommended in women with PCOS.                                                                                                                                                                      | SoF table 25     |
| 8 | 34 | Use of adjuvant growth hormone before and/or during ovarian stimulation is probably not recommended for poor responders.                             | Conditional | ⊕⊕○○ | Despite the possible beneficial effects in poor responders on live birth rate, the evidence is of too limited quality to recommend growth hormone during OS. The studies in the systematic review were generally underpowered and the definition of poor response very heterogeneous among studies. Furthermore, GH dosing schemes were very heterogeneous and no long-term safety data are available. | SoF table 26 a,b |
| 8 | 35 | Use of testosterone before ovarian stimulation is probably not recommended for poor responders.                                                      | Conditional | ⊕⊕⊕○ | Current evidence regarding adjuvant testosterone pre-treatment before OS is inconsistent. Also, due to insufficient data on dosage, administration duration and safety we cannot recommend testosterone use until a large RCT has been conducted.                                                                                                                                                      | SoF table 27     |
| 8 | 36 | Use of DHEA before and/or during ovarian stimulation is probably not recommended for poor responders.                                                | Conditional | ⊕⊕⊕○ | There is currently inconsistent evidence that adjuvant DHEA use before and during OS improves ovarian response in terms of live birth/ongoing pregnancy rate in poor responders following IVF treatment.                                                                                                                                                                                               | SoF table 28     |

L'utilisation systématique de metformine adjuvante avant et/ou pendant la stimulation n'est pas recommandée avec le protocole antagoniste de la GnRH pour les femmes atteintes du SOPK. Fort ⊕⊕

L'utilisation de GH adjuvante avant et/ou pendant la stimulation n'est probablement pas recommandée pour les mauvaises répondeuses. Conditionnel ⊕⊕

L'utilisation de la testostérone avant la stimulation n'est probablement pas recommandée pour les mauvaises répondeuses. Conditionnel ⊕⊕⊕

L'utilisation de la DHEA avant et/ou pendant la stimulation n'est probablement pas recommandée pour les mauvaises répondeuses. Conditionnel ⊕⊕⊕



# Les adjuvants

|   |    |                                                                                                                                        |        |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |              |
|---|----|----------------------------------------------------------------------------------------------------------------------------------------|--------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 8 | 37 | Use of aspirin before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population and for poor responders. | Strong | ⊕⊕⊕○ | <p>The existing evidence suggests that adjuvant aspirin before and/ or during ovarian stimulation does not improve ovarian response in terms of number of oocytes retrieved and clinical outcomes of clinical or ongoing pregnancy, or live birth rates following IVF treatment.</p> <p>Current evidence from one low-quality, pseudo-randomized study involving women considered as poor responders undergoing IVF showed no improvement in ovarian response with adjuvant sildenafil use during</p> | SoF table 29 |
| 8 | 38 | Use of sildenafil before and/or during ovarian stimulation is not recommended for poor responders.                                     | Strong | ⊕○○○ |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |              |

L'utilisation d'aspirine avant et/ou pendant la stimulation n'est pas recommandée dans la population générale FIV/ICSI et pour les mauvaises répondeuses. Fort ⊕⊕⊕

L'utilisation de sildénafil avant et/ou pendant la stimulation n'est pas recommandée pour les mauvaises répondeuses. Fort ⊕

# Démarrage non conventionnel de la stimulation

|   |    |                                                                                                       |               |      |                                                                                                                                                                                                                                                             |
|---|----|-------------------------------------------------------------------------------------------------------|---------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9 | 39 | Random-start ovarian stimulation is probably not recommended for the general IVF/ICSI population.     | Conditional   | ⊕○○○ | Current evidence in normal responders reported no difference in efficacy in terms of number of oocytes retrieved with non-conventional start stimulation as compared to conventional start stimulation, however, freeze-all oocytes or embryos is mandatory |
| 9 | 40 | Late luteal phase start of gonadotropins is probably not recommended for poor responders.             | Conditional   | ⊕○○○ | Oocyte competence is probably not impacted by the luteal stimulation; however, freeze-all of oocytes or embryos is mandatory. Absence of adverse effects on neonatal outcomes and long-term child health needs to be evaluated on a larger scale.           |
| 9 | 41 | Early luteal phase start of gonadotropins is probably not recommended for normal and poor responders. | Conditional   | ⊕○○○ |                                                                                                                                                                                                                                                             |
| 9 | 42 | Luteal phase stimulation could be used in non-transfer cycles.                                        | GPP           |      |                                                                                                                                                                                                                                                             |
| 9 | 43 | Double stimulation in poor responders should only be used in the context of clinical research.        | Research only |      | Due to absence of RCT, comparing a double stimulation within a same cycle with mandatory postponed transfer and a single stimulation with mandatory postponed transfer                                                                                      |

Le Random-start n'est probablement pas recommandé pour la population générale de FIV/ICSI. Conditionnel ⊕

Le démarrage à la phase lutéale tardive des gonadotrophines n'est probablement pas recommandée pour les mauvaises répondeuses. Conditionnel ⊕

Le démarrage à la phase lutéale précoce des gonadotrophines n'est probablement pas recommandée pour les normaux et mauvaises répondeuses. Conditionnel ⊕

La stimulation à la phase lutéale pourrait être utilisée dans les cycles sans transfert. GPP

La double stimulation chez les mauvaises répondeuses ne doit être utilisée que dans le cadre de la recherche clinique uniquement.

# Démarrage non conventionnel de la stimulation et préservation de la fertilité

|    |    |                                                                                                                                                                                     |             |      |                                                                                                                                                                                                                                                                                                                                                                                                       |
|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9  | 44 | Double stimulation can be considered for urgent fertility preservation cycles.                                                                                                      | GPP         |      | and two conventional stimulations, we cannot recommend the double stimulation in poor responder patients                                                                                                                                                                                                                                                                                              |
| 10 | 45 | For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is probably recommended.                                           | Conditional | ⊕○○○ | GnRH antagonist protocols are preferred since they shorten the duration of OS, offer the possibility of triggering final oocyte maturation with GnRH agonist in case of high ovarian response, and reduce the risk of OHSS.                                                                                                                                                                           |
| 10 | 46 | In urgent (oncology) fertility preservation cycles, random-start ovarian stimulation is an important option.                                                                        | Conditional | ⊕⊕○○ | Evidence indicate that oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase.                                                                                                                                                                                                                                                                            |
| 10 | 47 | In ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, can be considered. | GPP         |      | The existing literature concerning ovarian stimulation for fertility preservation in women with oestrogen sensitive cancer is limited by its observational nature, small patient numbers and relatively short duration of follow-up. Definitive statements regarding the safety of OS in women with a recent diagnosis of breast cancer would require long-term and large-scale studies, and these do |

La double stimulation peut être envisagée pour les cycles urgents de préservation de la fertilité. GPP

Pour la stimulation ovarienne chez les femmes cherchant à préserver leur fertilité pour des raisons médicales, le protocole d'antagoniste de la GnRH est probablement recommandé. Conditionnel ⊕

Dans les cycles de préservation de la fertilité urgents (en oncologie), la stimulation à démarrage aléatoire est une option importante. Conditionnel ⊕ ⊕

Dans la stimulation pour la préservation de la fertilité dans les maladies sensibles aux œstrogènes, l'utilisation concomitante d'un traitement anti-œstrogénique, tel que le létrozole ou le tamoxifène, peut être envisagée. GPP

# Le monitoring de l'ovulation

|    |    |                                                                                                                                                                    |             |      |                                                                                                                                                                                                                                              |              |
|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 11 | 48 | The addition of oestradiol measurements to ultrasound monitoring is probably not recommended.                                                                      | Conditional | ⊕⊕○○ | Based on the currently published evidence, monitoring of the stimulation phase by using serum oestradiol measurements and ultrasound is not superior to monitoring by ultrasound alone in terms of efficacy and safety                       | SoF table 30 |
| 11 | 49 | The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended. | Conditional | ⊕○○○ | According to one RCT, monitoring of the stimulation phase by using hormonal panel assessments (E2, LH, P) and ultrasound not beneficial in terms of efficacy and safety over monitoring by ultrasound alone in terms of efficacy and safety. | SoF table 31 |

Le dosages de l'œstradiol avec la surveillance échographique n'est probablement pas recommandé. Conditionnel ⊕⊕

Le dosage de l'œstradiol, de la progestérone et de LH avec la surveillance échographique n'est probablement pas recommandé. Pas de bénéfice en terme d'efficacité et de sécurité. Conditionnel ⊕

# Mesure de l'endomètre

|    |    |                                                                                                                                                                                                                  |             |      |                                                                                                                                                                                                                                                   |
|----|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 | 50 | Routine monitoring of endometrial thickness during ovarian stimulation is probably not recommended.                                                                                                              | Conditional | ⊕○○○ | There are indications that thin endometrium is related to lower ongoing/clinical pregnancy chances as an independent factor. Interventions to correct thin EMT have little rational basis and should be abandoned until contrary evidence arises. |
| 12 | 51 | The guideline group suggests performing a single measurement of the endometrium during ultrasound assessment on the day of triggering or oocyte pick-up to counsel patients on potential lower pregnancy chance. | GPP         |      | A single ultrasound assessment is necessary to identify patients with very thin or very thick EMT, and appropriate diagnostic work-up should be done.                                                                                             |

La surveillance de routine de l'épaisseur de l'endomètre pendant la stimulation n'est probablement pas recommandée. Conditionnel ⊕

Le GDG suggère d'effectuer une seule mesure de l'endomètre le jour du déclenchement ou de la ponction des ovocytes pour conseiller les patientes sur les risques potentiels de faible chance de grossesse . GPP

# Critères de déclenchement

|    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                        |             |      |                                                                                                                                                                                                                                                  |
|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13 | 52 | The association of follicle size as a triggering criterion with outcome has not been sufficiently studied. Physicians may choose the follicle size upon which final oocyte maturation is triggered on a case to case basis.                                                                                                                                                                                                                            | Conditional | ⊕⊕○○ | SoF table 32                                                                                                                                                                                                                                     |
| 13 | 53 | The decision on timing of triggering in relation to follicle size is multi-factorial, taking into account the size of the growing follicle cohort, the hormonal data on the day of pursued trigger, duration of stimulation, patient burden, financial costs, experience of previous cycles and organizational factors for the centre. Most often, final oocyte maturation is triggered at sizes of several of the leading follicles between 16-22 mm. | GPP         |      | Later hCG administration is associated with the retrieval of more oocytes. An effect on any other efficacy or safety or patient-related outcome was either not studied or not demonstrated in a consistent (e.g. homogenous) way across studies. |
| 13 | 54 | The GDG does not recommend to base timing of final oocyte maturation triggering on oestradiol levels alone.                                                                                                                                                                                                                                                                                                                                            | GPP         |      | The association of the serum oestradiol levels with clinical outcomes and OHSS risk has been studied in several observational studies, but management recommendations cannot be derived from these observational data.                           |
| 13 | 55 | The GDG does not recommended to base timing of final oocyte maturation on oestradiol/follicle ratio alone.                                                                                                                                                                                                                                                                                                                                             | GPP         |      | The association of the oestradiol-to-follicle ratio with clinical outcomes has been studied in several observational studies, but management                                                                                                     |

L'association de la taille du follicule comme critère de déclenchement avec le résultat n'a pas été suffisamment étudiée. Les médecins peuvent choisir la taille du follicule sur laquelle la maturation finale des ovocytes est déclenchée au cas par cas. Conditionnel ⊕⊕

La décision du moment de déclenchement par rapport à la taille du follicule est multifactorielle,. Le plus souvent, la maturation finale des ovocytes est déclenchée quand la taille de plusieurs follicules principaux est entre 16 et 22 mm. GPP

Le GDG ne recommande pas de décider le moment du déclenchement de la maturation finale des ovocytes sur les seuls niveaux d'œstradiol. GPP

Le GDG ne recommande pas de décider le moment de la maturation finale des ovocytes sur le seul rapport œstradiol/follicule. GPP

# Quels critères d'annulation

|    |    |                                                                                                                                                                                               |        |      |                                                                                                                                                                                                                                    |
|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 | 56 | A poor response to ovarian stimulation alone is not a reason to cancel a cycle.                                                                                                               | Strong | ⊕○○○ | For poor responders, pregnancy rates may be low but not absent. Therefore, the GDG recommends the physician to counsel patients individually regarding pregnancy prospects and the decision to continue this or further treatment. |
| 14 | 57 | The physician should counsel the individual poor responder regarding pregnancy prospects and decide individually whether to continue this and/or further cycles.                              | GPP    |      |                                                                                                                                                                                                                                    |
| 14 | 58 | In GnRH agonist cycles with an ovarian response of $\geq 18$ follicles, there is an increased risk of OHSS and preventative measures are recommended, which could include cycle cancellation. | Strong | ⊕○○○ | Regarding a high response there are also no solid criteria to cancel a cycle. A high response identifies women most at risk for OHSS. Therefore, preventive measures are recommended which could include cycle cancellation.       |

Une mauvaise réponse à la stimulation seule n'est pas une raison pour annuler un cycle. Fort ⊕

Le médecin doit conseiller une mauvaise répondeuse en ce qui concerne les perspectives de grossesse et décider individuellement de poursuivre ce cycle et/ou d'autres cycles. GPP

Dans les cycles d'agonistes de la GnRH avec une réponse ovarienne de  $\geq 18$  follicules, il existe un risque accru de OHSS et des mesures préventives sont recommandées, pouvant inclure l'annulation du cycle. Fort ⊕

# Déclenchement de l'ovulation et soutien de la phase lutéale

|    |    |                                                                                                                                                                      |             |      |                                                                                                                                                                                     |                 |
|----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 15 | 59 | The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation during ovarian stimulation protocols.                       | Strong      | ⊕⊕○○ | Cochrane meta-analysis shows equal efficacy and safety for urinary and recombinant hCG.                                                                                             | SoF table 33    |
| 15 | 60 | A reduced-dose of 5000 IU urinary hCG for final oocyte maturation is probably recommended over a 10.000 IU dose in GnRH agonist protocols, as it may improve safety. | Conditional | ⊕○○○ | A reduced-dose of urinary hCG (5000IU) does not appear to affect the probability of pregnancy compared to conventional dose (10.000IU).                                             | SoF table 34a,b |
| 15 | 61 | It is not recommended to administer recombinant LH for triggering final oocyte maturation.                                                                           | Strong      | ⊕○○○ | The available evidence is currently very limited to allow for solid conclusions to be drawn. Therefore, the GDG cannot recommend the use of rLH to trigger final oocyte maturation. | SoF table 35    |

L'utilisation hCG recombinante et hCG urinaire est également recommandée pour déclencher la maturation finale des ovocytes lors des protocoles de stimulation. Fort ⊕⊕

Une dose réduite de 5 000 UI de hCG urinaire pour la maturation finale des ovocytes est probablement recommandée plutôt qu'une dose de 10 000 UI dans les protocoles d'agonistes de la GnRH, car elle peut améliorer la sécurité. Conditionnel ⊕

Il n'est pas recommandé d'administrer de la rLH pour déclencher la maturation finale des ovocytes. Fort ⊕



# Le déclenchement par les agonistes

|    |    |                                                                                                                                                                         |             |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |              |
|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 15 | 62 | The use of GnRH agonist for final oocyte maturation with conventional luteal support and fresh transfer is not recommended in the general IVF/ICSI population.          | Strong      | ⊕⊕○○ | Current evidence shows a disadvantage in ongoing/clinical pregnancy rate with GnRH agonist and conventional luteal support as compared to hCG in normal responders. Recent evidence shows that this disadvantage could be overcome by adding LH-activity to the LPS, however, this effect needs to be studied in a large RCT. Thus, with the current knowledge we cannot recommend GnRH agonist triggering with modified LPS for the overall IVF/ICSI population. | SoF table 36 |
| 15 | 63 | The use of GnRH agonist for final oocyte maturation, luteal support with LH-activity and fresh transfer is probably not recommended for the predicted normal responder. | Conditional | ⊕○○○ | Current evidence is derived from an RCT in oocyte donors, however, the guideline group thinks that the findings can be extrapolated to the general IVF population.                                                                                                                                                                                                                                                                                                | SoF table 37 |
| 15 | 64 | If the GnRH agonist trigger with triptorelin is applied, dosages ranging of 0.1-0.4mg can be chosen.                                                                    | GPP         |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |              |

L'utilisation d'un agoniste de la GnRH pour la maturation finale des ovocytes avec un support lutéal conventionnel et un transfert frais n'est pas recommandée dans la population générale de FIV/ICSI. Forte ⊕⊕

L'utilisation d'un agoniste de la GnRH pour la maturation finale des ovocytes, le soutien lutéal avec activité LH et le transfert frais n'est probablement pas recommandée pour les normo-répondeuses. Conditionnel ⊕

Si le déclencheur agoniste de la GnRH avec la triptoréline est appliqué, des dosages allant de 0,1 à 0,4 mg peuvent être choisis. GPP

# Le double déclenchement

|    |    |                                                                                                                                                  |             |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |              |
|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 15 | 65 | The addition of a GnRH agonist to hCG as a dual trigger for final oocyte maturation is probably not recommended for predicted normal responders. | Conditional | ⊕⊕○○ | <p>Available meta-analysis has been rated of low quality. Current evidence in the form of RCT performed in normal responders suggests no improvement in the number of oocytes retrieved, with an improvement in pregnancy rate, but this finding needs to be further evaluated in well-designed RCTs. The additional intervention has not been shown to improve clinical outcomes in terms of live birth/ongoing pregnancy rate. Evidence in poor responders is very poor.</p> <p>Regarding patients with history of low fertilization rate or high number of immature oocytes, dual trigger in this subgroup of patients, cannot be recommended until data on its efficacy and safety from RCT's are available.</p> | SoF table 38 |
|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|

L'ajout d'un agoniste de la GnRH à la hCG comme double déclenchement pour la maturation finale des ovocytes n'est probablement pas recommandé pour les répondeurs normaux. Conditionnel ⊕⊕

Pour les mauvaises répondeuses, il n'y a pas d'évidence à l'ajout des agonistes.

Pour le taux bas de fécondation et le nombre élevé d'ovocytes immatures, les données ne sont pas encore valides.

# Soutien de la phase lutéale

|    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |        |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 | 66 | Progesterone is recommended for luteal phase support after IVF/ICSI.                                                                                                                                                                                                                                                                                                                                                                                                          | Strong | ⊕○○○ | SoF table 39                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 16 | 67 | Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.                                                                                                                                                                                                                                                                                                                                                | GPP    |      | SoF table 40                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 16 | 68 | The dosing of natural progesterone has evolved empirically, usually dosages used include:<br>50 mg once daily for intramuscular progesterone<br>25 mg once daily for subcutaneous progesterone<br>90 mg once daily for vaginal progesterone gel<br>200 mg three times daily for micronized vaginal progesterone in-oil capsules<br>100 mg two or three times daily for micronized vaginal progesterone in starch suppositories<br>400 mg two times daily for vaginal pessary. | GPP    |      | <p>Progesterone is recommended for luteal phase support for IVF/ICSI.</p> <p>Start of luteal support has not been studied in the correct manner. Luteal support should be provided in the window between the evening of the day of oocyte retrieval and D3 post oocyte retrieval.</p> <p>With the current evidence available, no major differences in efficacy have been found comparing the different administration routes of progesterone.</p> <p>SoF table 41 a,b,c,d</p> |

La progestérone est recommandée pour le soutien de la phase lutéale après FIV/ICSI. Fort ⊕

Toutes les voies d'administration (non orales) pour la progestérone naturelle comme support de la phase lutéale peuvent être utilisées. GPP

Le dosage de la progestérone naturelle, généralement utilisés incluent :

50 mg une fois par jour pour la progestérone IM, 25 mg une fois par jour pour la progestérone SC,

90 mg une fois par jour pour le gel de progestérone vaginale, 200 mg trois fois par jour pour les capsules progestérone vaginale micronisée, 400 mg deux fois par jour pour un pessaire vaginal. GPP

# Soutien de la phase lutéale

|    |    |                                                                                                                                                               |             |      |                                                                                                                                                                                                                                 |
|----|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 | 69 | Starting of progesterone for luteal phase support should be in the window between the evening of the day of oocyte retrieval and day 3 post oocyte retrieval. | GPP         |      | SoF table 42<br>a,b,c                                                                                                                                                                                                           |
| 16 | 70 | Progesterone for luteal phase support should be administered at least until the day of the pregnancy test.                                                    | GPP         |      | SoF table 43                                                                                                                                                                                                                    |
| 16 | 71 | Dydrogesterone is probably recommended for luteal phase support.                                                                                              | Conditional | ⊕⊕⊕○ | When compared to progesterone, dydrogesterone has similar ongoing pregnancy rate. Current evidence from large RCTs shows similar safety and tolerability compared to natural progesterone. Additionally,<br>SoF table 44<br>a,b |

Le démarrage de la progestérone pour le soutien de la phase lutéale doit se faire entre le soir du jour du prélèvement des ovocytes et le jour 3 après le prélèvement des ovocytes. GPP

La progestérone pour le soutien de la phase lutéale doit être administrée au moins jusqu'au jour du test de grossesse. GPP

La dydrogestérone est probablement recommandée pour le soutien de la phase lutéale. Conditionnel ⊕⊕⊕

# Soutien de la phase lutéale

|    |    |                                                                                                                                                                              |               |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                    |
|----|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| 16 | 72 | The addition of oestradiol to progesterone for luteal phase support is probably not recommended.                                                                             | Conditional   | ⊕⊕○○ | The data suggests that oestradiol is not recommended for LPS, since it does not improve efficacy in terms of live birth/ongoing pregnancy rate, or safety in terms of OHSS.                                                                                                                                                                                                                                                                                                               | SoF table 45       |
| 16 | 73 | In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is probably not recommended.                                         | Conditional   | ⊕⊕○○ | hCG is equal to progesterone protocols regarding efficacy. However, hCG increased the OHSS risk, specifically in high responders and with the dosages historically used (1500 IU).                                                                                                                                                                                                                                                                                                        | SoF table 46 a,b,c |
| 16 | 74 | A GnRH agonist bolus, in addition to progesterone for luteal phase support in hCG triggered cycles can only be used in the context of a clinical trial.                      | Research only |      | Current evidence indicates higher live birth /pregnancy rates with GnRH agonist bolus in addition to progesterone, repeated GnRH agonist injections alone or in addition to progesterone for LPS. Limited evidence suggests that GnRH agonist for LPS does not increase the risk of OHSS. However, long-term health effects in the new-born have not been studied. Until these data are available, the GDG recommends to use GnRH agonist for LPS only in the context of clinical trials. | SoF table 47       |
| 16 | 75 | Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles can only be used in the context of a clinical trial. | Research only |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | SoF table 48       |
| 16 | 76 | Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial.                                                                 | Research only |      | No conclusions can be drawn on the effect of LH supplementation for LPS from the available evidence, and this intervention cannot be recommended.                                                                                                                                                                                                                                                                                                                                         | SoF table 49       |

L'adjonction d'œstradiol à la progestérone pour le soutien de la phase lutéale n'est probablement pas recommandée. Conditionnel ⊕⊕

Dans les cycles déclenchés par l'hCG, l'hCG comme support de la phase lutéale à des doses standard de 1500 UI n'est probablement pas recommandée. Conditionnel ⊕⊕

Un bolus d'agoniste de la GnRH ou des injections répétées seules ou en plus de la progestérone pour le soutien de la phase lutéale dans les cycles déclenchés par l'hCG, ne peut être utilisé que dans le cadre d'un essai clinique. Recherche uniquement

L'addition de LH à la progestérone pour le soutien de la phase lutéale ne peut être utilisée que dans le cadre d'un essai clinique. Recherche uniquement

# Prévention du syndrome d'hyper-stimulation

|    |    |                                                                                                                                                                                                                                                                                  |             |      |                                                                                                                                                                                                                                       |                  |
|----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 17 | 77 | A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS.                                                                                                                                                                                      | Strong      | ⊕○○○ | Triggering final oocyte maturation with GnRH agonist significantly reduces the risk of early-onset OHSS in patients at risk of OHSS.                                                                                                  | SoF table 50 a,b |
| 17 | 78 | A freeze-all strategy is recommended to eliminate the risk of late-onset OHSS and is applicable in both GnRH agonist and GnRH antagonist protocols.                                                                                                                              | GPP         |      |                                                                                                                                                                                                                                       |                  |
| 17 | 79 | If a GnRH agonist trigger with freeze-all strategy is not used in patients at risk of OHSS, it is not clear whether the use of a 5000 IU hCG trigger or GnRH agonist trigger is preferred. The GnRH agonist trigger should be followed by luteal phase support with LH-activity. | Conditional | ⊕○○○ | A small non-significant difference in OHSS rates were observed, without an obvious effect on ongoing pregnancy rates. In the study, there was no comparison with freeze-all, which represents still the best option regarding safety. | SoF table 51     |

Un déclenchement agoniste de la GnRH est recommandé pour la maturation finale des ovocytes chez les femmes à risque de OHSS . Fort ⊕

Une stratégie freeze-all est recommandée pour éliminer le risque de OHSS d'apparition tardive et est applicable à la fois aux protocoles d'agonistes de la GnRH et d'antagonistes de la GnRH. GPP

Si un déclenchement par agoniste de la GnRH avec une stratégie de freeze-all n'est pas utilisé chez les patients à risque de OHSS,  
il n'est pas clair si l'utilisation d'un déclenchement par hCG de 5000 UI ou d'un déclenchement par agoniste de la GnRH est préférable.

Le déclenchement par l'agoniste de la GnRH doit être suivi d'un soutien de la phase lutéale avec activité LH.  
Conditionnel ⊕

# Prévention du syndrome d'hyper-stimulation

|    |    |                                                                                                                                                                    |             |      |                                                                                                                                                                                                                                            |
|----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 | 80 | In patients at risk of OHSS, the use of a GnRH agonist for final oocyte maturation is probably recommended over hCG in cases where no fresh transfer is performed. | Conditional | ⊕○○○ | Evidence from RCTs performed in oocyte donors indicates that GnRH agonist trigger is preferable over hCG when freeze-all is applied.                                                                                                       |
| 17 | 81 | A GnRH agonist trigger for final oocyte maturation with or without a freeze-all strategy is preferred over a coasting strategy in patients at risk of OHSS.        | GPP         |      | The two most relevant studies were both on retrospective data, with inherent methodological and risk of bias problems. Therefore, the GDG cannot recommend coasting and hCG trigger over GnRH agonist trigger for final oocyte maturation. |
| 17 | 82 | Cabergoline or albumin as additional preventive measures for OHSS are not recommended when GnRH agonist is used for triggering final oocyte maturation.            | GPP         |      |                                                                                                                                                                                                                                            |

Chez les patientes à risque de OHSS, l'utilisation d'un agoniste de la GnRH pour la maturation finale des ovocytes est probablement recommandée plutôt que l'hCG dans les cas de freeze-all. Conditionnel ⊕

Un déclenchement par agoniste de la GnRH pour la maturation finale des ovocytes avec ou sans stratégie de freeze-all est préférable à une stratégie de coasting chez les patientes à risque de OHSS. GPP

La cabergoline ou l'albumine comme mesures préventives supplémentaires pour le OHSS ne sont pas recommandées lorsqu'un agoniste de la GnRH est utilisé pour déclencher la maturation finale des ovocytes. GPP

# Prévention du syndrome d'hyper-stimulation

|    |    |                                                                                        |        |      |                                                                                                                                                                                                                                                                                   |                  |
|----|----|----------------------------------------------------------------------------------------|--------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 18 | 83 | A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS.   | Strong | ⊕⊕⊕○ | The current evidence suggests that not performing a fresh transfer lowers the OHSS risk for women at risk of OHSS, without completely eliminating the condition. The latter urges for follow up of haemo-concentration status even in cases with the freeze-all strategy applied. | SoF table 52 a,b |
| 18 | 84 | Prior to start of ovarian stimulation, a risk assessment for high response is advised. | GPP    |      |                                                                                                                                                                                                                                                                                   |                  |

Une stratégie de freeze-all est recommandée pour éliminer complètement le risque de OHSS d'apparition tardive. Fort ⊕⊕⊕

Avant le début de la stimulation, une évaluation des risques de réponse élevée est conseillée. GPP



# Résumé

Ces recommandations pour la stimulation ovarienne FIV/ICSI vise a nous fournir les meilleurs preuves disponibles pour les différentes étapes.

84 recommandations

- 61 fondés sur des données prouvées
- 21 Fortes
- 40 Conditionnelles
- 19 GPP
- 4 recommandations de recherche

Inconvénients : les preuves sont souvent limitées et de faible qualité.

# Principale difficulté

Absence de  
définitions uniformes

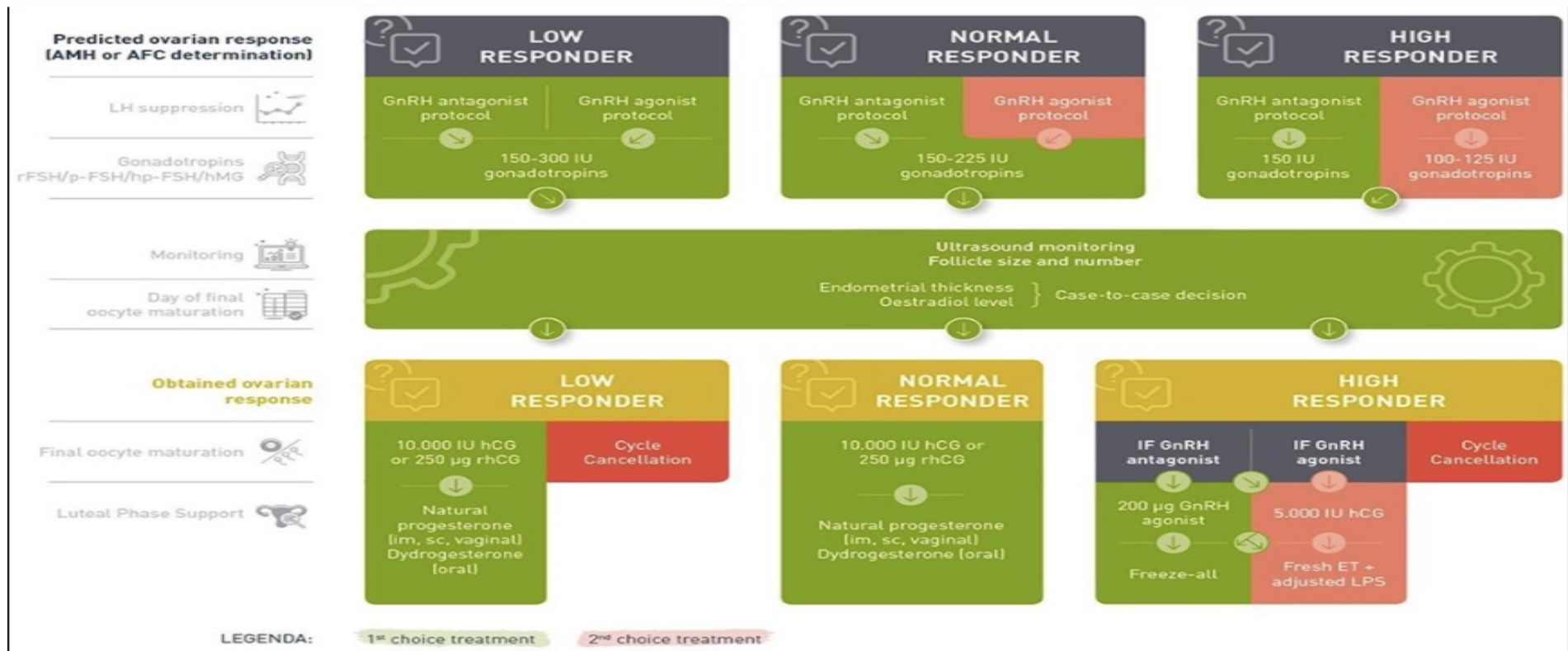
Mauvaise répondeuse

- Consensus de Bologne 2011
- Poseidon

Hyper-répondeuse

- Lien entre le nombre élevé d'ovocytes et le risque d'hyper-stimulation
- Diffère d'une publication à une autre

# Stratégie



## Directive ESHRE : stimulation ovarienne pour FIV/ICSI † 3

Le groupe d'orientation ESHRE sur la stimulation ovarienne, Ernesto Bosch, Simone Broer, Georg Griesinger, Michel Grynberg, Pierre Humaidan, Estratios Kolibianakis, Michal Kunicki, Antonio La Marca, Georges Lainas ... [Afficher plus](#)

Reproduction humaine ouverte, volume 2020, numéro 2, 2020, hoaa009,

# Impact de ces recommandations

Prévention du  
syndrome d'hyper-  
stimulation  
ovarienne

Amélioration des  
résultats chez les  
mauvaises  
répondeuses

- Absence de preuve sur le choix du protocole
- Plusieurs traitements adjuvants sont utilisés sans preuve
- peu de preuves concernant les doses de gonadotrophines

# Conclusion

Ce guideline de l'ESHRE fourni  
aux cliniciens des  
recommandations et des  
éléments de bonne pratique

Met le point sur la nécessité de  
recherches supplémentaires

- Dosage des gonadotrophines
- Les pré-traitements
- Support de la phase lutéale par les agonistes
- Efficacité et la sécurité du freeze-all