



OVARIAN STIMULATION FOR IVF/ICSI

Guideline of the European Society of Human Reproduction and Embryology

OCTOBER 2019
ESHRE Reproductive Endocrinology Guideline Group

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Introduction to the guideline

Ovarian stimulation for IVF/ICSI has not been addressed by existing evidence-based guidelines. Ovarian stimulation for IVF/ICSI has been discussed briefly in the NICE guideline on Fertility problems (<https://www.nice.org.uk/guidance/cg156>) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologist has published a statement on ovarian stimulation in assisted reproduction ([https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20Gynaecology/Ovarian-Stimulation-in-infertility-\(C-Gyn-2\)-Review-Mar-14.pdf?ext=.pdf](https://www.ranzcog.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical%20-%20Gynaecology/Ovarian-Stimulation-in-infertility-(C-Gyn-2)-Review-Mar-14.pdf?ext=.pdf)).

A narrative review of evidence provided for WHO guidance on management of ovarian stimulation for IVF was published in 2017, but this document did not include recommendations (Farquhar, et al., 2017).

Based on the lack of guidelines, the ESHRE SIG Reproductive Endocrinology initiated the development of an ESHRE guideline focussing on all aspects of ovarian stimulation.

The guideline was developed according to a well-documented methodology, universal to ESHRE guidelines and described in the Manual for ESHRE guideline development (www.eshre.eu). Details on the methodology of the current guideline are outlined in Annex 5.

The guideline development group (GDG) was composed of (previous) members of the co-ordination of the SIG, with addition of experts in the field that replied on a call for experts to the ESHRE audience. The members of the guideline development group are listed in Annex 1.

GUIDELINE SCOPE

The aim of this guideline is to provide clinicians with evidence-based information on the different options for ovarian stimulation for IVF/ICSI, taking into account issues such as the 'optimal' ovarian response, live birth rates, safety, patient compliance, and individualization. Knowledge gaps were identified and prioritized.

The following issues were outside the scope of the current document: patients with specific conditions (except for PCOS), oocyte donation, frozen embryo transfer, treatment of ovarian hyper-stimulation syndrome (OHSS), scheduling/programming.

TARGET USERS OF THE GUIDELINE

Infertility specialists performing ovarian stimulation for the purpose of IVF/ICSI.

TERMINOLOGY

Ovarian stimulation is defined as pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes: 1) for timed intercourse or insemination; 2) in ART, to obtain multiple oocytes at follicular aspiration (Zegers-Hochschild, et al., 2017). The GDG decided to use the term ovarian stimulation (OS) to confine to ovarian stimulation for IVF/ICSI.

The GDG would also like to point out that when comparing the different ovarian stimulation compounds, dosages or add-on treatments, the added benefit for the patient must be made clear compared to the more basic or standard option.

Response after ovarian stimulation is usually classified as poor, normal and excessive. However, this terminology can be potentially stigmatising/traumatising towards patients. Therefore, the GDG would like to propose to use the terminology low, normal and high response to categorize (predicted) response to OS for future referencing.

Due to the lack of universally accepted definitions of high and low ovarian response, the definitions and terminology in the studies included in the evidence synthesis were varied. However, for future practice and research, the GDG suggests using the following definitions:

- High ovarian response is an exaggerated response to conventional ovarian stimulation (150-225 IU FSH), characterized by the presence of more follicles and/or oocytes than intended (Griesinger, et al., 2016). Generally, more than 18 follicles ≥ 11 mm in size on day of oocyte maturation trigger and/or 18 oocytes collected characterize a high response (Griesinger, et al., 2016) defined by a risk increase in OHSS.
- Low ovarian response is a diminished response to conventional ovarian stimulation, characterized by the presence of a low number of follicles and/or oocytes (Ferraretti, et al., 2011). Generally, ≤ 3 follicles on day of oocyte maturation trigger and/or ≤ 3 oocytes obtained characterize a low response.

As the definition of low response proposed in this guideline is the same as the definition of Bologna poor responder and the poor responder as defined by ICMART (Ferraretti, et al., 2011, Zegers-Hochschild, et al., 2017) and for consistency, the term poor was used throughout the document.

Outcomes for this guideline

The guideline focuses on outcomes of efficacy, safety and patient-related outcomes.

The critical outcomes for this guideline are efficacy in terms of cumulative live birth rate (CLBR) per started cycle and live birth rate (LBR) per started cycle; and safety in terms of moderate and/or severe OHSS.

Other outcomes used for efficacy were (in order of importance) cumulative ongoing pregnancy rate per started cycle, clinical pregnancy rate per started cycle, number of oocytes retrieved, number of MII oocyte retrieved (yield).

Other outcomes used for safety include incidence of different grades of ovarian hyperstimulation syndrome (OHSS), cycle cancellation for hyper-response, bleeding, infection, torsion, long-term effects on maternal/child health, and other treatment-related adverse events.

Patient-related outcomes are compliance, drop-out rates, patient burden, quality of life (QoL), and patient preferences.

All outcomes were defined, where possible, as per started cycle.

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Introduction

IVF: the purpose and significance.

Infertility is a disease state with potential profound consequences for the quality of life of both men and women. Reproduction is one of the key elements of life and failing to achieve the creation of offspring may lead to lifelong mental and physical health problems. Also, couples faced with infertility are frequently subjected to long-lasting, time consuming and agonizing treatment schedules, living often between hope, fear and frustration (Brandes, et al., 2010, Brandes, et al., 2009, Gameiro and Finnigan, 2017). The development of IVF as a tool for treating infertility as a result of tubal disease, severe male factor causes, anovulation and even, although not convincingly proven, conditions like unexplained infertility, has brought enormous potential to the infertility treatment armamentarium. Still, of all couples visiting infertility centres, roughly 35-40% will not achieve the so desired goal, in spite of lengthy efforts, including IVF, and remain permanently childless (McLernon, et al., 2016, Olivius, et al., 2002). This indicates that currently we still have areas of low-level knowledge on the key factors of success, such as gamete quality, embryo quality and endometrial receptivity. Improving the IVF technology may well depend on progress in these fields of research.

Stimulation: how important is it.

Very soon after the development of the IVF technology, performing IVF in a natural menstrual cycle was superseded by the use of ovarian stimulation in order to obtain multiple oocytes. This was aimed at solving two problems: one was the elimination of the risk of having no oocyte at all. The other was the urge to improve efficiency by obtaining several embryos and replacing the best quality embryo to improve the probability of pregnancy. Ovarian stimulation has thereby become one of the cornerstones of the IVF treatment, next to the *in vitro* handling of gametes and embryos, and the embryo replacement process. The relative contribution to the overall success of IVF by the ovarian stimulation phase is difficult to assess. Many years of research have aimed at optimizing this specific phase. Issues have been addressed ranging from using urinary FSH products or recombinants, using high or low FSH dosages, final oocyte maturation with urinary or recombinant, high or low dosage of hCG, adding LH or LH like activity to the FSH as principal drug, management of high and poor responders, use of adjuvant medications to improve follicle availability, etcetera. At the same time, debates have been there on beliefs like “the more (oocytes) the better”, less (mild stimulation) is more (quality), “normal (8-17 oocytes) is the best”, and “we need eggs, not ALL the eggs”. It seems that agreement on the optimal ovarian stimulation approach, aimed at getting more than 1 oocyte, as in the normal menstrual cycle, is far from settled.

Basics: FSH elevation.

Complex as it seems, the endocrine background for ovarian stimulation is quite straightforward. FSH levels must become elevated above the level that normally will help to select and grow ONE follicle out of a group of antral follicles presenting in the FSH ‘window’. During this window, levels of FSH surpass a certain threshold above which follicle granulosa cells become responsive for proliferative actions, leading to expansion of the granulosa cell mass and the follicle fluid volume, typically of only one follicle, while other potential responsive follicles fall into atresia. In surpassing the threshold to a greater extent, and for a much longer period of time with use of ovarian stimulation, more than one follicle will become

capable of entering this dominant follicle development stage. The tools available for increasing FSH exposure are several, but basically most comprise preparations containing FSH. The source can be urinary (purified or highly purified) or recombinant. Some preparations combine FSH with of LH, or LH like activity. The vast majority of FSH compounds are distributed for dosing in International Units, as standardisation based on an oestradiol output bio-assay. Only one compound is delivered in micrograms, and dosing here is based on a dosing algorithm. Apart from administering FSH as an exogenous drug, compounds such as selective oestradiol receptor or biosynthesis inhibitors may yield the same effect: increase and prolonged FSH exposure. It may be noted that when comparing the different ovarian stimulation compounds, dosages or add-on treatments, the added benefit for the patient must be made clear compared to the more basic or standard option.

Source: Ovarian Antral Follicles, continuous versus cyclic recruitment.

The follicles presenting in the window of elevated FSH levels are part of a continuous recruitment process. Starting from the resting pool of primordial follicles, follicles develop through several phases, reaching the antral stages after approximately 200 days (McGee and Hsueh, 2000). At that time point they attain relevant FSH sensitivity. Without FSH exposure, such as in the prepubertal years, these follicles will reach maximum sizes of 2-3 mm and vanish into the process of atresia. Without any FSH exposure, this wastage process would continue until around the age of 50 years, when the ovarian primordial follicle pools will have become depleted. It is the presence of FSH in varying levels that allows the ovaries to pick up follicles in the antral stages, which become more prominent at ultrasound, and from there deliver the ovulating follicle of the month, or, as in ovarian stimulation, recruit several to many follicles from those that present in a window of opportunity to respond to FSH. This ovarian activity is referred to as cyclic recruitment. The number of follicles that present in the opportunity window of cyclic recruitment is highly variable between women and between age groups. As a general rule, the number of antral follicles that can be stimulated will decline gradually with increasing age, as an expression of the shrinking pool of primordial follicles.

Store of Antral Follicles: can we manipulate it?

Obtaining only few oocytes is an agonizing condition, as it may affect the prospects for a live birth in IVF, albeit that this prospect is also much determined by the age of the woman. Still, there is a continuous search for methods to improve the egg number in poor responders, and from the aforementioned, it can be deduced that such method should interfere with early stages of follicle development, where initial recruitment and/or later survival during continuous recruitment is promoted. Numerous strategies and interventions have been suggested to enhance this sequence of events; however, clinical useful strategies are still awaited.

Oocyte number and Dosage: what is the relation like?

The cohort of antral follicles being the finite source for oocytes, the level of exposure to FSH may add to the total number of oocytes obtained. With the need of a minimum exposure to grow more than 1 follicle, there seems to be a positive relation between FSH dosage and oocyte yield, ranging from about 50 IU daily for a minimal response of 2 oocytes up to about 225 IU to obtain a maximal response (Lensen, et al., 2017, Sterrenburg, et al., 2011). For the optimal response level in terms of oocytes a daily dosage of 150 to 225 IU is mostly considered as standard. This implies that when using a stimulation dosage of 150 IU per day and creating a low follicle response, the range of opportunities in dose adjustments is likely to be limited. This is certainly much dependant on the of Antral Follicle Count or AMH result. A predicted poor responder may not produce more oocytes with a higher dosage. An

unexpected poor responder may well obtain more oocytes with a higher dosage. but will it improve her prospects for a live birth? We still need to see evidence that a few oocytes more or less will make the desired or feared difference in terms of live birth rates. At this point it may be emphasized that the various cross-sectional cohort data on the relation between oocyte number and cumulative live birth rates have suggested that 'more is better' and 'less is bad'. These observations are correlation data, without the possibility to conclude that there is a causal relationship. With respect to the latter, we may reflect on the implications, of the randomised comparative trials demonstrating that a few more or less oocytes within the individual couple will fail to make an obvious difference.

At the other side of the spectrum, a high response to a standard dosage of 150 IU may be undesirable as it is a potential source for the development of the Ovarian Hyperstimulation Syndrome (OHSS), even today a potential life-threatening condition. Reduction of the FSH stimulation dosage may bring a more mitigated response, with better safety, without jeopardizing overall live birth prospects. However, it is to be understood that the driver of the syndrome occurring in high responder cases in fact is the exposure of the granulosa cells to human chorion gonadotropin (hCG). Necessary as this may be for the final oocyte competence attainment, circumventing administration of the drug by creation of an endogenous LH surge by applying a GnRH agonist trigger is certainly a way to improve safety. Finally, prevention of pregnancy derived hCG by freezing all embryos will be another logical step.

Control on ovulation: agonists and antagonist.

When stimulating the ovaries to create multifollicular development, the fast-rising oestradiol levels may elicit an untimely LH surge. Untimely, as follicles may not have grown sufficiently large to ensure the best quality oocytes, and when passed unnoticed, oocyte pick up may become a failed procedure. The use of agents that block the signalling by the GnRH pulse generator towards the pituitary, such as GnRH agonists, GnRH antagonists and progestins, have almost completely ruled such mishaps and have greatly contributed to the efficiency of ovarian stimulation for IVF/ICSI.

Oocytes, and then?

Although the primary goal of ovarian stimulation is obtaining several oocytes, the timed replacement of the embryo necessitates parallel and physiologically correct development of the endometrium. Implantation is dependent on proper endocrine conditions, such as oestradiol exposure in order to ensure proliferation, and progesterone exposure commencing around ovulation in order to have the endometrium differentiated into a receptive state. Stimulation per se is a guarantee for oestradiol synthesis and release from the many developing follicles. The LH peak, or as in many cases, hCG exposure, will enable granulosa cell differentiation into a progesterone producing system, that, in normal condition, will be driven by continued endogenous LH pulses. In the GnRH agonist suppression approach, the interruption of the GnRH agonist will lead to LH levels dropping to nearly undetectable state, and the hCG exposure here takes over the role of LH in maintaining luteal function up till 7-9 days. Thereafter, luteal support is almost exclusively applied in the form of exogenous natural progesterone, which is initiated often already at the day of follicle aspiration. However, pharmacokinetics may not always be very stable for these compounds, and when endogenous LH exposure by using an GnRH agonist trigger is applied, instead of the hCG signal, luteal phase becomes insufficient in many cases even with the current exogenous progesterone administration. The luteal phase support approach therefore remains an important area of research for improvement.

Many years of basic and clinical research have delivered us tools for ovarian stimulation that make this procedure effective, efficient, safe and an essential contribution to the total process of Assisted Reproduction. In this guideline, important knowledge is brought together using a set of relevant questions, for which searches and selections of the literature, grading of the knowledge base regards quality, and well-balanced recommendations will provide the best possible answers to the question. These recommendations will help clinicians to decide on what best to do or better not to do in clinical conditions where we wish to provide optimal care to our patients.

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List of all recommendations

Chapter	No.	Recommendation	Strength	Quality of evidence	Justification	Remarks
Pre-stimulation management						
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. <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
LH suppression and ovarian stimulation – stimulation protocols						
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.	
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	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
4A	/	There is no evidence to justify the use of NC or MNC for OS in high responders.	/	/	/	Conclusion
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

				antagonist protocol in regular IVF patients, the GnRH antagonist protocol is recommended in normal responder patients.		
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
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
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	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
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	⊕○○○	There is unlikely to be significant benefit with doses > 300 IU daily.	SoF table 14 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

LH suppression and ovarian stimulation – LH suppression and gonadotropins

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 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 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.	
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
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
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.	
LH suppression and ovarian stimulation – adjuvant therapies and non-conventional start stimulation						
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
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	⊕⊕⊕○	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.	SoF table 29
8	38	Use of sildenafil before and/or during ovarian stimulation is not recommended for poor responders.	Strong	⊕○○○	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	

					ovarian 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 two conventional stimulations, we cannot recommend the double stimulation in poor responder patients
9	44	Double stimulation can be considered for urgent fertility preservation cycles.	GPP		
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 not yet exist.

Monitoring

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
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.	
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	

					recommendations cannot be derived from these observational data.	
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 ≥ 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.	
Triggering ovulation and luteal support						
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
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	⊕○○○		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		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.	

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	⊕⊕○○	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. 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.	SoF table 38
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: 50 mg once daily for intramuscular progesterone 25 mg once daily for subcutaneous progesterone 90 mg once daily for vaginal progesterone gel 200 mg three times daily for micronized vaginal progesterone in-oil capsules 100 mg two or three times daily for micronized vaginal progesterone in starch suppositories 400 mg two times daily for vaginal pessary.	GPP		Progesterone is recommended for luteal phase support for IVF/ICSI. 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. With the current evidence available, no major differences in efficacy have been found comparing the different administration routes of progesterone.	SoF table 41 a,b,c,d
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 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,	SoF table 44 a,b

					patients prefer the oral administration route of dydrogesterone over the vaginal route of progesterone. However, the GDG considers these safety data insufficient to make a firm statement and there is a lack of long-term offspring health studies.	
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		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 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
Prevention of OHSS						
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

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			
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			

PART A: Ovarian response testing

1. Pre-stimulation management

KEY QUESTION: IS THE ASSESSMENT OF THE PREDICTED RESPONSE TO OVARIAN STIMULATION SUFFICIENTLY RELIABLE?

Implications following the prediction of an extreme ovarian response is relevant for both the clinicians and patients. Clinicians may suggest personalizing the treatment based on that prediction, such strategies will be discussed elsewhere in this guideline. For the patients, ovarian response prediction provides information about the chances of success, the safety risks and complications.

1.1 ANTRAL FOLLICLE COUNT (AFC)

Evidence

A high number of studies have investigated the role of AFC in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of poor and high response has not been uniform. AFC has been studied in GnRH agonist and antagonist cycles and in patients stimulated with different dosages and protocols of FSH. Also, several narrative reviews and meta-analyses have been conducted on the subject.

Two individual patient data (IPD) meta-analysis have been performed (Broer, et al., 2013, Broer, et al., 2013). These IPD meta-analyses have studied the accuracy of AFC in the prediction of a poor and of a high response in 5705 and 4786 women respectively, while taking account for heterogeneity between the original studies. These analyses showed a high predictive power of AFC in predicting both a poor response (ROC-AUC of 0.73 (95% CI 0.69-0.77)) and a high response (ROC-AUC of 0.73 (95% CI 0.69-0.77)) (Broer, et al., 2013, Broer, et al., 2013). Furthermore, it has been demonstrated that AFC has an added value to female age alone in the prediction of ovarian response

Several studies were identified assessing the predictive accuracy for AFC in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards, which show similar results to the IPD meta-analyses (Arce, et al., 2013, Bancsi, et al., 2002, Bancsi, et al., 2004, Elgindy, et al., 2008, Jayaprakasan, et al., 2009, Jayaprakasan, et al., 2010, Khairy, et al., 2008, Kwee, et al., 2007, Lan, et al., 2013, Mutlu, et al., 2013, Oehninger, et al., 2015, Penarrubia, et al., 2010, Soldevila, et al., 2007, Tolikas, et al., 2011, Tsakos, et al., 2014).

Table 1: Accuracy of AFC in predicting ovarian response.

AFC Study	Cohort (n)	High ovarian response		Poor ovarian response		Remark
		Criterion	ROC-AUC	Criterion	ROC-AUC	
Broer 2013a/b	4786/5705	>15 oocytes	0.73	≤4 oocytes	0.73	
Other studies:						
Bancsi 2002	120			<4 oocytes	0.87	
Bancsi 2004	130			<4 oocytes	0.87	
Kwee 2007	110	>20 oocytes	0.92	<6 oocytes	0.83	
Soldevila 2007	327			≤5 oocytes	0.73	
Elgindy 2008	33			<4 oocytes	0.94	
Khairy 2008	148			<4 oocytes	0.79	
Jayaprakasan 2009	141			<4 oocytes	0.89	
Jayaprakasan 2010	150			≤3 oocytes	0.94	
Penarrubia 2010	98			≤3 oocytes	0.90	
Tolikas 2011	90			<4 oocytes	0.81	
Arce 2013	374	≥15 oocytes	0.65	≤3 oocytes	0.67	hMG stimulation
Arce 2013	375	≥15 oocytes	0.64	≤3 oocytes	0.74	rFSH stimulation
Lan 2013	382	>20 oocytes	0.81	≤3 oocytes	0.80	
Mutlu 2013	192			<4 oocytes	0.93	
Tsakos 2014	105	>12 oocytes	0.86	<4 oocytes	0.86	
Oehninger 2015	686	>18 oocytes	0.88	<6 oocytes	0.88	

Conclusion

The prediction of ovarian response categories by AFC alone is reliable.

1.2 ANTI-MÜLLERIAN HORMONE (AMH)

Evidence

A high number of studies have investigated the role of AMH in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and studies have used different assays for the measurement of the AMH values. AMH has been studied in GnRH agonist and antagonist cycles and in patients stimulated with different dosages and protocols of FSH. Moreover, the definition of a poor and high response has not been uniform, which nevertheless showed AMH to be a good predictor of ovarian response. Several narrative reviews have been written next to different meta-analyses on the subject.

The IPD meta-analyses mentioned earlier also assessed the accuracy of AMH and reported a high predictive power of AMH in predicting both a poor response (ROC-AUC of 0.81 (95% CI 0.77-0.84)) and a high response (ROC-AUC of 0.82 (95% CI 0.77-0.86)) (Broer, et al., 2013, Broer, et al., 2013). Furthermore, it has been demonstrated that AMH has an added value to female age alone in the prediction of ovarian response.

Several studies were identified assessing the predictive accuracy for AMH in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards, which show similar results to the IPD meta-analyses (Andersen, et al., 2011, Arce, et al., 2013, Elgindy, et al., 2008, Heidar, et al., 2015, Jayaprakasan, et al., 2010, Lan, et al., 2013, Li, et al., 2016, Mutlu, et al., 2013, Oehninger, et al., 2015, Tolikas, et al., 2011, Tsakos, et al., 2014).

Table 2: Accuracy of AMH in predicting ovarian response.

AMH		High ovarian response		Poor ovarian response		
Study	Cohort (n)	Criterion	ROC-AUC	Criterion	ROC-AUC	Remark
Broer 2013a/b	4786/5705	>15 oocytes	0.82	≤4 oocytes	0.81	
Other studies:						
Elgindy 2008	33			<4 oocytes	0.90	
Jayaprakasan 2010	150			≤3 oocytes	0.91	
Andersen 2011	442	>18 oocytes	0.77	<6 oocytes	0.84	
Tolikas 2011	90			<4 oocytes	0.70	
Arce 2013	374	≥15 oocytes	0.77	≤3 oocytes	0.78	hMG stimulation
Arce 2013	375	≥15 oocytes	0.81	≤3 oocytes	0.90	rFSH stimulation
Lan 2013	382	>20 oocytes	0.76	≤3 oocytes	0.88	
Mutlu 2013	192			<4 oocytes	0.86	
Tsakos 2014	105	>12 oocytes	0.66	<4 oocytes	0.63	
Heidar 2015	188	>12 oocytes	0.69	≤3 oocytes	0.76	
Oehninger 2015	686	>18 oocytes	0.86	<6 oocytes	0.87	
Li 2016	615	>15 oocytes	0.76	≤5 oocytes	0.70	

Conclusion

The prediction of ovarian response categories by AMH alone is reliable.

1.3 BASAL FOLLICLE STIMULATING HORMONE (FSH)

Evidence

A high number of studies have investigated the role of basal FSH levels in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of a poor and high response has not been uniform. Also, several narrative reviews and meta-analyses have been conducted on the subject.

The IPD meta-analyses mentioned earlier also assessed the accuracy of basal FSH and reported moderate accuracy of basal FSH in predicting both a poor response (ROC-AUC of 0.66 (95% CI 0.62-0.69) and an excessive response (ROC-AUC of 0.64 (95% CI 0.61-0.67)) (Broer, et al., 2013, Broer, et al., 2013).

Several studies were identified assessing the predictive accuracy for basal FSH in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards, which show similar results to the IPD meta-analyses (Arce, et al., 2013, Bancsi, et al., 2002, Elgindy, et al., 2008, Jayaprakasan, et al., 2009, Khairy, et al., 2008, Kwee, et al., 2007, Mutlu, et al., 2013, Oehninger, et al., 2015, Penarrubia, et al., 2010, Soldevila, et al., 2007, Tolikas, et al., 2011, Tsakos, et al., 2014).

Table 3: Accuracy of basal FSH in predicting ovarian response.

Study	Cohort (n)	High ovarian response		Poor ovarian response		Remark
		Criterion	ROC-AUC	Criterion	ROC-AUC	
Broer 2013a/b	4786/5705	>15 oocytes	0.64	≤4 oocytes	0.66	
Other studies:						
Bancsi 2002	120			<4 oocytes	0.84	
Kwee 2007	110	>20 oocytes	0.80	<6 oocytes	0.83	
Soldevila 2007	327			≤5 oocytes	0.63	
Elgindy 2008	33			<4 oocytes	0.85	
Khairy 2008	148			<4 oocytes	0.69	
Jayaprakasan 2009	141			<4 oocytes	0.69	
Penarrubia 2010	98			≤3 oocytes	0.62	
Tolikas 2011	90			<4 oocytes	0.65	
Arce 2013	374	≥15 oocytes	0.71	≤3 oocytes	0.73	hMG stimulation
Arce 2013	375	≥15 oocytes	0.73	≤3 oocytes	0.72	rFSH stimulation
Mutlu 2013	192			<4 oocytes	0.75	
Tsakos 2014	105	>12 oocytes	0.72	<4 oocytes	0.67	
Oehninger 2015	686	>18 oocytes	0.88			

Conclusion

The prediction of ovarian response categories by basal FSH alone is not sufficiently reliable.

1.4 INHIBIN B

Evidence

A high number of studies have investigated the role of inhibin B in the prediction of ovarian response to ovarian stimulation (OS). In 2006 a systematic review and meta-analysis (9 studies, 788 cycles) has been performed including inhibin B (Broekmans, et al., 2006). Although variations between studies regarding definition of poor response, study quality and study characteristics existed, statistical analysis showed these not related to the predictive performance of inhibin B. The sensitivity of inhibin B in the prediction of a poor response ranged from 32 to 89%, the specificity ranged from 29-95%. The spearman correlation coefficient for sensitivity and specificity was -0.93. From logistic regression the pre- and post-test probabilities of a poor response were calculated. These demonstrated that inhibin B has a modest accuracy in the prediction of a poor response (Broekmans, et al., 2006).

Since the publication of this meta-analysis a few more studies have been published assessing the predictive accuracy for inhibin B in ovarian response prediction (Arce, et al., 2013, Fawzy, et al., 2002, Hendriks, et al., 2005, Kwee, et al., 2007, Penarrubia, et al., 2010, van Rooij, et al., 2002).

Table 4: Accuracy of Inhibin B in predicting ovarian response.

Inhibin B Study	Cohort (n)	High ovarian response		Poor ovarian response		Remark
		Criterion	ROC-AUC	Criterion	ROC-AUC	
Fawzy 2002	54			<8 MII oocytes	0.96	
Van Rooij 2002	119			<4 oocytes	0.76	
Hendriks 2005	63			<4 oocytes	0.76	
Kwee 2007	110	>20 oocytes	0.93	<6 oocytes	0.86	for the increment of inhibin B in the EFORT
Penarrubia 2010	98			≤3 oocytes	0.61	
Arce 2013	374	≥15 oocytes	0.60	≤3 oocytes	0.62	hMG stimulation
Arce 2013	375	≥15 oocytes	0.53	≤3 oocytes	0.64	rFSH stimulation

Conclusion

The prediction of ovarian response categories by inhibin B alone is not sufficiently reliable.

1.5 BASAL OESTRADIOL

Evidence

Basal oestradiol has also been studied as a predictor of ovarian response to ovarian stimulation. The systematic review by Broekmans et al., mentioned before, also investigated the performance of basal oestradiol in predicting ovarian response (10 studies, 3911 women) (Broekmans, et al., 2006). The sensitivity of basal oestradiol in the prediction of a poor response ranged from 3 to 83%, the specificity ranged from 13-98%. The spearman correlation coefficient for sensitivity and specificity was -0.50. From LR the pre- and post-test probability of a poor response was calculated. This demonstrated that basal oestradiol has a low accuracy in the prediction of a poor response (Broekmans, et al., 2006).

Since the publication of this meta-analysis a few more studies have been published assessing the predictive accuracy for basal oestradiol in ovarian response prediction (Hendriks, et al., 2005, Khairy, et al., 2008, Kwee, et al., 2007, Penarrubia, et al., 2010, van Rooij, et al., 2002). These have confirmed the low accuracy of basal oestradiol.

Table 5: Accuracy of basal oestradiol in predicting ovarian response.

basal estradiol Study	Cohort (n)	High ovarian response		Poor ovarian response		Remark
		Criterion	ROC-AUC	Criterion	ROC-AUC	
Van Rooij 2002	119			<4 oocytes	0.52	
Hendriks 2005	63			<4 oocytes	0.54	
Kwee 2007	110	>20 oocytes	0.83	<6 oocytes	0.75	for the increment of basal oestradiol in the EFORT
Khairy 2008	148			<4 oocytes	0.51	
Penarrubia 2010	98			≤3 oocytes	0.55	

Conclusion

Basal oestradiol alone is not a predictor of ovarian response.

1.6 AGE

Evidence

A high number of studies have investigated the role of age in the prediction of ovarian response to ovarian stimulation. Most of these studies have a limited number of patients, and the definition of poor and high response has not been uniform. However, all these studies show an unsatisfactory ROC curve for age as predictor of ovarian response. Several meta-analyses have been conducted on the subject.

The IPD meta-analyses mentioned earlier also assessed the accuracy of age and reported a limited accuracy of age alone in predicting both a poor response (ROC-AUC of 0.60 (95% CI 0.57-0.64)) and an excessive response (ROC-AUC of 0.61 (95% CI 0.58-0.64)) (Broer, et al., 2013, Broer, et al., 2013).

Several studies were identified assessing the predictive accuracy for age in ovarian response prediction which were not included in the IPD meta-analysis or were published afterwards (Bancsi, et al., 2002, Jayaprakasan, et al., 2009, Khairy, et al., 2008, Kwee, et al., 2007, Mutlu, et al., 2013, Oehninger, et al., 2015, Penarrubia, et al., 2010).

Table 6: Accuracy of age in predicting ovarian response.

Age Study	Cohort (n)	High ovarian response		Poor ovarian response	
		Criterion	ROC-AUC	Criterion	ROC-AUC
Broer 2013a/b	4786/5705	>15 oocytes	0.61	≤4 oocytes	0.60
Other studies:					
Bancsi 2002	120			<4 oocytes	0.61
Kwee 2007	110	>20 oocytes	0.71	<6 oocytes	0.63
Khairy 2008	148			<4 oocytes	0.71
Jayaprakasan 2009	141			<4 oocytes	0.74
Penarrubia 2010	98			≤3 oocytes	0.75
Mutlu 2013	192			<4 oocytes	0.76
Oehninger 2015	686	>18 oocytes	0.55	<6 oocytes	0.55

Conclusion

The prediction of ovarian response categories by age alone is not sufficiently reliable.

1.7 BODY MASS INDEX (BMI)

Evidence

With the growing interest for ovarian response prediction, the role of BMI in ovarian response has been questioned. However, there are only a few studies actually assessing the accuracy of BMI as a predictor of ovarian response. In these studies, BMI was found to have a small to no predictive accuracy for ovarian response to ovarian stimulation.

The IPD meta-analyses mentioned earlier also assessed the accuracy of BMI and concluded that BMI was not a significant predictor of ovarian response, neither for poor nor a high response (Broer, et al., 2013, Broer, et al., 2013).

Khairy et al. reported an ROC-AUC of 0.68 for prediction of poor response in a cohort of 148 patients (Khairy, et al., 2008).

Conclusion

BMI alone is not a predictor of ovarian response.

1.8 OVERALL RECOMMENDATION

Evidence

Based on the available evidence both AFC and AMH show a high accuracy in the predication of a poor and high response (Table 1 and 2). The accuracy of Basal FSH and Inhibin B levels is moderate (Table 3 and 4). Basal oestradiol, age and BMI are not good predictors of ovarian response to hyperstimulation (Table 5 and 6).

Recommendation

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.

Strong ⊕○○○

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.

Justification

AFC and AMH both have a high accuracy in the prediction of ovarian response category (high or poor). Taking into account false positive and negative rate of the test it may be recommended for clinical application. The clinician can decide which test is most appropriate for their clinical setting.

In this guideline, we did not compare AMH and AFC with each other nor studied the added effect of using both tests for ovarian response prediction. However, the IPD meta-analysis did demonstrate that these tests do have added value to female age alone. Moreover, there was no difference in the performance of these tests and combining them did not improve the prediction of ovarian response (Broer, et al., 2013, Broer, et al., 2013).

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. This implies that only very few women will have such an abnormal FSH or Inhibin B test results. This results in hardly any clinical value, especially since there are other tests available with a higher accuracy. Age also has some predictive value, however assessment of ovarian response category by age alone is not sufficiently reliable. Basal oestradiol and BMI alone are not predictors of ovarian response. Therefore, we recommend not using basal FSH, inhibin B, basal oestradiol, age or BMI for the prediction of ovarian response.

As all original studies have been performed using different assays or ranges for AFC and AMH, it is not possible to combine these data to calculate cut-offs for the prediction of a poor or high response. Regarding the use of AMH and AFC for individualised gonadotropin dose selection, the reader is referred to the Cochrane review by Lensen et al. since this was not investigated in this guideline (Lensen, et al., 2017).

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2. Additional hormonal assessment at baseline

KEY QUESTION: WHAT IS THE PROGNOSTIC VALUE OF HORMONAL ASSESSMENT AT BASELINE?

2.1 BASELINE OESTRADIOL

Assessment of oestradiol at initiation of stimulation is frequently performed in IVF/ICSI and an elevated level usually signifies the presence of a simple follicular cyst, which is then confirmed at ultrasound. However, prediction of the outcome of stimulation has also been attempted using E2 level at initiation of stimulation.

Evidence

One retrospective study in patients with unexplained infertility undergoing ovarian stimulation and intercourse shows a significantly lower chance of pregnancy in women with higher oestradiol levels at initiation of stimulation (Costello, et al., 2001).

Conclusion

No recommendation can be given in view of the total lack of evidence on the prognostic role of baseline oestradiol in women undergoing ovarian stimulation for IVF/ICSI.

2.2 PROGESTERONE

In a proportion of cycles, progesterone remains elevated at menstruation. Elevated progesterone levels at the intended starting date of ovarian stimulation could be associated with reduced pregnancy rates. The proportion of patients with progesterone levels >1.6 ng/ml on cycle day 2 was 4.9% (95% CI 3.2-7.4) in a cohort study by Kolibianakis et al. (2004) and 6.2% (95% CI 4-9) in a cohort study by Blockeel et al. (Blockeel, et al., 2011, Kolibianakis, et al., 2004). A more recent study by Hamdine et al. reported 13.3% (95% CI 8-20) of patients with progesterone levels >1.5 ng/ml. Faulisi et al. reported 0.3% (95% CI 0.01-1.15) of patients with progesterone levels >1.6 ng/ml on cycle day 3 (Faulisi, et al., 2017, Hamdine, et al., 2014). Due to the low incidence it seems unnecessary to evaluate this research question for progesterone levels >1.6 ng/ml on cycle day 3.

Evidence

A recent meta-analysis combining three prospective cohort studies (1052 women) reported that elevated progesterone level (>1.5-1.6 ng/ml) on cycle day 2 prior to initiation of stimulation is associated with a 15% decreased probability of ongoing pregnancy in patients treated by gonadotrophins and GnRH antagonist for IVF (risk difference -0.15, 95% CI -0.23 to 0.07) (Hamdine, et al., 2014). A more recent retrospective cohort study (418 women, 461 cycles) also reported lower live birth rates of 18.2% (2/11) and 16.7% (1/6) with progesterone < or >1.5 on hCG day respectively, in

patients with elevated (>1.5) levels at the start of ovarian stimulation, compared to 33.8% in controls (progesterone <1.5 both at the start of OS and on hCG day) (Panaino, et al., 2017).

Fausili et al. showed that progesterone assessment on day 3 of stimulation is inaccurate in predicting clinical pregnancy (ROC-AUC 0.54, 95%CI 0.47-0.61) (Faulisi, et al., 2017).

Recommendation

Assessment of progesterone level on day 2 of the cycle at the start of ovarian stimulation is probably not recommended.

Conditional ⊕○○○

Justification

Assessment of progesterone prior to initiation of stimulation on cycle day 2 in women undergoing ovarian stimulation with GnRH antagonist and gonadotrophins may be beneficial to identify cases with a lower than normal 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. Moreover, as a diagnostic test it has no meaningful and evidence-based link to a change of the treatment strategy, in order to undo the potential negative effect on prognosis. Also, cycle cancellation or delaying stimulation initiation has not been shown to improve clinical outcomes. However, since a blood test is required at initiation of stimulation (cycle day 2), progesterone assessment can be incorporated in the patient evaluation prior to FSH administration. The recommendation is not applicable to patients >39 years of age.

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3. Pre-treatment therapies

KEY QUESTION: DOES HORMONE PRE-TREATMENT IMPROVE EFFICACY AND SAFETY OF OVARIAN STIMULATION?

Pre-treatment therapies aim to suppress or to reduce LH and/or FSH secretion prior to gonadotrophin stimulation in IVF cycles. They are used by clinicians for different purposes such as synchronisation of follicular development, prevention of occurrence of early large follicle or spontaneous LH-surge, reduction of cyst formation. Pre-treatment is also used for scheduling IVF cycles for the benefit of clinicians and people in the laboratory as well as patients. It allows to plan IVF activity within weeks and months and to avoid work on weekends and holidays. The use of pre-treatment for scheduling purpose is not addressed in this guideline.

3.1 OESTROGEN PRE-TREATMENT

Evidence

A Cochrane meta-analysis on oestrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques (ART) combined four RCTs including 744 women. When oestrogen pre-treatment was compared with no pre-treatment in GnRH antagonist protocols, there was no difference between the groups in rates of live births/ongoing pregnancy rate (2 RCT, OR 0.79, 95% CI 0.53-1.17, 502 women), clinical pregnancy rate (4 RCT, OR 0.91, 95% CI 0.66-1.24, 688 women) (Farquhar, et al., 2017).

Significantly more oocytes were retrieved in the group treated with oestrogen compared to no intervention in GnRH antagonist protocol (2 RCT, MD 2.23, 95% CI 0.71 to 3.75, 139 women) (Farquhar, et al., 2017).

One RCT, more recent than the meta-analysis, including 140 women compared oestrogen pre-treatment with no pre-treatment in the GnRH antagonist protocol and reported no significant difference in clinical pregnancy rate (42.9% (27/63) vs. 34.3% (24/70)) or number of mature oocytes retrieved (10.71±3.73 vs. 10.40±4.38). No cases of OHSS occurred (Shahrokh Tehrani Nejad, et al., 2018).

Recommendation

Pre-treatment with oestrogen before ovarian stimulation using the GnRH antagonist protocol is probably not recommended for improving efficacy and safety.

Conditional ⊕○○○

Justification

There is no evidence of a beneficial effect on live birth rate/ongoing pregnancy rate using oestrogen as pre-treatment in GnRH antagonist protocol, compared to no pre-treatment. The evidence regarding the effect of oestradiol pre-treatment on the number of oocytes retrieved is conflicting.

This recommendation is not restricted to a specific group of women, although women with premature ovarian insufficiency (POI) and PCOS were excluded from the meta-analysis by Farquhar et al. (Farquhar, et al., 2017).

3.2 PROGESTOGEN PRE-TREATMENT

Evidence

The Cochrane meta-analysis, mentioned before, also investigated the effect of progesterone pre-treatment for OS in 4 RCTs including 421 women. When progestogen pre-treatment was compared with no intervention, there was no difference between the groups in live birth/ongoing pregnancy rate in GnRH agonist protocols (2 RCT, OR 1.35, 95% CI 0.69-2.65, 222 women). There was insufficient evidence to determine whether there was a difference in live birth/ongoing pregnancy rate in the GnRH antagonist protocol (1 RCT, OR 0.67, 95% CI 0.18-2.54, 47 women) (Farquhar, et al., 2017).

There was insufficient evidence to determine whether pre-treatment with progestogen resulted in a difference between the groups in the mean number of oocytes retrieved, both in GnRH agonist (2RCT, MD -0.52, 95%CI -2.07 to 1.02 and GnRH antagonist protocols (1 RCT, MD 2.70, 95% CI -0.98 to 6.38) (Farquhar, et al., 2017).

Recommendation

Pre-treatment with progesterone before ovarian stimulation is probably not recommended for improving efficacy and safety.

Conditional ⊕⊕○○

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

Justification

The available evidence indicates no beneficial effect on live birth/ongoing pregnancy rate, using progestogen as pre-treatment in GnRH agonist nor GnRH antagonist protocols. There is low quality evidence of an increased clinical pregnancy rate with progestogen pre-treatment in GnRH agonist protocols.

This recommendation is not restricted to a specific group of women, although women with PCOS were excluded from the meta-analysis by Farquhar et al. (Farquhar, et al., 2017).

3.3 COMBINED ORAL CONTRACEPTIVE PILL PRE-TREATMENT

Evidence

In the GnRH antagonist protocol with COCP pre-treatment (12-28 days), the rate of live birth/ongoing pregnancy was lower than with no pre-treatment (6 RCT, OR 0.74, 95% CI 0.58-0.95, 1335 women).

There was no evidence of a difference between the groups in OHSS rates (2 RCT, OR 0.98, 95% CI 0.28-3.40, 642 women) or number of oocytes (6 RCT, MD 0.44, 95% CI -0.11 to 0.99) (Farquhar, et al., 2017).

In a subgroup of poor responders (80 women) there was no difference for live birth/ongoing pregnancy rate (1 RCT, OR 1.71, 95% CI 0.61-4.79) or number of oocytes (1 RCT, MD 0.70, 95% CI -0.11 to 1.51) (Farquhar, et al., 2017, Kim, et al., 2011).

One RCT, more recent than the meta-analysis, including 140 women compared COCP pre-treatment (10 days) with no pre-treatment in the GnRH antagonist protocol and reported no significant difference in clinical pregnancy rate (39.6% (21/53) vs. 34.3% (24/70)) or number of mature oocytes retrieved (10.55±3.38 vs. 10.40±4.38). No cases of OHSS occurred (Shahrokh Tehrani Nejad, et al., 2018).

Recommendations

COCP pre-treatment (12-28 days) is not recommended in the GnRH antagonist protocol because of reduced efficacy.

Strong

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Justification

There is moderate quality evidence of a lower live birth/ongoing pregnancy rate using COCP pre-treatment in GnRH antagonist protocols compared with no pre-treatment. There is low-quality evidence regarding OHSS incidence. However, a small RCT showed no effect on clinical pregnancy rate when a short COCP pre-treatment (10 days) was applied (Shahrokh Tehrani Nejad, et al., 2018).

The type of COCP pre-treatment used in the studies was heterogenous regarding the oestrogen and progestogen components, as well as the starting days or duration of COCP. The duration varied from 12 to 28 days, and 3 consecutive cycles in one study. In some studies, the duration was fixed and variable in others, depending on the purpose of scheduling or not (Farquhar, et al., 2017). Another important condition with heterogeneity between studies is the wash-out period between the stop of COCP pre-treatment and the start of stimulation. This may have an important impact on hormonal environment (Cedrin-Durnerin, et al., 2007).

Lastly, it is important to note however that the available evidence comes predominantly from rFSH stimulation in GnRH-antagonist protocols and the usage of ethinyl oestradiol combined with either levonorgestrel or desogestrel as COCP. Whether a negative COCP effect exists in other treatment protocols or when using other COCPs is unknown.

3.4 GNRH ANTAGONIST PRE-TREATMENT

Evidence

One small RCT in 69 normogonadotropic women (not PCOS, not-poor responder) reported no difference in ongoing pregnancy rate (42% vs. 33%, 95% CI -13-3) and number of oocytes (12.8±7.8 vs. 9.9±4.9) comparing early follicular pre-treatment with GnRH antagonist (delayed start protocol) compared to no pre-treatment in fixed antagonist protocol (Blockeel, et al., 2011).

Similar results were reported by DiLuigi et al. in 54 predicted poor responder patients, who showed no difference in live birth rate (23.1% (6/26) vs. 25% (7/28)) or number of retrieved oocytes (5.2±4.0 vs. 5.4±4.7)-with the delayed start protocol (DiLuigi, et al., 2011).

In Bologna poor responders, there are conflicting results from 2 RCTs. One small RCT in 160 Bologna poor responder patients reported significantly higher clinical pregnancy rate (30% (24/80) vs. 10% (8/80)) and number of oocytes (4.3±2.5 vs. 2.4±2.1) with the delayed start protocol in GnRH antagonist protocol but after preparation with COCP and oestradiol (Maged, et al., 2015). However, a more recent small RCT including 60 Bologna poor responders showed no significant difference in clinical pregnancy rate (13.3% (4/30) vs. 3.3% (1/30)) or number of retrieved oocytes (3.63±3.02 vs. 5.06±4.37) comparing the delayed-start with conventional start GnRH antagonist protocol (Aflatoonian, et al., 2017).

Recommendation

GnRH antagonist pre-treatment before ovarian stimulation in a delayed-start gonadotrophin protocol is probably not recommended.

Conditional ⊕○○○

Justification

There is very low-quality evidence that ongoing pregnancy rate per embryo transfer and number of oocytes are not statistically different with GnRH antagonist pre-treatment in young normogonadotropic women (Blockeel, et al., 2011). In poor responder patients, evidence on the beneficial effect of the delayed start protocol is conflicting (Aflatoonian, et al., 2017, DiLuigi, et al., 2011, Maged, et al., 2015). There is no research for PCOS patients.

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PART B: LH suppression and ovarian stimulation

4. Ovarian stimulation protocols

KEY QUESTION: ACCORDING TO PREDICTED RESPONSE-BASED STRATIFICATION, WHICH STIMULATION PROTOCOL IS MOST EFFICIENT AND SAFE?

A. HIGH RESPONDER

4A.1 GNRH ANTAGONIST VS GNRH AGONIST

Evidence

We did not find a meta-analysis including RCTs or RCTs in non-PCOS high responders.

A meta-analysis including PCOS women, randomized to either the use of a GnRH antagonist or long GnRH agonist protocol, demonstrated a comparable live birth rate (3 RCT, RR 0.90, 95% CI 0.69–1.19, 363 women) (Lambalk, et al., 2017). The use of GnRH antagonist significantly reduced the risk of OHSS as compared to the GnRH agonist protocol (9 RCT, RR 0.53, 95% CI 0.30–0.95, 1294 women) (Lambalk, et al., 2017).

One RCT, not included in the meta-analysis, including 90 PCOS patients, compared the long GnRH agonist with the GnRH antagonist protocol (Trenkic, et al., 2016). There was no significant difference in clinical pregnancy rate (44.4% (20/45) vs. 46.7% (21/45)) or OHSS rate (15.6% (7/45) vs. 6.7% (3/45)) between the long GnRH agonist and GnRH antagonist protocol (Trenkic, et al., 2016).

One RCT published after the meta-analysis, including 22 PCOS patients, also compared the long GnRH agonist protocol with the conventional GnRH antagonist protocol and reported no significant difference in moderate-to-severe OHSS (27.3% (3/11) vs. 18.2% (2/11)), clinical pregnancy rate (22.2% (2/9) vs. 11.1% (1/9)) or number of oocytes retrieved (19 (2–46) vs. 12 (0–47)) (Shin, et al., 2018).

Recommendation

The GnRH antagonist protocol is recommended for PCOS women with regards to improved safety and equal efficacy.

Strong

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The GnRH antagonist protocol is recommended for predicted high responders with regards to improved safety and equal efficacy.

GPP

Justification

Evidence indicates that GnRH antagonist protocol is as effective as the GnRH agonist protocol, and significantly reduces the risk of OHSS in PCOS women.

Even though there is no specific evidence on predicted non-PCOS high responders or PCOM patients, consensus of the guideline group is that GnRH antagonist protocol should be recommended in these patient groups, as this protocol allows for the best options for prevention of the OHSS in these patient groups.

4A.2 MILD STIMULATION

Mild ovarian stimulation for IVF is defined as a protocol in which the ovaries are stimulated with gonadotropins, and/or other pharmacological compounds, with the intention of developing a few follicles (GLOSSARY). The definition of mild stimulation in studies and practice is variable. The conventional daily dose of FSH is 150-225 IU, while mild stimulation is achieved by using a lower dose of FSH, or a delayed start.

4A.2.1 CLOMIPHENE CITRATE (CC)

Evidence

We did not retrieve any RCTs comparing clomiphene citrate (CC) alone or as part of a OS protocol in high responders. However, there is evidence from a prospective cohort study with a retrospective control group (Saleh, et al., 2014) and a retrospective study in PCOS patients (Jiang and Kuang, 2017) and one case-control study in previous excessive responders (Lin et al., 2007) investigating CC as part of a OS protocol.

In the prospective study by Saleh et al. (including 128 PCOS patients) the study group received a stimulation protocol consisting of CC, combined with a GnRH antagonist and rFSH, compared to GnRH antagonist with rFSH in the control group (Saleh, et al., 2014). There was no significant difference in the clinical pregnancy rate (43.8% vs. 45.3%), number of oocytes retrieved (7.7 ± 1.3 vs. 8.1 ± 1.4) or number of mature oocytes (5.7 ± 1.1 vs. 6.1 ± 1.3) between the study group and the control group (Saleh, et al., 2014). In the retrospective study by Jiang et al. (174 PCOS patients) the study group received a stimulation protocol consisting of CC combined with medroxyprogesterone acetate (MPA) and hMG, compared to MPA with hMG in the control group (Jiang and Kuang, 2017). There were significantly more oocytes retrieved (13 (0–42) vs. 5 (0–30)) and mature oocytes (11 (0–35) vs. 4 (0–26)) in the control group as compared to the study group. There were no cases of moderate or severe OHSS in either group (Jiang and Kuang, 2017).

In the case-control study by Lin et al., 50 women with previous excessive response when stimulated with a GnRH agonist long protocol, underwent stimulation with CC combined with GnRH antagonist and hMG (Lin, et al., 2007). There was a significant difference in live birth rate/ongoing pregnancy rate (0%

(0/50) vs. 38% (19/50)) and moderate OHSS (16% (8/50) vs. 2% (1/50)). There was however no difference in severe OHSS (2% (1/50) vs. 0% (0/50)) (Lin, et al., 2007).

Recommendation

The addition of Clomiphene Citrate to gonadotropins in stimulation protocols is probably not recommended for predicted high responders	Conditional ⊕○○○
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Conclusion

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. Based on the lack of good-quality evidence, the guideline group does not recommend the use of CC in stimulation protocols for predicted high responders.

4A.2.2 AROMATASE INHIBITORS

Evidence

One retrospective study in 181 PCOS patients was retrieved, investigating the effect of letrozole addition in the long GnRH agonist protocol compared to no letrozole, reported no significant differences in OHSS rate (7.8% (8/103) vs. 2.6% (2/78)), clinical pregnancy rate (47.4% (27/57) vs. 60.5% (23/38)), or the number of oocytes retrieved (18.9±6.4 vs. 19.9±6.2) (Chen, et al., 2018).

Recommendation

There is insufficient evidence to recommend the addition of letrozole to gonadotropins in stimulation protocols for predicted high responders	Conditional ⊕○○○
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Justification

There is only limited evidence from non-randomised studies for the addition of letrozole to FSH for OS indicating that there is no benefit in terms of efficacy and safety. Based on the lack of good-quality evidence, the guideline group does not recommend the use of letrozole in stimulation protocols for predicted high responders. Moreover, use of letrozole is off-label for ovarian stimulation and safety concerns have been raised regarding possible teratogenicity associated with letrozole.

4A.2.3 REDUCED DOSE PROTOCOL

Evidence

One RCT, including 521 predicted high responders, compared mild stimulation (100 IU FSH) with conventional (150 IU FSH) stimulation either in a GnRH agonist or GnRH antagonist protocol (Oudshoorn, et al., 2017). Comparable rates of ongoing pregnancy within 18 months of FU resulting in live birth were reported (66.3% vs. 69.5%; RR 0.953, 95% CI 0.85–1.07) and 1st cycle live birth (fresh and

cryopreserved embryos) (36.0% vs. 39.1%). Mild stimulation resulted in significantly lower OHSS rate (5.2% vs. 11.8%) as compared with conventional ovarian stimulation (Oudshoorn, et al., 2017).

Recommendation

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 ⊕○○○

Justification

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. However, the mix of GnRH agonist and antagonist protocols, the per protocol allowance of dose adjustments in 2nd cycle and the very high cycle cancellation rate in high responders should be carefully considered when interpreting the available evidence. Furthermore, the fact that a freeze-all policy was not adopted in the trial, a strategy which may reflect current clinical practice, questions the potential negative effects of conventional dosage stimulation in terms of cumulative pregnancy rate and OHSS rates.

4A.3 MODIFIED NATURAL CYCLE

Modified natural cycle (MNC) for IVF is defined as a procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle. Pharmacological compounds are administered with the sole purpose of blocking the spontaneous LH surge and/or inducing final oocyte maturation (GLOSSARY).

There is no evidence to justify the use of NC or MNC for OS in high responders.

B. NORMAL RESPONDER

4B.1 GNRH ANTAGONIST VS GNRH AGONIST

Evidence

The meta-analysis by Lambalk et al., mentioned before, also compared the GnRH antagonist with the GnRH agonist protocol in the general population (supposedly normal responders) and reported no difference in live birth rate (10 RCT, RR 0.91, 95% CI 0.79–1.04, 1590 women) (Lambalk, et al., 2017). However, a significantly lower risk of OHSS (22 trials, RR 0.63, CI 0.50–0.81, 5598 women) was found with the use of GnRH antagonists compared to the long GnRH agonist protocol (Lambalk, et al., 2017).

Recommendation

The GnRH antagonist protocol is recommended for predicted normal responder women with regards to improved safety.

Strong ⊕⊕○○

Justification

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 antagonist protocol in the general IVF population, the GnRH antagonist protocol is recommended in normal responder patients.

4B.2 MILD STIMULATION

4B.2.1 CLOMIPHENE CITRATE (CC)

Evidence

A meta-analysis was found, investigating the effect of CC as part of a OS protocol in women without expected poor response (Bechtejew, et al., 2017). However, we could not verify whether the study population in the individual studies were normal or high responders. Therefore, this meta-analysis was excluded.

One cohort study was identified, including 25 ‘good prognosis patients’, comparing a protocol with clomiphene citrate addition to GnRH antagonist protocol. Significantly less oocytes were retrieved with the CC addition protocol (6.4 ± 0.7 vs. 10.7 ± 0.9). However, there was no difference in clinical pregnancy rate between CC addition and GnRH antagonist protocol (27.3% (6/22) vs. 49.0% (24/49) (Zander-Fox, et al., 2018).

Conclusion

There is no evidence to support the recommendation for the use of Clomiphene Citrate in stimulation protocols for predicted normal responders.

Justification

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. The only study that was retrieved was a non-randomized pilot study. Therefore, the conclusions from these studies could not be extrapolated.

4B.2.2 AROMATASE INHIBITORS

Evidence

A small RCT with only 20 patients randomized, investigated the addition of letrozole to FSH in an GnRH antagonist protocol for OS (Verpoest, et al., 2006). No significant differences were reported in ongoing pregnancy rate (50% (5/10) vs. 20% (2/10)) or number of oocytes retrieved (13.8 ± 9.2 vs. 9.6 ± 7.7) in the letrozole + FSH group compared to the FSH only group (Verpoest, et al., 2006).

A small RCT including 94 women also investigated the addition of letrozole to FSH in an GnRH antagonist protocol for OS (Mukherjee, et al., 2012). No differences were reported in clinical pregnancy rate (36% (15/42) vs. 33% (17/52)) or number of mature oocytes (4.6 ± 2.5 vs. 4.9 ± 2.3). There were no cases of OHSS in the letrozole group compared to 7 in the control group (Mukherjee, et al., 2012).

Recommendation

The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted normal responders.	Conditional ⊕○○○
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Justification

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.

4B.2.3 REDUCED DOSE PROTOCOL

Evidence

A meta-analysis including 5 RCTs (960 women) investigated the effect of 100 compared to 200 IU/day of rFSH for OS and reported no significant difference in clinical pregnancy rate (OR 0.95, 95% CI 0.69-1.30) or risk of OHSS (OR 0.58, 95% CI 0.18-1.90) (Sterrenburg, et al., 2011). However, significantly less oocytes were retrieved with the lower dose (MD -3.5, 95% CI -4.86 to -2.27) (Sterrenburg, et al., 2011).

Three RCTs compared the late-start FSH (fixed dose of 150 IU starting on cycle day 5) with conventional-start FSH (Baart, et al., 2007, Blockeel, et al., 2011, Hohmann, et al., 2003). The RCT by Baart et al. compared late-start FSH in the GnRH antagonist protocol with conventional FSH stimulation in the long GnRH agonist protocol in 111 women and reported no significant difference in ongoing pregnancy rate (19% (12/63) vs. 17% (7/41)). However, significantly less oocytes retrieved with the late-start FSH protocol (8.3±4.7 vs. 12.1±5.7) (Baart, et al., 2007). The RCT by Hohmann et al. including 104 predicted normal responders, compared late-start with conventional-start FSH in the GnRH antagonist protocol and reported no difference in ongoing pregnancy rate (16% (8/49) vs. 17% (8/48) or number of oocytes retrieved (7 (1-27) vs. 8 (2-31)) (Hohmann, et al., 2003). The RCT by Blockeel et al. including 76 predicted normal responders also compared late-start with conventional-start FSH in the GnRH antagonist protocol and also reported no significant difference in ongoing pregnancy rate (25% 10/40 vs. 28% (10/36) (Blockeel, et al., 2011).

Recommendation

A reduced gonadotrophin dose is probably not recommended over a conventional gonadotrophin dose for predicted normal responders.	Conditional ⊕⊕○○
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Justification

The meta-analysis suggests that the optimal daily rFSH stimulation dose is 150 IU/day in predicted normal responders. 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.

The recommendation is based on studies conducted in GnRH agonist protocols, however, the guideline group thinks that the recommendation may also apply to GnRH antagonist protocol due to the increased safety with the option of the GnRH agonist trigger.

C. POOR RESPONDER

4C.1 GNRH ANTAGONIST VS GNRH AGONIST

Evidence

The meta-analysis by Lambalk et al., mentioned before, also compared the GnRH antagonist with the long GnRH agonist protocol in poor responders and did not show any difference in live birth rates (3 RCT, RR 0.89, 95% CI 0.56–1.41, 544 women) (Lambalk, et al., 2017).

Another meta-analysis compared the GnRH antagonist with the short GnRH agonist protocol in poor responders (Xiao, et al., 2013). There was no statistically significant difference in the clinical pregnancy rate (7 RCT, OR 1.33, 95% CI 0.88-2.01, 735 women) between the GnRH antagonist group and the short GnRH agonist protocol group. However, significantly fewer oocytes were retrieved in the GnRH antagonist group (5 RCT, MD -0.54, -0.98 to -0.10, 417 women) (Xiao, et al., 2013).

An RCT, more recent than the meta-analysis, including 146 poor responders also compared the short GnRH agonist with the GnRH antagonist protocol (Schimberni, et al., 2016). The clinical pregnancy rate was significantly higher with the short GnRH agonist protocol as compared to the GnRH antagonist protocol (29.3% (22/75) vs. 14.1% (10/71)). There was no significant difference in number of oocytes retrieved between groups (3.8±2.4 vs. 3.4±1.9) (Schimberni, et al., 2016).

Two RCTs, including respectively 90 and 440 poor responders compared the microdose flare-up GnRH agonist with the GnRH antagonist protocol (Demirel and Gurgan, 2009, Merviel, et al., 2015). Demirel et al. reported no significant difference in clinical pregnancy rate (28.6% (12/42) vs. 15% (6/40)) However, significantly less mature oocytes were retrieved in the GnRH antagonist protocol group (4.3±2.1 vs. 3.1±1.1) (Demirel and Gurgan, 2009). Merviel et al. reported no significant difference in ongoing pregnancy rate (14.6% vs. 14.2%) or number of oocytes retrieved (6.0±4.1 vs. 6.2±4.9) (Merviel, et al., 2015).

Recommendation

GnRH antagonists and GnRH agonists are equally recommended for predicted poor responders.	Conditional ⊕⊕○○
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Justification

In women with poor ovarian response, no differences exist in terms of safety and efficacy between the GnRH agonist and GnRH antagonist protocol. The GnRH antagonist protocol is associated with a shorter length of treatment compared to the long GnRH agonist protocol.

4C.2 MILD STIMULATION

4C.2.1 CLOMIPHENE CITRATE (CC)

Evidence

Studies comparing CC with the standard of care (FSH ovarian stimulation) are very scarce. Only one RCT, including 249 poor responder women, has compared CC with a short GnRH agonist FSH protocol and showed similar live birth rate (5/145 vs. 7/146; RR 0.72, 95% CI 0.23-2.21) (Ragni, et al., 2012).

The meta-analysis by Bechtejew et al. mentioned before, also investigated the combination of CC and gonadotrophins in an GnRH antagonist protocol and reported that it was not superior to gonadotrophins in an GnRH agonist protocol in terms of live birth rate (3 RCT, RR 0.88, 95% CI 0.62–1.26, 874 women) (Bechtejew, et al., 2017).

An RCT not included in the meta-analysis, also investigating the combination of CC and gonadotrophins in an antagonist protocol in 250 poor responders. A significantly lower clinical pregnancy rate (5.9% vs. 14.1%) was reported with CC addition compared to no CC, which was not associated with a difference in the number of oocytes retrieved (3.8 ± 2.9 vs. 3.41 ± 1.9) (Schimberni, et al., 2016).

Recommendation

Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are equally recommended for predicted poor responders.	Strong ⊕⊕○○
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Justification

In women with poor ovarian response, no differences were reported in terms of safety and efficacy between CC alone, CC in combination with gonadotropins or gonadotropin stimulation alone.

4C.2.2 AROMATASE INHIBITORS

Evidence

In the meta-analysis by Bechtejew, mentioned before, letrozole with FSH in a GnRH antagonist protocol did not differ from conventional ovarian stimulation for IVF/ICSI in terms of clinical pregnancy rates (2 RCT, RR 0.94, 95% CI 0.43-2.03, 155 women). Also, no significant difference was observed in the number of oocytes retrieved (2 RCT, MD, -0.06, 95% CI, -0.66 to 0.54, 155 women) (Bechtejew, et al., 2017).

After publication of the meta-analysis, an RCT was published also investigating the addition of letrozole to rFSH in an GnRH antagonist protocol in 70 Bologna poor responders (Ebrahimi, et al., 2017). There was no difference in clinical pregnancy rate (14.3% (5/35) vs. 11.4% (4/35)) or the number of oocytes retrieved (2.80 ± 1.09 vs. 2.60 ± 1.51) with or without letrozole addition (Ebrahimi, et al., 2017).

One RCT was found comparing the addition of letrozole with the addition of CC to gonadotropins in an GnRH antagonist protocol in 184 poor responder women and reported no significant difference in clinical pregnancy rate between groups (11.3% (9/87) vs. 8% (7/80)) (Eftekhari, et al., 2014).

Recommendation

The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted poor responders.	Conditional ⊕⊕○○
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Justification

Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of OS. There are no studies comparing the use of letrozole alone with gonadotropin stimulation alone for IVF/ICSI. Moreover, use of letrozole is off-label for ovarian stimulation and safety concerns have been raised regarding possible teratogenicity associated with letrozole.

4C.2.3 REDUCED DOSE PROTOCOL

Evidence

No studies were found comparing a reduced FSH dose (<150 IU/day) to conventional FSH stimulation in poor responders.

4C.3 HIGHER GONADOTROPIN DOSE

Evidence

A Cochrane meta-analysis including 5 RCTs, including poor responder women, investigated direct gonadotropin dose comparisons (Lensen, et al., 2017).

150 IU vs 300/450 IU

The Cochrane meta-analysis reported no significant difference in live birth/ongoing pregnancy rates (2 RCT, OR 0.71, 95% CI 0.32-1.58, 286 women) between the 150 IU and 300/450 IU dose of gonadotropins and no cases of moderate or severe OHSS were observed in either group. However, slightly more oocytes were retrieved in the higher gonadotropin dose group (2 RCT, MD 0.69, 95% CI 0.5 to 0.88, 286 women) (Lensen, et al., 2017).

300 IU vs 400/450 IU

The Cochrane meta-analysis reported no significant difference in ongoing pregnancy rate (1 RCT, OR 0.77, 95% CI 0.19-3.19, 62 women) or number of oocytes retrieved (2 RCT, MD -0.03, 95% CI -0.30 to 0.24, 110 women) between the 300 IU and 400/450 IU dose of gonadotropins and no cases of moderate or severe OHSS in either group (Lensen, et al., 2017).

450 IU vs 600 IU

The Cochrane meta-analysis reported no significant difference in live birth rate (1 RCT, OR 1.33, 95% CI 0.71-2.52, 356 women) or number of oocytes retrieved (1 RCT, MD 0.08, 95% CI -0.04 to 0.20, 356 women) between the 450 IU and 600 IU dose of gonadotropins and one case of moderate OHSS in the 600 IU dose group (Lefebvre, et al., 2015, Lensen, et al., 2017).

Recommendation

It is unclear whether a higher gonadotropin dose is recommended over 150 IU for predicted poor responders.	Conditional ⊕○○○
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Justification

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.

A gonadotropin dose higher than 300 IU is not recommended for predicted poor responders.	strong ⊕○○○
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Justification

There is unlikely to be significant benefit with doses > 300 IU daily, as comparisons with doses >300 IU did not show significant differences in the above mentioned pre-clinical outcomes.

4C.4 MODIFIED NATURAL CYCLE

Evidence

One RCT compared modified natural cycle with a microdose GnRH agonist flare protocol in 125 poor responder women (215 cycles) and reported no significant difference in pregnancy rate (6.1% vs. 6.9%) (Morgia, et al., 2004).

Recommendation

The use of modified natural cycle is probably not recommended over conventional stimulation for predicted poor responders.	Conditional ⊕○○○
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Justification

There are no good-quality, controlled studies available to support the use of Modified natural cycle or Natural cycle IVF in poor responders.

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5. LH suppression regimes

KEY QUESTION: WHICH LH SUPPRESSION PROTOCOL IS PREFERABLE?

5.1 GnRH AGONIST PROTOCOLS

Evidence

A Cochrane meta-analysis including 37 RCTs compared different GnRH agonist protocols (Siristatidis, et al., 2015).

Long vs short GnRH agonist protocol

The Cochrane meta-analysis found no evidence of a difference in live birth (4 RCT, OR 1.60, 95% CI 0.85-3.03, 295 women) between the long and the short GnRH agonist protocol (Siristatidis et al., 2015). There were no data on adverse outcomes reported.

Two RCTs, not included in the Cochrane meta-analysis, including respectively 186 and 131 women also reported no significant difference in clinical pregnancy rate between the long and the short GnRH agonist protocol (respectively 20.2% vs. 16.3% and 19.6% vs. 8.3%) (Frydman, et al., 1988, Ravhon, et al., 2000).

However, another RCT, not included in the Cochrane meta-analysis, including 220 women ≥ 40 years of age, reported a significantly reduced clinical pregnancy rate with the short GnRH agonist protocol as compared to the long (10.9% (12/110) vs. 22.7% (25/110)) (Sbracia, et al., 2005).

A meta-analysis including 2656 women investigated the effect of uterine adenomyosis on IVF outcome in the long and the short GnRH agonist protocol (Vercellini, et al., 2014). When the long GnRH agonist protocol was adopted, clinical pregnancy rate was similar in women with and without adenomyosis (2 RCT, RR 1.05, 95% CI 0.75-1.48, 550 women). In contrast, when the short GnRH agonist protocol was adopted, clinical pregnancy rate was reduced in patients with adenomyosis (4 RCT, RR 0.58, 95% CI 0.38-0.88, 2106 women) (Vercellini, et al., 2014).

Long vs ultrashort GnRH agonist protocol

The Cochrane meta-analysis found no evidence of a difference in live birth rate when a long protocol was compared with an ultrashort GnRH agonist protocol (1 RCT, OR 1.78, 95% CI 0.72-4.36, 150 women) (Kingsland, et al., 1992, Siristatidis, et al., 2015). There were no data on adverse outcomes reported.

Short vs ultrashort GnRH agonist protocol

The Cochrane meta-analysis reported no evidence of a difference in the clinical pregnancy rate when a short protocol was compared with an ultrashort protocol (1 RCT, OR 1.33, 95% CI 0.47-3.81, 82 women) (Berker, et al., 2010, Siristatidis, et al., 2015). There were no data on adverse outcomes reported.

Long GnRH agonist protocol: luteal vs follicular start

The Cochrane meta-analysis found no evidence of a difference in live birth/ongoing pregnancy rates when GnRH agonist was commenced in the luteal or follicular phase for the long protocol (1 RCT, OR 1.89, 95% CI 0.87-4.10, 223 women) (Siristatidis, et al., 2015, Urbancsek and Witthaus, 1996). There were no data on adverse outcomes reported.

The RCT by Ravhon et al., including 125 women, also reported no significant difference in pregnancy rate when GnRH agonist was started on day 2 versus day 21 (19.6% vs. 18.6%) (Ravhon, et al., 2000).

Long GnRH agonist protocol: continuation vs stopping GnRH agonist at start of stimulation

The Cochrane meta-analysis found no evidence of a difference in the number of ongoing pregnancies (3 RCT, OR 0.75, 95%CI 0.42-1.33, 290 women) or OHSS (1 RCT, OR 0.47, 95% CI 0.04-5.35, 96 women) when GnRH agonist was stopped compared with when it was continued (Siristatidis, et al., 2015).

Long agonist protocol: continuation of same-dose vs reduced-dose GnRH agonist until trigger

The Cochrane meta-analysis found no evidence of a difference in pregnancy rate when the dose of GnRH agonist was reduced compared with when the same dose was continued (4 RCT, OR 1.02, 95% CI 0.68-1.52, 407 women) (Siristatidis, et al., 2015). There were no data on adverse outcomes reported.

Recommendation

If GnRH agonists are used, the long GnRH agonist protocol is probably recommended over the short or ultrashort GnRH agonist protocol.

Conditional ⊕⊕○○

Justification

The long GnRH agonist protocol has proven to be highly efficient for preventing LH surge. Since its introduction, there has been a reduction of cycle cancellation, increased number of oocytes retrieved and higher pregnancy rates. Compared to other GnRH agonist protocols, the long protocol provides better efficacy and is supported by a larger body of evidence.

The short GnRH agonist protocol appeared as a modification of the classic long protocol with the aim of improving cycle outcome in poor responders and older patients. The current evidence available shows that this goal is not achieved.

5.2 GNRH ANTAGONIST PROTOCOL

Evidence

A Cochrane meta-analysis including 73 RCTs, compared the GnRH antagonist protocol with the long GnRH agonist protocol (Al-Inany, et al., 2016). There was no evidence of a difference in live birth rate

following GnRH antagonist compared with GnRH agonist (12 RCT, OR 1.02, 95% CI 0.85-1.23, 2303 women). On the other hand, there was evidence of a lower OHSS rate in women who received GnRH antagonist compared with those treated with GnRH agonist (6% (290/4474) vs. 11% (396/3470); 36 RCT, OR 0.61, 95% CI 0.51-0.72, 7944 women) (Al-Inany, et al., 2016). A small RCT including 78 women, not included in the Cochrane meta-analysis reported no significant difference in clinical pregnancy rate (21.6% (8/37) vs. 36.0% (13/36)) between GnRH antagonist and GnRH agonist protocol (Friedler, et al., 2006). After the publication of the meta-analysis, an RCT including 1099 women was conducted, reporting no significant difference in live birth rate (22.2% (117/528) vs. 21.6% (107/495) between GnRH antagonist and GnRH agonist protocol (Toftager, et al., 2016). However, significantly fewer patients in the GnRH antagonist group had severe OHSS (5.1% (27/528) vs. 8.9% (44/495)) or moderate OHSS (10.2% (54/528) vs. 15.6% (77/495)) compared with the GnRH agonist group (Toftager, et al., 2016). In a post-hoc analysis of the trial, cumulative live birth rate was calculated, confirming that there was no significant difference between GnRH antagonist and GnRH agonist protocol (34.1% (182/534) vs. 31.2% (161/516); OR 1.14, 95% CI 0.88–1.48) (Toftager, et al., 2017). Another RCT published after the meta-analysis, including 132 women, reported a significantly higher clinical pregnancy rate with the long GnRH agonist protocol as compared to the GnRH antagonist protocol (49.2% vs. 26.2%). One case of mild OHSS developed in each group (Verpoest, et al., 2017).

Two RCTs including respectively 160 cycles and 96 women, compared the GnRH antagonist protocol with the short GnRH agonist protocol (Gordts, et al., 2012, Maldonado, et al., 2013). Gordts et al. reported an ongoing pregnancy rate of 21% and a live birth rate of 19% in GnRH antagonist cycles compared to 20% and 20% respectively in GnRH agonist cycles, which are both not statistically different (Gordts, et al., 2012). However, Maldonado et al. reported a significantly lower clinical pregnancy rate (31.0% (13/48) vs. 52.1% (25/48)) in the short GnRH agonist protocol as compared to the GnRH antagonist protocol (Maldonado, et al., 2013).

Recommendation

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

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Justification

The introduction of GnRH antagonist allowed overcoming the significant undesirable effects of the GnRH agonist protocols. 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. There is far less evidence for the short GnRH agonist protocol (2 RCTs), however, results are expected to be similar as for the long GnRH agonist protocol.

Regarding the moment of the introduction of the GnRH antagonist during stimulation, no differences in terms of cycle outcome have been shown between a fixed (day 6) compared to flexible (leading follicle of 14 mm) protocol (Escudero, et al., 2004).

5.3 PROGESTIN

The use of oral progestins to prevent LHs surge is a novel protocol in which GnRH analogues are not used. Progestin administration along the whole stimulation maintains the pituitary suppressed and has shown to prevent LH surge effectively. Nevertheless, the use of this protocol implies the freezing of all the embryos and transfer in a subsequent endometrial preparation cycle, as the endometrium would not be receptive in a fresh cycle due to the effect of the progestins.

Evidence

Three prospective cohort studies have been conducted, comparing the outcomes of progestin LH suppression to other protocols (Chen, et al., 2017, Hamdi, et al., 2018, Kuang, et al., 2015). Chen et al. reported no difference in live birth rate between a progestin protocol and a natural cycle (8.3% (10/102) vs. 3.92% (4/102)) in 204 women (Chen, et al., 2017). However, significantly more oocytes were retrieved after the progestin protocol (1.09 (0.93-1.18) vs. 0.76 (0.65-0.86)) (Chen, et al., 2017). Hamdi et al. compared a progestin protocol with a GnRH antagonist protocol in 99 women, and reported no significant difference in clinical pregnancy rate (23% vs. 27%) or number of oocytes retrieved (9.95±0.91 vs. 10.02±0.88) (Hamdi, et al., 2018). Kuang et al. reported no difference in live birth rate between progestin and short GnRH agonist protocol (42.6% (49/115) vs. 35.5% (50/141)) or number of oocytes retrieved (9.9±6.7 vs. 9.0±6.0) and none of the patients experienced moderate or severe OHSS during the study (Kuang, et al., 2015).

One RCT including 516 women compared dydrogesterone with MPA for LH suppression and reported no significant difference in clinical pregnancy rate (57.6 (125/217) vs. 62.3% (132/212); OR 0.82, 95% CI 0.56-1.21) or number of oocytes retrieved (10.8±6.3 vs. 11.1±5.8) (Yu, et al., 2018).

Recommendation

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 ⊕○○○

Justification

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. In addition, this approach is only feasible for OS cycles in which a fresh embryo transfer is not scheduled, such as fertility preservation, oocyte donors, or freeze-all cycles.

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6. Types of gonadotropins

KEY QUESTION: IS THE TYPE OF STIMULATION DRUG ASSOCIATED WITH EFFICACY AND SAFETY?

6.1 RECOMBINANT FSH (rFSH)

6.1.1 RECOMBINANT FSH (rFSH) VS HUMAN MENOPAUSAL GONADOTROPIN (hMG)

Evidence

A Cochrane meta-analysis including 3197 women, reported significantly fewer live births after rFSH as compared to hMG for ovarian stimulation (OS) (11 RCT, OR 0.84, 95% CI 0.72-0.99). The meta-analysis reported no difference in OHSS rate for rFSH compared to hMG (11 RCT, OR 1.00, 95% CI 0.58-1.71) (van Wely, et al., 2011).

Since the publication of the meta-analysis, a few RCTs have been published. An RCT including 749 women reported that highly purified hMG is at least as effective as rFSH in GnRH antagonist cycles in terms of cumulative live birth rate (40% vs. 38%). OHSS was experienced by 3% (10 women) in each treatment group (Devroey, et al., 2012). The most recent RCT included 160 women and also reported no significant differences in live birth rate (27.5% (11/40) vs. 40% (16/40)) between hMG and rFSH for OS (Parsanezhad, et al., 2017).

A small RCT including 80 PCOS patients reported no significant difference in live birth rate (23.1% vs. 35.7%) or mild OHSS rate (0.0% (0/38) vs. 11.9% (5/42)) between hMG and rFSH for OS (Figen Turkcapar, et al., 2013).

A small RCT including 127 women of advanced reproductive age reported no significant difference in live birth rate between hMG and rFSH groups (44.4% (28/63) vs. 29.7% (19/64)) (Ye, et al., 2012).

Recommendation

The use of recombinant FSH (rFSH) and human menopausal gonadotropin (hMG) for ovarian stimulation is equally recommended.

Strong

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Justification

The results from the meta-analysis suggest a slightly higher efficacy (LBR/PR) with hMG compared to rFSH in GnRH agonist cycles. However, according to the Cochrane meta-analysis, this difference is not considered clinically significant, and with no difference in safety, the GDG concluded that hMG is not superior to rFSH.

For GnRH antagonist cycles, the evidence is less extensive, however Devroey et al. showed highly purified hMG to be at least as effective as rFSH in antagonist cycles (Devroey, et al., 2012).

Studies for this question in PCOS and women of advanced age were limited, so that a potential difference between compounds in these subgroups cannot be ruled out based on the current evidence.

6.1.2 RECOMBINANT FSH (rFSH) VS PURIFIED FSH (p-FSH)

Evidence

In the Cochrane meta-analysis mentioned before, use of rFSH was not associated with a higher probability of live birth as compared to p-FSH when downregulation was achieved with GnRH agonists (5 RCT, OR 1.26, 0.96-1.64, 1430 women). The meta-analysis reported no significant difference in OHSS rate between rFSH and p-FSH (6 RCT, OR 1.79, 95% CI 0.89 to 3.62, 1490 women) (van Wely, et al., 2011).

Recommendation

The use of recombinant FSH (rFSH) and purified FSH (p-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended.

Strong

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Justification

In patients undergoing ovarian stimulation for IVF/ICSI, the use of p-FSH is not preferable to rFSH when downregulation is achieved with GnRH agonists, according to the Cochrane meta-analysis. Studies comparing the use of the two FSH preparations (p-FSH and rFSH) in GnRH antagonist cycles are not present to allow evaluation of this statement in such a setting.

6.1.3 RECOMBINANT FSH (rFSH) VS HIGHLY PURIFIED FSH (hp-FSH)

Evidence

In the Cochrane meta-analysis mentioned before, use of rFSH compared to hp-FSH was not associated with a higher probability of live birth/ongoing pregnancy (13 RCT, OR 1.03, 95% CI 0.86-1.22, 2712 women) when downregulation is achieved with GnRH agonists (van Wely, et al., 2011). The OHSS rate was also not significantly different between groups (16 RCT, OR 1.11, 95% CI 0.70-1.75, 3053 women) (van Wely, et al., 2011).

These observations have been further confirmed in subsequently published relevant RCTs in GnRH agonist cycles (Gholami, et al., 2010, Murber, et al., 2011, Parsanezhad, et al., 2017, Selman, et al., 2010, Selman, et al., 2013). Three RCTs including respectively 70, 127 and 160 women reported no significant difference in live birth rate between rFSH and hp-FSH (respectively 31.3% vs. 31.4%; 16.1% vs. 18.4% and 40% vs. 22.5%) (Murber, et al., 2011, Parsanezhad, et al., 2017, Selman, et al., 2013). Two RCTs reported no difference in clinical pregnancy rate between rFSH and hp-FSH (respectively 39.6% vs. 38.7% and 33.3% (21/65) vs. 39% (23/60)) (Gholami, et al., 2010, Selman, et al., 2010).

Two RCTs including respectively 84 and 160 women investigated the comparison of rFSH compared to hp-FSH in PCOS patients. There was no difference in clinical pregnancy rate (50% (21/42) vs. 50.2% (22/42) and 41.2% (33/80) vs. 45% (36/80)) or number of oocytes retrieved (13.83±7.07 vs. 17.1±8.66 and 13.03±5.56 vs. 14.17±4.89) between both groups (Aboulghar, et al., 2010, Sohrabvand, et al., 2012). Sohrabvand et al. also reported no difference in live birth rate (21.3% (17/80) vs. 23.8% (19/80)), slight OHSS (5% (4/80) vs. 6.3% (5/80)) or moderate to severe OHSS (2.5% (2/80) vs. 2.5% (2/80)) between groups (Sohrabvand, et al., 2012).

Recommendation

The use of recombinant FSH (rFSH) and highly purified FSH (hp-FSH) for ovarian stimulation in GnRH agonist protocol is equally recommended.

Strong

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Justification

In patients undergoing ovarian stimulation, the use of hp-FSH is not preferable to rFSH, when downregulation is achieved by GnRH agonists according to a Cochrane meta-analysis and confirmed in subsequently published studies. Studies comparing the use of the two FSH preparations (hp-FSH and rFSH) in GnRH antagonist cycles are not present to allow evaluation of this statement in such a setting.

Studies for this question in PCOS patients were limited, so that a potential difference between compounds in this subgroup cannot be ruled out based on the current evidence.

6.1.4 RECOMBINANT (rFSH) VS RECOMBINANT FSH + RECOMBINANT LH (rFSH+rLH)

Evidence

A Cochrane meta-analysis including 499 women found insufficient evidence to determine if there was a difference in live birth rate in patients treated with rFSH+rLH compared to those treated with rFSH only (4 RCT, OR 1.32, 95% CI 0.85-2.06) (Mochtar, et al., 2017). In a subgroup analysis in patients treated with GnRH agonists, although no difference has been observed in live birth rates between the two treatment groups compared (3 RCT, OR 1.73, 95% CI 0.95-3.16, 259 women), a higher probability of ongoing pregnancy has been observed with rLH addition (12 RCT, OR 1.27, 95% CI 1.02-1.57, 1980 women). The meta-analysis reported no difference in OHSS rate with rLH supplementation to rFSH compared to rFSH alone (6 RCT, OR 0.38, 95%CI 0.14-1.01, 2178 women). In a subgroup analysis in patients treated with GnRH agonists, a lower probability of OHSS has been observed with rLH addition (Mochtar, et al., 2017). An RCT, more recent than the meta-analysis, including 238 women also reported no difference in live birth rate with rLH supplementation to rFSH (RR 0.78, 95% CI 0.4-1.53) (Lahoud, et al., 2017).

In the meta-analysis, a small RCT in poor responders showed a beneficial effect of rLH pre-treatment to rFSH on live birth rate (OR 9.33, 95% CI 1.03-84.20, 43 women) (Ferraretti, et al., 2014, Mochtar, et al., 2017). However, a large RCT (939 women), more recent than the meta-analysis, reported no effect of rLH addition to rFSH in Bologna poor responders on live birth rate (10.6% (49/462) vs. 11.7% (56/477)) (Humaidan, et al., 2017). In this trial, only one event of mild early OHSS occurred in the rFSH+rLH group.

In the meta-analysis, one RCT including women of advanced reproductive age showed no effect of LH addition on live birth rate (OR 0.94, 95% CI 0.48-1.85, 240 women) (Mochtar, et al., 2017, Vuong, et al., 2015).

A small RCT, more recent than the meta-analysis, including 66 women with repeated implantation failure compared rFSH with rFSH+rLH for ovarian stimulation and reported significantly more clinical pregnancies with LH supplementation as compared to rFSH alone (20/29 vs. 9/32). However, there was

no significant difference in the number of retrieved oocytes (7.2 ± 4.8 vs. 7.3 ± 5.3) or mature oocytes (5.8 ± 4.0 vs. 5.9 ± 4.3) (Rahman, et al., 2017).

Conclusion

After extensive discussion, the GDG could not reach consensus with regards to rFSH+rLH, either as one compound or as separate preparations and decided not to formulate any recommendations on the topic.

Justification

According to the best available evidence, the addition of rLH to rFSH or the use of combination preparations of rLH and rFSH results in similar live birth rates compared to rFSH alone. For the general population, addition of rLH to rFSH is probably not recommended, however it could be applied in specific patient groups such as WHO-I anovulatory patients. Further studies would be necessary to strengthen this conclusion in GnRH antagonist treated patients.

Current evidence from a large RCT in poor responders indicated no beneficial effect of the combination of rLH and rFSH on live birth rate. Evidence from a small RCT in women of advanced age also showed no beneficial effect of LH supplementation on live birth rates.

The GDG would also like to point out that when comparing the different ovarian stimulation compounds, dosages or add-on treatments, the added benefit for the patient must be made clear compared to the more basic or standard option.

6.2 HIGHLY PURIFIED FSH (HP-FSH) VS HUMAN MENOPAUSAL GONADOTROPIN (HMG)

Evidence

Three RCTs including resp. 20, 80 and 218 women, compared hp-FSH with hMG for ovarian stimulation in the long GnRH agonist protocol and reported similar clinical pregnancy rate (10% (1/10) vs. 10% (1/10); 37.5% (15/40) vs. 45% (18/40) and 34% (35/104) vs. 36% (41/114)) and number of oocytes retrieved (8 (4-11) vs. 13 (4-23); 13.4 ± 0.6 vs. 13.7 ± 0.7 and 8.2 ± 4.7 vs. 9.5 ± 4.83) between both groups (Duijkers, et al., 1993, Parsanezhad, et al., 2017, Westergaard, et al., 1996).

Recommendation

The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for ovarian stimulation in GnRH agonist protocols is equally recommended.	Conditional ⊕⊕○○
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Justification

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, according to three RCTs.

6.3 HUMAN MENOPAUSAL GONADOTROPIN (HMG) VS RECOMBINANT FSH + RECOMBINANT LH (rFSH+rLH)

Evidence

In a small RCT including 122 patients undergoing ovarian stimulation with GnRH agonists, use of rFSH+rLH was not associated with increased pregnancy rate compared to hMG (28.3% (15/53) vs. 29.3 (17/58)). However, significantly more cycles were cancelled to prevent OHSS in the rFSH+rLH group compared to the hMG group (11.1% (7/53) vs. 1.7% (1/58)) (Pacchiarotti, et al., 2010).

Recommendation

The use of recombinant LH (rLH) + recombinant FSH (rFSH) for ovarian stimulation is probably not recommended over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety.

Conditional ⊕○○○

Justification

HMG and rFSH+rLH 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. The recommendation is not applicable to GnRH antagonist cycles.

6.3 AROMATASE INHIBITORS

The combining of the aromatase inhibitor letrozole with gonadotropin during OS has been suggested as a method to reduce the total gonadotropin requirement in IVF. In recent years, the use of letrozole along with gonadotropins has grown, particularly in women predicted to respond poorly to OS (Goswami, et al., 2004).

Evidence

Although substitution of FSH in the early follicular phase with letrozole has been examined in several RCTs, only a limited number has examined the substitution of FSH by letrozole for OS.

Three RCTs, including resp. 70, 20 and 50 women, investigated the effect of FSH substitution with letrozole for OS (Ebrahimi, et al., 2017, Verpoest, et al., 2006, Yasa, et al., 2013). Ebrahimi et al. and Verpoest et al. reported no difference in clinical pregnancy rate with letrozole substitution compared to no letrozole (resp. 14.3% (5/35) vs. 11.3% (4/35) and 50% (5/10) vs. 20% (2/10)) (Ebrahimi, et al., 2017, Verpoest, et al., 2006). Yasa et al. reported no difference in ongoing pregnancy rate with letrozole compared to no letrozole (20% (5/25) vs. 20% (5/25)) (Yasa, et al., 2013).

Recommendation

Letrozole is probably not recommended as a substitute for gonadotropins in poor responders.

Conditional ⊕○○○

Justification

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. The use of letrozole is off-label for OS.

6.4 CLOMIPHENE CITRATE

Evidence

There are no studies investigating the benefit of adding clomiphene citrate to gonadotropins for OS. Published studies investigate the substitution of gonadotropins by clomiphene citrate in the early follicular phase.

Conclusion

There is no evidence available to recommend the substitution of FSH by Clomiphene Citrate in ovarian stimulation.

6.5 LONG-ACTING VS DAILY rFSH

Evidence

An IPD meta-analysis has been performed investigating the efficacy of long-acting rFSH compared to daily injections in 3292 women (3 RCTs) (Griesinger, et al., 2016). This meta-analysis showed that a single injection of long-acting rFSH is equivalent to daily rFSH injections for live birth rate and the number of oocytes retrieved, with an overall difference of resp. -2.0% (95% CI -5.0%-1.1%) for live birth rate and 1.0 (95% CI 0.5 to 1.5) for number of oocytes. Also, the incidence of moderate to severe OHSS was similar between both groups (overall OR 1.29 (95% CI 0.81-2.05)) (Griesinger, et al., 2016).

An RCT, not included in the IPD meta-analysis, in 79 women with a previous poor response also reported no significant difference in the probability of live birth per patient reaching oocyte retrieval (7.9% (3/38) vs. 2.6% (1/38) or number of oocytes (2.5 (2-4) vs. 2.0 (2-3)) (Kolibianakis, et al., 2015).

Recommendation

The use of long-acting and daily recombinant FSH (rFSH) is equally recommended in GnRH antagonist cycles for normal responders.

Strong

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Justification

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.

There are no controlled studies in high responders.

The GnRH antagonist protocol is recommended for the use of long-acting rFSH.

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7. Adjustment of gonadotropin dose

KEY QUESTION: IS ADJUSTMENT OF THE GONADOTROPIN DOSAGE DURING THE STIMULATION PHASE MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

Evidence

An RCT including 151 women compared increasing hMG dose (with 75 IU) on the day of GnRH antagonist initiation with not increasing hMG dose and reported no difference in clinical pregnancy rate (36.2% vs. 32.1%, OR 1.3, 95% CI 0.63-2.6) or number of oocytes retrieved (9.2 ± 2.1 vs. 10.1 ± 3.8) between both groups (Aboulghar, et al., 2004).

A more recent retrospective study reported that changing the dose of gonadotropins during stimulation (increasing or decreasing) had no effect on clinical or ongoing pregnancy rates. Clinical pregnancy rate was 28.2% (11/39) with dose increase vs. 32.1% (27/84) with dose decrease vs. 25.8% (110/427) with no dose adjustments. Similarly, ongoing pregnancy rate was resp. 23.1% (9/39) vs. 25.0% (21/84) vs. 22.5% (96/427) (Martin, et al., 2006).

Two RCTs investigated the effect of gonadotropin dose modulation in poor responder patients. Van Hooff et al. investigated the effect of doubling hMG dose on day 6 of OS in 47 low responders and reported no difference in pregnancy rate (2/25 vs. 1/22) or number of oocytes retrieved (4.7 ± 1.0 vs. 4.6 ± 0.8). No cases of severe OHSS were reported (van Hooff, et al., 1993). A more recent RCT including 73 poor responders investigated the effect of reducing gonadotropin dose (step-down FSH protocol: 450 IU starting dose, reduced to 300 IU/d when serum E2 values reached 200 pg/mL and again reduced to 150 IU/d when 2 follicles of 12 mm in diameter were detected on ultrasound) during OS and reported no difference in number of pregnancies (3/34 vs. 4/39) or number of oocytes retrieved (6.4 ± 0.6 vs. 6.3 ± 0.6) (Cedrin-Durnerin, et al., 2000).

Aboulghar et al. investigated the effect of reducing hMG dose before coasting in 49 women at risk for developing OHSS. They found that reducing the hMG dose before coasting compared to not reducing hMG dose significantly reduced the duration of coasting (1.8 ± 0.65 vs. 2.92 ± 0.92 days) without influencing pregnancy rate (33.3% (8/25) vs. 35% (7/24) (Aboulghar, et al., 2000).

Recommendation

Adjustment (increase or decrease) of the gonadotrophin dose in the mid-stimulation phase during ovarian stimulation is probably not recommended.

Conditional ⊕○○○

Justification

The current evidence does not support changing gonadotropin dose during OS in the mid-stimulation phase. Modification (higher or lower) of gonadotrophin dose during ovarian stimulation for IVF/ICSI does not influence pregnancy rate. There is no evidence regarding dose modifications before the mid-stimulation phase during OS.

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8. Adjuvant therapies

KEY QUESTION: IS THE ADDITION OF ADJUVANTS IN OVARIAN STIMULATION MEANINGFUL IN TERMS OF EFFICACY AND SAFETY?

8.1 METFORMIN

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant metformin compared to control or placebo were considered for inclusion to address the efficacy and safety of metformin use during ovarian stimulation in IVF/ICSI treatment. All studies addressing the role adjuvant metformin were in women with PCOS.

A Cochrane meta-analysis including 551 women found no conclusive evidence that metformin before or during ovarian stimulation improves live birth rate compared to controls in women with PCOS (5 RCT, OR 1.39, 95% CI 0.81-2.40) (Tso, et al., 2014). A lower incidence of OHSS (severity of OHSS not specified) was found in the metformin group as compared to placebo/no treatment (8 RCT, OR 0.29; 95% CI 0.18-0.49). The majority of the studies in the meta-analysis involved the use of GnRH agonist and only one study used the GnRH antagonist protocol. Subgroup analysis based on the type of GnRH analogue showed no significant difference in OHSS between the metformin group compared to control group when used with a GnRH antagonist protocol (1 RCT, OR 0.30, 95%CI 0.03-3.15, 40 women) (Doldi, et al., 2006, Tso, et al., 2014). The Cochrane meta-analysis also showed no significant difference in number of oocytes retrieved in the metformin compared to control group (8 RCT, MD -0.76; 95% CI -2.02 to 0.50) (Tso, et al., 2014).

In a more recent RCT (153 women) of metformin compared to placebo with a GnRH antagonist protocol in women with PCOS a reduced live birth rate was found in the metformin group (27.6% (16/58) vs. 51.6% (33/64)) (Jacob, et al., 2016). Furthermore, no difference in the incidence of OHSS was found between the metformin and placebo groups (OR 1.376, 95% CI 0.54–3.49). Similar to the Cochrane meta-analysis, no significant difference was reported in number of oocytes retrieved in the metformin compared to control group (14 vs. 15, 95% CI -2.37 to 4.37) (Jacob, et al., 2016).

Another recent RCT (102 women) of metformin compared to placebo in an GnRH agonist protocol, reported no significant difference in live birth rate (25.5% (13/51) vs. 17.6% (9/51)) with adjuvant metformin compared to placebo treatment. However, significantly less oocytes were retrieved in the metformin group compared to placebo (9.06±4.23 16.86±8.3) (Abdalmageed, et al., 2018).

Recommendations

Routine use of adjuvant metformin before and/or during ovarian stimulation is not recommended with the GnRH antagonist protocol for women with PCOS.

Strong ⊕⊕○○

Justification

The GDG recommends the use of GnRH antagonist for high responders and in women with PCOS. 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.

8.2 GROWTH HORMONE (GH)

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant growth hormone (GH) compared to control or placebo were considered for inclusion to address the efficacy and safety of GH use during ovarian stimulation in IVF/ICSI treatment.

Dose and administration of GH that was administered varied among studies from 4 IU – 12 IU daily to 4 IU – 24 IU on alternate days.

GH for normal responders

A Cochrane meta-analysis including 80 women in women considered as normal responder undergoing IVF treatment reported no significant difference in live birth rate (2 RCT, OR 1.32, 95% CI 0.40–4.43) with routine use of GH in women undergoing IVF treatment compared to placebo (Duffy, et al., 2010).

GH for poor responders

A recent systematic review and meta-analysis reported significantly higher live birth rate (9 RCT, RR 1.73, 95% CI 1.25–2.40, 562 women) in the GH compared to control group in poor responders undergoing IVF treatment (Li, et al., 2017). The meta-analysis also reported significantly higher number of oocytes retrieved (6 RCT, SMD 1.09, 95% CI 0.54 to 1.64, 523 women) and mature oocytes (5 RCT, SMD 1.48, 0.84 to 2.13, 469 women) in the GH compared to control group in poor responders undergoing IVF treatment (Li, et al., 2017).

An RCT, more recent than the above mentioned meta-analysis, including 127 Bologna criteria poor responders, compared adjuvant GH with no adjuvant treatment in the GnRH antagonist protocol (Choe, et al., 2018). There was no significant difference in ongoing pregnancy rate (8.1% (5/62) vs. 9.2% (6/65)) or number of retrieved oocytes (3.7±2.6 vs. 3.4±2.5) with GH compared to control group (Choe, et al., 2018).

Recommendations

Use of adjuvant growth hormone before and/or during ovarian stimulation is probably not recommended for poor responders.

Conditional ⊕⊕○○

Justification

Collective evidence from 2 small RCTs (included in meta-analysis by Duffy et al.) reported no effect on live birth rate in normal responders (Duffy, et al., 2010). There is collective evidence from small RCTs (included in meta-analysis by Li et al.) that adjuvant GH before and/ or during ovarian stimulation

improves live birth rates in poor responders following IVF treatment (Li, et al., 2017). Similar results were also reported by older meta-analysis (Duffy, et al., 2010, Kolibianakis, et al., 2009, Kyrrou, et al., 2009). Despite the possible beneficial effects in poor responders on live birth rate, the evidence is of too limited quality to recommend GH during OS. The studies in the systematic review were generally underpowered and the definition of poor response very heterogenous among studies. Furthermore, GH dosing schemes were very heterogenous and no long-term safety data are available.

8.3 TESTOSTERONE

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant testosterone pre-treatment compared to control or placebo were considered for inclusion to address the efficacy and safety of pre-treatment testosterone during ovarian stimulation in IVF/ICSI treatment. All studies addressing the role adjuvant testosterone were in predicted poor responders.

Testosterone was administered transdermally as gel or patches. Duration and dose of testosterone pre-treatment was either 10 mg/day or 12.5 mg/day of testosterone gel for 15 to 21 days during pituitary downregulation, or 2.5 mg testosterone patches for five days during pituitary downregulation preceding gonadotrophin stimulation using a long GnRH agonist protocol. One RCT had four arms (three study and one control arm) with 12.5 mg testosterone gel daily for two, three and four weeks preceding OS with the GnRH antagonist protocol (Kim, et al., 2014).

A Cochrane meta-analysis investigated the effect of testosterone pre-treatment before ovarian stimulation in poor responder women and reported improved live birth rate with testosterone pre-treatment (4 RCT, OR 2.60, 95% CI 1.30-5.20, 345 women) (Nagels, et al., 2015). However, in a sensitivity analysis removing all studies at high risk of performance bias there was no evidence of an association between pre-treatment with testosterone and improved live birth rates in the remaining study (1 RCT, OR 2.00, 95%CI 0.17-23.49, 53 women) (Nagels, et al., 2015).

After the publication of the Cochrane meta-analysis, two RCTs were published reporting conflicting results (Bosdou, et al., 2016, Kim, et al., 2014). The RCT by Kim et al. including 120 poor responders demonstrated an improvement in live birth rate with 3 and 4 weeks testosterone pre-treatment compared to controls (resp. 20.0% (6/30) vs. 30% (9/30) vs. 6.7% (2/30)) (Kim, et al., 2014). However, no significant difference in live birth rate in women was found in women who received 2 weeks testosterone pre-treatment compared to control group (13.4% (4/30) vs. 6.7% (2/30)) (Kim, et al., 2014). In contrast, the RCT by Bosdou et al. in 50 Bologna poor responders found no difference in live birth rate with 3 weeks testosterone pre-treatment compared to no pre-treatment (7.7% vs. 8.3%, 95% CI -20.2-21.7) (Bosdou, et al., 2016).

Recommendations

Use of testosterone before ovarian stimulation is probably not recommended for poor responders.

conditional ⊕⊕⊕○

Justification

There is currently inconsistent evidence that adjuvant testosterone pre-treatment before ovarian stimulation improves ovarian response in terms of number of oocytes retrieved and clinical outcomes of live birth rates in poor responders undergoing IVF treatment. Also, due to insufficient data on dosage, administration duration and safety we cannot recommend testosterone use until a large RCT has been conducted.

8.4 DEHYDROEPIANDROSTERONE (DHEA)

Evidence

Systematic reviews, meta-analyses of RCTs and RCTs comparing adjuvant Dehydroepiandrosterone (DHEA) compared to control or placebo were considered for inclusion to address the efficacy and safety of DHEA use during ovarian stimulation in IVF/ICSI treatment.

The dose of DHEA used was 75 mg/day and varied in duration, starting either 6, 8 or 12 weeks before the start of ovarian stimulation and continued during ovarian stimulation. Most studies started DHEA 12 weeks prior to ovarian stimulation.

The Cochrane meta-analysis, mentioned before, also compared pre-treatment with DHEA with placebo/no treatment and combined 2 RCTs in normal responders and 10 RCTs in poor responders. DHEA pre-treatment was associated with improved live birth/ongoing pregnancy rates (8 RCT, OR 1.81, 95% CI 1.25-2.62, 878 women) (Nagels, et al., 2015). However, in a sensitivity analysis removing trials at high risk of performance bias, the effect size was reduced and no longer reached significance (5 RCT, OR 1.50, 95% CI 0.88-2.56, 306 women) (Nagels, et al., 2015).

The Cochrane meta-analysis also performed a sensitivity analysis including only RCTs including poor responders and found that DHEA pre-treatment was associated with an increase in clinical pregnancy rate (10 RCT, OR 1.44, 95% CI 1.06-1.94, 1122 women) (Nagels, et al., 2015).

After the publication of the Cochrane meta-analysis, two RCTs were published reporting conflicting results (Kotb, et al., 2016, Narkwichean, et al., 2017). The RCT by Kotb et al. including 140 Bologna criteria poor responders showed a beneficial effect of DHEA on clinical pregnancy rate (32.8% (23/70) vs. 15.7% (11/70)) in line with the findings of the meta-analysis (Kotb, et al., 2016). However, the RCT by Narkwichean et al. including 60 predicted poor responders reported no significant difference in live birth rate between the DHEA and control group (26% (7/27) vs. 32% (8/25)) (Narkwichean, et al., 2017).

An RCT by Yeung et al. in 72 normal responders showed no significant difference in the number of oocytes retrieved between DHEA and placebo group (6 (4-9) vs. 7 (3-10)) (Yeung, et al., 2016).

Recommendations

Use of DHEA before and/or during ovarian stimulation is probably not recommended for poor responders

Conditional ⊕⊕⊕○

Justification

There is currently inconsistent evidence that adjuvant DHEA use before and during ovarian stimulation improves ovarian response in terms of live birth/ongoing pregnancy rate in poor responders undergoing IVF treatment. The studies varied in duration of DHEA treatment, possibly contributing towards the inconsistency in observed results. Also, due to insufficient data on administration duration and safety we cannot recommend DHEA use until a large RCT has been conducted.

8.5 ASPIRIN

Evidence

To address the efficacy and safety of adjuvant aspirin use with ovarian stimulation in IVF/ICSI treatment, studies were selected if aspirin was used before and/or during ovarian stimulation. Studies commencing aspirin after ovarian stimulation were excluded. Systematic reviews, meta-analyses and eligible RCTs (not included in the selected systematic reviews or meta-analyses) comparing adjuvant aspirin alone (without other co-interventions) compared to control or placebo were included.

Doses of aspirin used in the studies varied between 75 mg daily, 80 mg daily or 100 mg daily and aspirin was continued until hCG administration for final oocyte maturation, 12 weeks of pregnancy or until delivery.

A Cochrane meta-analysis combining 3 RCTs with 1053 women reported no significant difference in the live birth rate (3 RCT, RR 0.91, 95% CI 0.72-1.15) or ongoing pregnancy rate (2 RCT, RR 0.94, 95% CI 0.69-1.27) between the aspirin and control group (Siristatidis, et al., 2016). Due to technical limitations of the meta-analysis to specifically address the role of adjuvant aspirin use before and/or during ovarian stimulation, all other outcomes were assessed from individual studies.

Results from 4 RCTs in the general IVF/ICSI population showed that adjuvant aspirin has no beneficial effect on the number of oocytes retrieved (Table 7) (Dirckx, et al., 2009, Lambers, et al., 2009, Moini, et al., 2007, Pakkila, et al., 2005). One RCT, Rubinstein et al. reported a significantly higher number of oocytes with aspirin compared to placebo treatment (16.2±6.7 vs. 8.6±4.6) (Rubinstein, et al., 1999).

There was one RCT including poor responders which demonstrated no significant difference in number of oocytes retrieved and clinical pregnancy rate between the aspirin compared to control group (Lok, et al., 2004).

Table 7: Number of oocytes retrieved.

Study	Cohort (n)	Aspirin	Placebo
Lok 2004	60	3.0 (2.0–7.25)	4.0 (3.0–7.25)
Pakkila 2005	374	12.0 ± 7.0	12.7 ± 7.2
Moini 2007	145	6.9 ± 5.6	8.6 ± 6.8
Dirckx 2009	193	12.6 ± 7.6	12.9 ± 7.9
Lambers 2009	169	13.7	13.5
Rubinstein 1999	298	16.2 ± 6.7	8.6 ± 4.6

Recommendation

Use of aspirin before and/or during ovarian stimulation is not recommended in the general IVF/ICSI population and for poor responders.	Strong ⊕⊕⊕○
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Justification

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.

Evidence could not be formulated on the outcome of OHSS due to poor study quality and reporting method (Varnagy, et al., 2010).

8.6 INDOMETACIN

Evidence

Current evidence is limited to one case report (Nargund and Wei, 1996).

Conclusion

There are no controlled studies nor RCT addressing the efficacy and safety of adjuvant indomethacin use during ovarian stimulation in IVF treatment. Thus, there is no evidence to recommend the use of indomethacin during OS.

8.7 SILDENAFIL

Sildenafil is used in ovarian stimulation to increase ovarian vascularization and hence increase live birth.

Evidence

Studies on sildenafil administered (for improving endometrial thickness) after oocyte pick-up were not included.

A small pseudo-randomised RCT including 60 patients classified as poor responders reported no significant difference in the clinical pregnancy rate (16.7% (5/30) vs. 13.3% (4/30)) or number of oocytes retrieved between the sildenafil and control group (3.95±1.40 vs. 3.65± 1.14) (Ataalla, et al., 2017).

Recommendations

Use of sildenafil before and/or during ovarian stimulation is not recommended for poor responders	Strong ⊕○○○
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Justification

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 ovarian stimulation. Furthermore, a Dutch trial using sildenafil to try to correct foetal growth restriction (STRIDER study) has been halted after 11 babies subsequently died (Ganzevoort, et al., 2014, Hawkes, 2018).

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9. Non-conventional start of ovarian stimulation

KEY QUESTION: WHAT IS THE SAFETY AND EFFICACY OF NON-CONVENTIONAL START STIMULATION COMPARED TO STANDARD EARLY FOLLICULAR PHASE STIMULATION?

9.1 NON-CONVENTIONAL START

Evidence

A retrospective study in 150 normal responders reported comparable ongoing pregnancy rates (39.4% (13/33) vs. 33.3% (12/36) vs. 39.0% (16/41)) and number of oocytes retrieved (6.6 ± 3.8 vs. 5.9 ± 4.3 vs. 5.9 ± 4.2) when stimulation was started in the late follicular or luteal phase as compared to conventional start (day 2-5) (Qin, et al., 2016). Similarly, a more recent, large retrospective study in 1302 normal responders (non-oncologic fertility preservation) reported no difference in number of oocytes retrieved (12.7 ± 2.7 vs. 13.0 ± 3.1 vs. 13.2 ± 2.9 vs. 13.1 ± 2.3) between early follicular (day 4-7), late follicular (> day 7), and luteal start stimulation as compared to conventional start (day 2/3) (Pereira, et al., 2017).

Recommendation

Random-start ovarian stimulation is probably not recommended for the general IVF/ICSI population.

Conditional ⊕○○○

Justification

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 (early follicular) start stimulation. This validates the feasibility of random-start protocols; however, freeze-all oocytes or embryos is mandatory. A medico-economic study is needed as non-conventional stimulation might require a higher consumption of FSH and the long-term child health has to be carefully monitored as the hormonal environment of the oocytes is modified.

9.2 LUTEAL PHASE STIMULATION

Luteal phase stimulation can be regarded as an extension to urgent oncologic fertility preservation. A distinction must be made between gonadotropin pre-treatment in the luteal phase before follicular stimulation with fresh transfer, and ovarian stimulation in the luteal phase (day 15-19) with mandatory frozen oocytes/embryos.

Evidence

Regarding the pre-treatment of the preceding luteal phase with gonadotropins prior to follicular phase stimulation (and fresh transfer), 3 very small RCTs in poor ovarian reserve patients reported conflicting

results on the number of oocytes retrieved (Kansal Kalra, et al., 2008, Kucuk, et al., 2008, Rombauts, et al., 1998). A very small RCT (18 women) reported no difference in number of oocytes retrieved (5.0 (3-8) vs. 5.5 (1-14)) between gonadotropin pre-treatment and normal-start stimulation in GnRH antagonist protocol (Kansal Kalra, et al., 2008). Another very small RCT (40 women) reported similar findings in the short GnRH agonist protocol, with median number of oocytes collected: 4.5 (2-12) in the experimental group vs. 6 (1-10) in the control group (Rombauts, et al., 1998). However, a more recent very small RCT (42 women) reported an increased number of mature oocytes (mean number: 6.8 vs. 3.2) with luteal gonadotropin pre-treatment as compared to the normal-start stimulation in the long GnRH agonist protocol (Kucuk, et al., 2008).

Regarding luteal phase ovarian stimulation, 5 cohort studies reported conflicting results for the number of oocytes (Kuang, et al., 2014, Liu, et al., 2017, Vaiarelli, et al., 2018, Wu, et al., 2017, Zhang, et al., 2016, Zhang, et al., 2018). A retrospective study comprising 274 patients found no difference in number of oocytes retrieved (3.5 ± 2.5 vs. 3.5 ± 2.9) with luteal stimulation compared to normal stimulation in the GnRH antagonist protocol (Wu, et al., 2017). However, two prospective study (38 and 310 women resp.) and 2 retrospective studies (116 and 153 women, resp.) reported increased numbers of retrieved oocytes after luteal pick-up compared to follicular in duostim cycles (resp. 3.5 ± 3.2 vs. 1.7 ± 1.0 ; 3.5 ± 3.55 vs. 2.33 ± 1.99 ; 4.7 ± 3.0 vs. 4.0 ± 2.5 and 3.3 ± 2.6 vs. 2.2 ± 1.6) (Kuang, et al., 2014, Liu, et al., 2017, Vaiarelli, et al., 2018, Zhang, et al., 2016).

One retrospective study including 446 women (507 cycles) compared early follicular (231 women) with luteal stimulation (154 women) and double stimulation (61 women, 122 cycles). There was no significant difference in number of oocytes retrieved between luteal and early follicular stimulation (2.7 ± 2.1 vs. 2.4 ± 1.5). However, significantly more oocytes were retrieved in the luteal phase compared to follicular phase with double stimulation (1.8 ± 1.1 vs. 1.3 ± 0.9) (Zhang, et al., 2018).

Recommendations

Late luteal phase start of gonadotropins is probably not recommended for poor responders.

Conditional ⊕○○○

Early luteal phase start of gonadotropins is probably not recommended for normal and poor responders.

Conditional ⊕○○○

Luteal phase stimulation could be used in non-transfer cycles.

GPP

Justification

The quality of evidence is very low and controversial regarding the luteal start of FSH in normal and poor responders, and there are no data for PCOS patients. However, the oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase. Absence of adverse effects on neonatal outcomes and long-term child health needs to be evaluated on a larger scale.

An important disadvantage of the luteal start stimulation is the mandatory freeze-all of oocytes or embryos. One study reported on neonatal outcomes comparing frozen/thawed from follicular and luteal phase stimulation (Chen, et al., 2015). Therefore, luteal phase stimulation could be considered as an option in specific cases, for organization and shortened time to oocyte retrieval, for example in urgent oncologic fertility preservation, as well as in freeze-all policy programs.

Also, the drug marketing approval for gonadotropin use in luteal phase needs to be considered.

9.3 DOUBLE STIMULATION

Evidence

Double stimulation or “dual stimulation” or “duostim” (Vaiarelli, et al., 2018) or “Shanghai protocol” (Kuang, et al., 2014) is experimented in poor responder patients or in urgent oncologic fertility preservation. It corresponds to the sequencing of 2 stimulation protocols within the same menstrual cycle: first in the follicular phase then second, immediately after the oocyte pick up, in the luteal phase of the same cycle. So, two oocyte pick-ups are performed at approximately 2 weeks apart. This protocol uses the physiological principles of multiple waves of folliculogenesis within one cycle (Baerwald, et al., 2003). It allows to recover more oocytes in a shorter time period. As shown in luteal phase stimulation protocols, the quality of oocytes retrieved in the second stimulation seems as good as the ones retrieved in the first stimulation (same euploid embryo rate) (Vaiarelli, et al., 2018). Since there are no studies performing the direct comparison of double stimulation with 2 consecutive conventional stimulations, there are no relevant data to show in this guideline. However, in theory, current evidence shows that double stimulation is feasible, and provides oocytes with sufficient quality for IVF/ICSI. The advantages/disadvantages of double stimulation compared to conventional stimulation need to be addressed in randomized controlled studies.

Recommendation

Double stimulation in poor responders should only be used in the context of clinical research

Research
only

Double stimulation can be considered for urgent fertility preservation cycles.

GPP

Justification

Due to absence of RCT, comparing a double stimulation within a same cycle with mandatory postponed transfer and two conventional stimulations, we cannot recommend the double stimulation in poor responder patients.

Two prospective and five retrospective studies reported the double number of oocytes with double stimulation compared to follicular phase stimulation and comparable pregnancy rate from oocytes obtained in luteal or follicular phase (Cimadomo, et al., 2018, Kuang, et al., 2014, Liu, et al., 2017,

Rashtian and Zhang, 2018, Vaiarelli, et al., 2018, Zhang, et al., 2016, Zhang, et al., 2018). An important disadvantage of the luteal start stimulation is the mandatory freeze-all of oocytes or embryos.

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10. Ovarian stimulation for fertility preservation

KEY QUESTION: WHAT IS THE PREFERRED STIMULATION PROTOCOL FOR FERTILITY PRESERVATION AND FREEZING FOR SOCIAL REASONS?

Fertility preservation represents a major issue for young women suffering from diseases that might impact their reproductive potential (Recommendations ASCO, ISFP). OS followed by oocyte or embryo vitrification constitutes the best option. Collecting as much oocytes as possible, sometimes in an extremely reduced time frame represents an important issue. Fertility preservation has emerged relatively recently in the field of reproductive medicine. Therefore, many questions raised, in particular regarding the preferred protocol and the feasibility of random-start ovarian stimulation. In addition, the specificity of OS performed in contexts of oestrogen-sensitive diseases has led, in the name of the precautionary principle, to the development of protocols using anti-oestrogen therapies. Considering the motivation for this treatment, critical and important outcomes in this chapter are different from the rest of this guideline. Critical outcomes for fertility preservation in this guideline are the number of oocytes/embryo's and preventing OHSS and other complications.

More information and recommendations on female fertility preservation for women with cancer, benign diseases, and also transgender patients and women undergoing elective freezing, will be covered in the ESHRE guideline on female fertility preservation (expected 2020).

10.1 PREFERRED PROTOCOL

Evidence

Only one retrospective analysis, including 24 women, compared the long GnRH agonist and GnRH antagonist protocols in women with breast cancer who were treated with FSH plus letrozole (Ben-Haroush, et al., 2011). The number oocyte recovered was higher with GnRH agonist protocol (24.8 ± 24.6 vs. 12.0 ± 8.8), however this difference was not statistically significant. Furthermore, one patient had 82 oocytes retrieved after long GnRH agonist protocol. When this patient is excluded, the mean of oocytes was 9.6 oocytes (range 0–30) (Ben-Haroush, et al., 2011).

Two systematic reviews including a total of 33 studies (Boots et al., 2016; Rodgers et al., 2017) and 14 other investigations (Alvarez and Ramanathan, 2016, Cardozo, et al., 2015, Chan, et al., 2015, Das, et al., 2011, Devesa, et al., 2014, Druckenmiller, et al., 2016, Garcia-Velasco, et al., 2013, Johnson, et al., 2013, Lawrenz, et al., 2010, Lee, et al., 2010, Muteshi, et al., 2018, Pereira, et al., 2016, Shapira, et al., 2015) reported data of cancer patients having undergone ovarian stimulation for oocyte and/or embryo cryopreservation. More than 2200 cycles were described, most of them (>90%) with GnRH antagonist protocols. Among them, random-start ovarian stimulation or protocols using aromatase inhibitors or tamoxifen were considered. In addition, different methods of final oocyte maturation were used. The main outcome measure was usually the overall number of oocytes recovered and the number of mature oocytes obtained.

Recommendation

For ovarian stimulation in women seeking fertility preservation for medical reasons the GnRH antagonist protocol is probably recommended.

Conditional ⊕○○○

Justification

There is moderate quality evidence of the necessity of considering a specific GnRH analogue protocol. 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. Moreover, especially in cancer patients, who are at higher risk of thrombosis due to their oncologic status, seem to be preferred since they enable GnRH agonist trigger, therefore reducing the risk of OHSS.

RCTs aiming to compare GnRH agonist and GnRH antagonist protocols for fertility preservation may be interesting. However, considering such studies may be difficult since GnRH agonist trigger represents an important advantage in this field.

Data on live births are dramatically lacking, in particular in cancer patients having vitrified oocytes.

10.2 RANDOM-START PROTOCOL

Evidence

A systematic review of 8 (non-randomized) studies of which 6 were performed in context of fertility preservation, showed in 251 women, that cycles initiated in the luteal were slightly longer (WMD 1.3 days, 95 % CI 0.37–2.1) and required more total doses of exogenous gonadotropins (WMD 683 IU, 95 % CI 369–997) when compared with stimulation started in the follicular phase (Boots, et al., 2016). Peak serum oestradiol (WMD –337 pg/mL, 95% CI –849–175) and number of oocytes recovered (WMD –0.6 oocytes, 95 % CI –2.8 to 1.6) did not differ whatever the phase of the cycle at which FSH was started. Interestingly, oocytes obtained in cycles initiated in the luteal phase fertilized more efficiently (WMD 0.16, 95 % CI 0.13 to 0.19). No conclusion can be drawn on pregnancy and live birth rates regarding the very small number of patients and the extremely low re-utilization rates of cryopreserved oocytes and embryo in cancer patients (Boots, et al., 2016).

Two more recent retrospective cohort studies, including resp. 127 and 220 cancer patients undergoing ovarian stimulation for fertility preservation, also compared conventional follicular stimulation with random-start stimulation (Muteshi, et al., 2018, Pereira, et al., 2016). Muteshi et al. reported no significant differences in number of oocytes retrieved (11.9 (95% CI 10.3–13.5) vs. 12.9 (95% CI 9.6–16.2)), total Gonadotropin dose used (mean 2543.4 (2328.3–2758.5) vs. 2811.9 (2090.8–3533.1) IU), total duration of stimulation (11.5 (11.2–12.0) vs. 12.2 (10.7–13.7) days) or peak serum oestradiol (5426.3 (4682.9–6169.7) vs. 4423.1 (2866.9–5979.3) pmol/L) (Muteshi, et al., 2018). Similarly, Pereira et al. reported no significant difference in number of oocytes retrieved (12.1±5.78 vs. (12.6±6.23); OR 1.05, 95% CI 0.45–2.45), total gonadotropin dose used (3498.3±1563.1 vs. 3527.4±1668.9 IU), or peak serum oestradiol (473.3 (262.4-615.7) vs. 443.8 (285.2-603.5) pg/ml). However, total duration of

stimulation was significantly longer in the luteal phase compared to the follicular phase (11.8 (\pm 2.41) vs. 10.7 (\pm 2.71) days) (Pereira, et al., 2016)

Recommendation

In urgent (oncology) fertility preservation cycles, random-start ovarian stimulation is an important option.

Conditional ⊕⊕○○

Justification

The quality of evidence is still low given the few studies available. However, evidence indicates that oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase. Absence of adverse effects on neonatal outcomes and long-term child health need to be evaluated on a larger scale, especially in cancer patients.

The drug marketing approval for gonadotropin use in luteal phase needs to be considered.

10.3 ANTI-OESTROGEN THERAPIES

Fertility preservation in breast cancer represents a complex issue since this disease is considered as oestrogen sensitive. Indeed, ovarian stimulation for the purpose of freezing oocytes or embryos is associated with supra-physiological serum oestradiol levels that could theoretically result in the proliferation of malignant cells.

Therefore, innovative stimulation protocols have been developed in an effort to reduce potential harm associated with high oestradiol levels. Co-administration of either aromatase inhibitors or selective oestrogen receptor modulators during ovarian stimulation is used frequently.

Evidence

A systematic review recently published analysed the results of 12 prospective and retrospective cohort studies having used aromatase inhibitors protocols for fertility preservation (Rodgers, et al., 2017). Peak oestradiol concentrations were 337-829 pg/mL, when letrozole was commenced on day 2-3, but still higher than that observed in natural cycle IVF. Regarding the oocytes yield, in the systematic review, two studies failed to report any difference between aromatase inhibitor protocols and conventional stimulation (Checa Vizcaino, et al., 2012, Oktay, et al., 2006) while 2 other investigators observed a small but significant decrease with letrozole administration (Domingo, et al., 2012, Revelli, et al., 2013). However, the amount of FSH administration in Revelli's study was lower in the aromatase inhibitor group, which may have biased the results.

Rodgers et al., also reviewed the 4 prospective and retrospective cohort studies having used tamoxifen administration during ovarian stimulation. Peak oestradiol levels in women stimulated with tamoxifen co-administration were higher than observed in natural cycle IVF (Oktay, et al., 2003), however, remained comparable in women undergoing OS without tamoxifen (Meirow, et al., 2014). One study in the systematic review compared OS with letrozole to OS with tamoxifen (Oktay, et al., 2005). Number of oocytes retrieved, and mature oocytes obtained was lower when stimulation was performed with tamoxifen than with letrozole (6.9 \pm 1.1 vs. 12.3 \pm 2.5) and (5.1 \pm 1.1 vs. 8.5 \pm 2.6), respectively. However,

this study presents a dramatic lack of power (7 women and 9 cycles in Tamoxifen group and 11 women with 11 cycles in letrozole group).

Data on relapse-free survival and mortality were available only in 4 studies of the systematic review, encompassing 464 women with a maximum of 5-year follow-up.

A retrospective cohort study including 639 women compared OS with letrozole in breast cancer patients with OS without letrozole in women presenting for elective cryopreservation (Pereira, et al., 2016). There was no significant difference in the duration of stimulation (10.9 ± 3.46 vs. 10.4 ± 3.69 days), total amount of gonadotropins administered (3502.4 ± 1372.1 vs. 3607.8 ± 1848.6 IU). However, peak serum oestradiol was significantly lower in women receiving letrozole (464.5 (315.5-673.8) vs. 1696 (1058-2393) pg/ml). Furthermore, significantly more oocytes were retrieved in women receiving letrozole (12.3 ± 3.99 vs. 10.9 ± 3.86) (Pereira, et al., 2016).

Recommendation

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

Justification

The quality of evidence is still low given the number and quality of studies available. 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 not yet exist. Undertaking RCTs in this patient population represents a major limitation. It is not known whether the transient period of raised oestrogen concentrations during ovarian stimulation is harmful to women with breast cancer. A study aiming to compare the short- and long-term effects of ovarian stimulation with or without letrozole co-administration is ongoing. However, the use of letrozole is off-label for OS and safety concerns have been raised regarding possible teratogenicity associated with letrozole.

Aromatase inhibitors protocols enable GnRH agonist trigger (Oktay, et al., 2010, Reddy, et al., 2014).

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PART C: Monitoring

11. Hormonal assessment during ovarian stimulation

KEY QUESTION: IS THE ADDITION OF HORMONAL ASSESSMENT (OESTRADIOL/PROGESTERONE/LH) TO ULTRASOUND MONITORING IMPROVING EFFICACY AND SAFETY?

11.1 ULTRASOUND AND OESTRADIOL MEASUREMENTS

Evidence

A Cochrane meta-analysis on monitoring of ovarian stimulation in IVF/ICSI with ultrasound alone compared to ultrasound plus serum oestradiol concentration combined 6 RCTs including 781 women (Kwan, et al., 2014). Monitoring of the stimulation phase by using serum oestradiol measurements and ultrasound did not appear to decrease the probability of OHSS (6 RCT, OR 1.03, 95% CI 0.48-2.20, 781 women), nor increase the probability of clinical pregnancy (4 RCT, OR 1.10, 95% CI 0.79-1.54, 617 women), or the number of oocytes retrieved (5 RCT, WMD 0.32, 95% CI -0.60 to 1.24, 596 women) (Kwan, et al., 2014).

Recommendation

The addition of oestradiol measurements to ultrasound monitoring is probably not recommended.

Conditional ⊕⊕○○

Justification

On the basis of the currently published evidence, monitoring of the stimulation phase by serum oestradiol measurements and ultrasound is not superior to monitoring by ultrasound alone in terms of efficacy and safety. The addition of oestradiol in the monitoring does not appear to increase the probability of pregnancy, the number of oocytes retrieved, or to decrease the probability of OHSS.

From the six studies included in the meta-analysis, a GnRH agonist protocol was used exclusively in four of them, while in the remaining two both GnRH agonists and antagonists were used (Kwan, et al., 2014). Thus, it is not known whether the recommendation is valid in patients treated exclusively with GnRH antagonists.

11.2 ULTRASOUND AND PROGESTERONE MEASUREMENTS OR ULTRASOUND AND LH MEASUREMENTS.

Currently no published evidence exists to allow for a recommendation to be formulated answering these questions.

11.3 ULTRASOUND AND COMBINATION OF HORMONAL MEASUREMENTS

Evidence

One RCT (114 women) reported no difference in OHSS (5.3% (3/57) vs. 7.0% (4/57)), pregnancy rate (22.2% vs. 25%), or number of oocytes retrieved (11.7±8.4 vs. 13.4±7.5) when monitoring was performed with ultrasound with or without hormonal measurements (Golan, et al., 1994). Similarly, a more recent RCT (63 women) reported no difference in clinical pregnancy rate (40.0% (12/30)) vs. 57.5% (19/33) or number of oocytes retrieved (10.0±5.5 vs. 11.7±8.0) with ultrasound and hormone panel monitoring compared with ultrasound only (Wiser, et al., 2012). Furthermore, no cases of OHSS were reported in either the study or control group (Wiser, et al., 2012).

Recommendation

The addition of a hormonal panel consisting of a combination of oestradiol, progesterone and LH measurements to ultrasound monitoring is probably not recommended.	Conditional ⊕○○○
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Justification

According to one RCT, monitoring of the stimulation phase by using hormonal panel assessments (oestradiol, LH, progesterone) and ultrasound is not beneficial in terms of efficacy and safety over monitoring by ultrasound alone in terms of efficacy and safety. The addition of hormonal assessments in the monitoring does not appear to increase the probability of pregnancy, the number of COCs retrieved, or to decrease the probability of OHSS or cycle cancellation for high response.

In the two studies, LH suppression was performed with GnRH agonists (Golan, et al., 1994) or either GnRH agonists/antagonists (Wiser, et al., 2012). Thus, it is not known whether the recommendation is valid in patients treated exclusively with GnRH antagonists.

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12. Endometrial thickness

KEY QUESTION: DOES MONITORING OF ENDOMETRIAL THICKNESS AFFECT THE EFFICACY AND SAFETY?

Human endometrium has a key role in implantation process. Adequate endometrial development is required for pregnancy to occur. Thin endometrium on ultrasound during ovarian stimulation has been thought to be associated with poor success rates after IVF, even in the absence of prior intrauterine surgery or infection. At present, results from studies that investigated the relationship between endometrial thickness (EMT) and IVF outcomes are conflicting (Kasius, et al., 2014). A meta-analysis by Kasius et al. reported a thin endometrium (≤ 7 mm) in 2.4% (10.724 women) of patients (Kasius, et al., 2014). A more recent retrospective study reported 11% (517 women) of patients presenting with thin endometrium in ICSI cycles (Coelho Neto, et al., 2015). However, in a large retrospective study by Holden et al. the proportion of patients with thin endometrium < 7 mm was 5.5% (6331 women) in IVF cycles (Holden, et al., 2017).

Evidence

There are no studies comparing monitoring endometrial thickness compared to no monitoring, which would be the ideal study to answer this question. Alternatively, we looked at studies investigating whether endometrial thickness is predictive for implantation and live birth.

A meta-analysis combining 22 prospective and retrospective studies (10.724 patients and cycles) and several more recent studies found EMT having little to no discriminatory capacity for clinical pregnancy (Table 8) (Griesinger, et al., 2018, Kasius, et al., 2014, Lamanna, et al., 2008, Rehman, et al., 2015, Zhao, et al., 2014). In addition, the study by Griesinger et al. reported that the independent contribution of EMT (assessed on day of embryo transfer) to live birth likelihood is small and may result from (undetermined) confounding factors. If EMT indeed is an independent factor affecting outcome, this finding implies that at a baseline live birth rate of 20% an increase of 2 mm in EMT should result in an increase of the live birth rate of $\sim 1.6\%$ (Griesinger, et al., 2018).

Table 8: Accuracy of EMT in predicting pregnancy outcome

Predictive power of EMT on pregnancy outcome		
Study	Cohort (n)	ROC-AUC
Kasius 2014	10.724 women and cycles	0.56
Other studies:		
Lamanna 2008	685 women	< 0.70
Zhao 2014	3319 women	0.60
Rehman 2015	282 women	0.88
Griesinger 2018	1483 women	0.53

The meta-analysis and several more recent studies also reported a significantly lower probability of conceiving with EMT <8 mm as compared to EMT >8 mm (table 9) (Aydin, et al., 2013, Gallos, et al., 2018, Kasius, et al., 2014, Rehman, et al., 2015, Ribeiro, et al., 2018, Wu, et al., 2014, Yuan, et al., 2016).

Table 9: Probability of pregnancy with thin endometrium.

Probability of pregnancy with EMT				
Study	Cohort (n)	<8 mm	>8 mm	No pregnancy
Kasius 2014	10.724 women and cycles	OR 0.42, 95% CI 0.27–0.67		
Other studies:				
Aydin 2013	593 women	7.1%	35.5%-43.9%	
Wu 2014	2.106 women	13.8%	38.2%-47.6%	<6 mm
Rehman 2015	282 women	5%	57.2%	
Yuan 2016	10.787 cycles	23.0%	37.2%-53.3%	<4 mm
Ribeiro 2018	3.350 cycles	21.8%	35.2%	
Gallos 2018	45.279 cycles	15.6%	33.1%	

A large retrospective cohort study (3319 women) reported significant thicker EMT on the hCG day in the clinical pregnancy group compared with the not pregnant group (11.0±2.2 vs. 10.3±2.2 mm) (Zhao, et al., 2014). In contrast, a large prospective study in 435 women reported no difference in endometrial thickness between pregnant and non-pregnant patients (11.2 mm (9.8-12.7) vs. 11.1 mm (9.5-12.9) (Zhang, et al., 2016).

The thinnest endometrial thickness at which pregnancy occurred was 3.7 mm, in the study by Holden et al. and 5.6 mm in the study by Coelho Neto et al. Both pregnancies resulted in a live birth (Coelho Neto, et al., 2015, Holden, et al., 2017).

Recommendations

Routine monitoring of endometrial thickness during ovarian stimulation is probably not recommended.

Conditional ⊕○○○

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

Justification

There are indications that thin endometrium is related to lower ongoing/clinical pregnancy chances as an independent factor. This condition of thin endometrium occurs infrequent (2-5%). Interventions to correct thin EMT have little rational basis and should be abandoned until contrary evidence arises.

A single ultrasound assessment is necessary to identify patients with very thin or very thick EMT, and appropriate diagnostic work-up should be done.

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13. Criteria for triggering

KEY QUESTION: IS THE OUTCOME OF OVARIAN STIMULATION DEPENDENT ON THE CRITERIA FOR TRIGGERING?

13.1 FOLLICLE SIZE

Evidence

A meta-analysis including 7 RCTs investigating the effect of postponing final oocyte maturation by 24-48 hours. There was no significant difference in live birth rate (3 RCT, RR 1.14, 0.46-2.83, 354 women) or ongoing pregnancy rate per oocyte pick-up (4 RCT, RR 0.97, 95% CI 0.54–1.74, 743 women) between early hCG and the late hCG group. However, significantly more oocytes were retrieved in late hCG group than in early hCG group (4 RCT, MD 1.2, 95% CI 1.11–1.30, 743 women) (Chen, et al., 2014).

In the meta-analysis there was one study comparing triggering at different follicular sizes, the only trial identified by the literature search investigating this research question. In this RCT (190 women), triggering was performed when the leading follicle reached either 18 or 22 mm. There was no significant difference in live birth rate when trigger was administered when the leading follicle was 22 mm (35% (34/97)) compared to 18 mm (23% (21/93)) (RR 1.6 (0.98–2.47)). However, more women reached an ongoing pregnancy (38% (37/97)) compared with the 18-mm group (24% (22/93)) (RR 1.6, 95% CI: 1.03–2.5) and significantly more oocytes were retrieved (11.7 ± 5.7 vs. 9.7 ± 4.1) (Mochtar, et al., 2011).

Recommendations

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 ⊕⊕○○

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 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

Justification

The available studies have compared, except for one (Mochtar et al., 2011), not different follicle sizes as trigger criteria but postponing hCG administration after a given sonographic follicular criterion had been reached. 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.

13.2 OESTRADIOL LEVEL

Evidence

There are no interventional studies investigating triggering based on oestradiol levels.

Recommendations

The GDG does not recommended to base timing of final oocyte maturation triggering on oestradiol levels alone.

GPP

Justification

No interventional study has been performed assessing the use of serum oestradiol as a criterion for when to trigger final oocyte maturation. Serum oestradiol levels during ovarian stimulation vary depending on the size of the growing follicular cohort, the distribution of follicles between different size classes within the growing cohort as well as the endocrine situation of the patient and the endocrine milieu of the stimulation cycle. 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.

13.3 OESTRADIOL/FOLLICLE RATIO

Evidence

There are no interventional studies investigating triggering based on the oestradiol/follicle ratio.

Recommendations

The GDG does not recommended to base timing of final oocyte maturation on oestradiol/follicle ratio alone.

GPP

Justification

No interventional study has been performed assessing the use of serum oestradiol-to-follicle ratio as a criterion for when to trigger final oocyte maturation. The oestradiol-to-follicle ratio will vary depending on the size of the growing follicular cohort, the distribution of follicles between different size classes within the growing cohort as well as the endocrine situation of the patient and the endocrine milieu of the stimulation cycle. The association of the oestradiol-to-follicle ratio with clinical outcomes has been

studied in several observational studies, but management recommendations cannot be derived from these observational data.

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14. Criteria for cycle cancellation

KEY QUESTION: WHICH CRITERIA FOR CYCLE CANCELLATION ARE MEANINGFUL REGARDING PREDICTED POOR/HIGH OOCYTE YIELD?

Since the year 1983 –when the term „poor responder” was described for the first time (Garcia, et al., 1983), no international consensus regarding the definition of a poor response was available and different definitions were used. In 2011, the European Society of Human Reproduction and Endocrinology (ESHRE) defined poor response as: ‘cycle cancellation or retrieval of fewer than four oocytes with a conventional ovarian stimulation protocol’ (Ferraretti, et al., 2011).

Similarly, there is no international consensus definition for high response, which would help to identify women who can develop OHSS and allow undertaking interventions to avoid developing the condition.

Evidence

Poor oocyte yield

The occurrence of poor response is reported to vary between 5.6% and 35.1% or 9% to 24 % depending on the definition of poor response (Oudendijk, et al., 2012). The decision making to stop the treatment, or to encourage to start another cycle is always difficult in respect to low number of oocytes and should be individually taken. Other factors, which influence pregnancy rate (e.g. age of patient) and burden of therapy, should be taken into account. The data also demonstrated that the pregnancy could still occur even in the first cycle the women is defined as poor responder (Baka, et al., 2006).

In a meta-analysis combining prospective and retrospective cohort studies, the pooled estimate of pregnancy rate for poor responders was 14.8%, compared with 34.5% for normal responders (6 cohort studies, n=14338 women/cycles) (Oudendijk, et al., 2012). The chance of pregnancy in respect to number of oocytes varied across studies. Women with 1 oocyte retrieved had 0-7%, 2 oocytes 4.3-15.2%, 3 oocytes 8.7-15.6%, and 4 oocytes 11.5–18.6% (4 cohort studies, 8744 women/cycles) (Oudendijk, et al., 2012). Finally, in one study where 5 oocytes were obtained, pregnancy rate was up to 22 % (Oudendijk, et al., 2012, Timeva, et al., 2006). A more recent, large retrospective study reported a predicted live birth rate of 2% (n=541 cycles, 95% CI 2-3%) in women >40 years of age with one oocyte retrieved (Sunkara, et al., 2011).

A large prospective study (1012 women, long GnRH agonist protocol) reported no live birth in women with AFC <4 (0%), but a live birth rate of 5% with an AFC of 4 (Jayaprakasan, et al., 2012). The presence of one or two follicles in poor responders still could lead to obtain pregnancy. A large retrospective study (800 cycles, long GnRH agonist/GnRH antagonist protocols) in poor responders with 1 or 2 follicles >12 mm after ovarian stimulation, reported a clinical pregnancy rate of resp. 5.4% (12/223) and 9.2% (53/577) and an ongoing pregnancy rate of resp. 4.5% (10/223) and 7.6% (44/577) (Nicopoullos and Abdalla, 2011). A more recent, large retrospective study (256.381 cycles) reported a live birth rate of 17% when the number of retrieved oocytes was between 0-5 (Steward, et al., 2014).

High oocyte yield

The incidence of severe OHSS reported in clinical studies varies from 2% (Papanikolaou, et al., 2006) to almost 9% (Toftager, et al., 2016). The incidence of high response varied from >14 to >16 retrieved

oocytes (Broer, et al., 2013). It has been demonstrated in several prospective studies that a high number of growing follicles is an independent predictor of OHSS (Jayaprakasan, et al., 2012, Papanikolaou, et al., 2006).

A large prospective study with 2362 women advised cycle cancellation with >30 follicles of 12 mm during OS with long GnRH agonist protocol (Mathur, et al., 2000). In a large prospective cohort study with 1801 women (2524 cycles), the threshold of ≥ 18 follicles ≥ 11 mm during OS with GnRH antagonist protocol predicted severe OHSS with 83% sensitivity rate with a specificity as high as 84% (Papanikolaou, et al., 2006). According to the SART registry, analysis of 256,381 cycles revealed that retrieval of >15 oocytes significantly increases the risk of OHSS and does not lead to an increased live-birth rate in fresh cycles (Steward, et al., 2014). A recent large retrospective analysis of the Engage, Ensure and Trust trials found that the threshold of 19 follicles of ≥ 11 mm on hCG day predicted moderate to severe OHSS with 62.3% sensitivity and 75.6% specificity (ROC-AUC 0.73), and predicted severe OHSS with 74.3% sensitivity and 75.3% specificity (ROC-AUC 0.77) in GnRH antagonist protocol (Griesinger, et al., 2016).

There was a strong association between the number of oocytes and LBR; LBR rose with an increasing number of oocytes up to 15, plateaued between 15 and 20 oocytes and steadily declined beyond 20 oocytes. The LBR for women with 15 oocytes retrieved in age groups 18–34, 35–37, 38–39 and 40 years and over was 40, 36, 27 and 16% respectively (Sunkara, et al., 2011).

Recommendations

A poor response to ovarian stimulation alone is not a reason to cancel a cycle.

Strong

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The physician should counsel the individual poor responder regarding pregnancy prospects and decide individually whether to continue this and/or further cycles.

GPP

In GnRH agonist cycles with an ovarian response of ≥ 18 follicles, there is an increased risk of OHSS and preventative measures are recommended, which could include cycle cancellation.

Strong

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Justification

Reported pregnancy rates among poor responders to ovarian stimulation differ between 0 – max reported 18%. These differences could be explained by the exact number of oocytes retrieved, as well as the age of the patient and indication for treatment.

Although pregnancy rates may be low, they are not absent per se. Therefore, we recommend the physician to counsel patients individually regarding pregnancy prospects and the decision to continue this or further treatment.

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.

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PART D: Triggering ovulation and luteal support

15. Triggering of final oocyte maturation

KEY QUESTION: WHAT IS THE PREFERRED DRUG FOR TRIGGERING OF FINAL OOCYTE MATURATION IN TERMS OF EFFICACY AND SAFETY IN THE OVERALL IVF/ICSI POPULATION?

15.1 URINARY (UHCG) VS RECOMBINANT HUMAN CHORIONIC GONADOTROPHIN (RHCG)

Evidence

A Cochrane meta-analysis found no difference in live birth/ongoing pregnancy rate (7 RCT, OR 1.15, 95% CI 0.89-1.49, 1136 women), moderate to severe OHSS (3 RCT, OR 1.76, 95%CI 0.37-8.45, 417 women), moderate OHSS (1 RCT, OR 0.78, 95% CI 0.27-2.27, 243 women), mild to moderate OHSS (2 RCT, OR 1.00, 95%CI 0.42-2.38, 320 women), undefined OHSS (3 RCT, OR 1.18, 95%CI 0.50-2.78, 495 women) or number of oocytes (12 RCT, MD-0.11, 95% CI -0.70 to 0.47, 1744 women) between recombinant and urinary hCG when used for triggering final oocyte maturation (Youssef, et al., 2016).

One RCT including 100 women compared 10.000 IU with 5000 IU of urinary hCG for triggering final oocyte maturation in the long GnRH agonist protocol (Shaltout, et al., 2006). There was no significant difference in pregnancy rate (not specified) (35.4% vs. 33.3%, incidence of OHSS (8.3% (4/48) vs. 2% (1/50)) or number of oocytes retrieved (7.4±3 vs. 7±3.5) between 10.000 IU and 5000 IU of uhCG for final oocyte maturation (Shaltout, et al., 2006).

One RCT including 80 PCOS patients randomized to receive 10.000 IU, 5000 IU, or 2500 IU of uhCG for triggering final oocyte maturation in the GnRH antagonist protocol as soon as 3 or more follicles of 17 mm or larger were present at ultrasound (Kolibianakis, et al., 2007). There was no significant difference in ongoing pregnancy rate ((25.0% (7/28) vs. 30.8% (8/26) vs. 30.8% (8/26)), severe OHSS (1/28 vs. 1/26 vs. 0/26) or number of oocytes retrieved (median 14 vs. 11.5 vs. 9) between 10.000 IU, 5000 IU and 2500 IU uhCG (Kolibianakis, et al., 2007).

One RCT including 180 women compared 500 µg with 250 µg recombinant hCG for triggering final oocyte maturation in the long GnRH agonist protocol (Madani, et al., 2013). There was no significant difference in clinical pregnancy rate (34.5% (19/55) vs. 42.2% (19/45)), occurrence of OHSS (10% (6/60) vs. 6.7% (4/60)) or number of oocytes retrieved (12.25±5.30 vs. 12.40±6.44) between 500 µg and 250 µg rhCG (Madani, et al., 2013).

Recommendation

The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation during ovarian stimulation protocols.	Strong ⊕⊕○○
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A reduced-dose of 5.000 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 ⊕○○○
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Justification

The Cochrane meta-analysis shows equal efficacy and safety for urinary and recombinant hCG. The grand majority of the trials (17 out of 18) included in the meta-analysis by Youssef et al. 2016, performed pituitary downregulation using a long GnRH agonist protocol, only one trial was performed using a GnRH antagonist protocol (Youssef, et al., 2016). The evidence regarding antagonist protocol is inconclusive so the recommendation might not be applicable for GnRH antagonist cycles, although there is no evidence to suggest a difference in safety and efficacy.

Different doses of uhCG have been described in the literature ranging from 2.000 IU to 10.000 IU. According to 2 RCTs, a reduced-dose of urinary hCG (5.000 IU) does not appear to affect the probability of pregnancy compared to conventional dose (10.000 IU). Similarly, data from 1 RCT suggests that a low dose (250µg) of recombinant hCG does not appear to influence the probability of pregnancy as compared to a higher dose (500 µg). The probability of OHSS was reduced when lower doses of hCG were administered but this did not reach statistical significance in any of the 3 RCTs. Lower doses of hCG could be considered when an unpredicted high response has occurred, and GnRH long agonist protocol is applied.

15.2 RECOMBINANT LH (RLH) VS URINARY HCG (UHCG)

Evidence

The trials had administered different dosages of rLH which varied from 5000 IU (Manau, et al., 2002) to 15000 IU and an additional 10000 IU three days post the first injection (2001).

The Cochrane meta-analysis, mentioned before, reported no difference in live birth/ongoing pregnancy rate (2 RCT, OR 0.95, 95% CI 0.51-1.78, 289 women), moderate OHSS (2 RCT, OR 0.83, 95% CI 0.40-1.70, 289 women) or number of oocytes retrieved (2 RCT, MD-1.33, 95%CI -3.26 to 0.60, 103 women) between rLH and uHCG when used for triggering final oocyte maturation (Youssef, et al., 2016).

Recommendation

It is not recommended to administer recombinant LH for triggering final oocyte maturation.

Strong ⊕○○○

Justification

The available evidence is currently very limited to allow solid conclusions to be drawn. There was large heterogeneity between the three trials included with respect to study methods. Therefore, we cannot recommend the use of rLH to trigger final oocyte maturation.

15.3 GnRH AGONIST TRIGGER VS HCG

Evidence

A meta-analysis including 3 RCT (275 women) reported a significant difference in clinical pregnancy rate in favour of hCG (OR 0.21, 95% CI 0.05–0.84) (Griesinger, et al., 2006). No significant difference in number of oocytes retrieved was reported (MD –0.94, –0.33 to 0.14) (Griesinger, et al., 2006).

However, four RCTs published after the meta-analysis showed that there is no significant difference in live birth rate (24% (36/152) vs. 31% (47/150) and 23.5% (4/17) vs. 22.2% (4/18) resp.) (Humaidan, et al., 2010, Papanikolaou, et al., 2011), ongoing pregnancy rate (Humaidan, et al., 2013) or clinical pregnancy rate (53% (8/15) vs. 46% (6/13) (Humaidan, et al., 2006) between GnRH agonist and hCG triggering when modified luteal support with LH-activity is administered after GnRH agonist trigger. A Cochrane meta-analysis reported no significant difference in OHSS rate between GnRH agonist and hCG for OHSS rate in women at low risk of OHSS (6 RCT, OR 0.79, 95% CI 0.18-3.47, 777 women) (Youssef, et al., 2014). Due to technical limitations of the meta-analysis, pregnancy outcomes from the meta-analysis could not be used.

Recommendation

The use of GnRH agonist for final oocyte maturation with conventional luteal phase support and fresh transfer is not recommended in the general IVF/ICSI population.

Strong ⊕⊕○○

The use of GnRH agonist for final oocyte maturation, luteal phase support with LH-activity and fresh transfer is probably not recommended for the predicted normal responder.

Conditional ⊕○○○

Justification

Current evidence shows a disadvantage in ongoing/clinical pregnancy rate with GnRH agonist and conventional luteal support as compared to hCG in normal responders. Two of the studies in the meta-analysis by Griesinger (Humaidan et al., 2005; Kolibianakis et al., 2005) were prematurely

stopped due to significant differences between study groups in clinical pregnancy rates (Griesinger, et al., 2006).

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/ISCI population.

GnRH agonist triggering for (predicted) high responder is discussed further in the guideline (chapter 17).

15.3.1 TRIPTORELIN 0.1 MG VS HIGHER DOSAGES

Evidence

One RCT including 165 oocyte donors compared different dosages (0.2 mg vs. 0.3 mg vs. 0.4 mg) of triptorelin for final oocyte maturation in GnRH antagonist protocol and reported no significant differences in number of oocytes retrieved (18.4 ± 8.8 vs. 18.7 ± 8.9 vs. 17.8 ± 10.7) or mature oocytes (16.0 ± 8.5 vs. 15.9 ± 7.8 vs. 14.7 ± 8.4). One case of OHSS in the 0.3 mg group (Vuong, et al., 2016).

Recommendation

If the GnRH agonist trigger with triptorelin is applied, dosages ranging of 0.1-0.4 mg can be chosen.

GPP

Justification

There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with triptorelin. 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.

15.3.2 BUSERELIN 0.2 MG VS 0.5 – 1 – 2 MG

Evidence

There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with buserelin. No controlled studies or RCT could be found comparing different dosages of Buserelin for final oocyte maturation. Therefore, no recommendation can be formulated regarding optimal dosage.

15.3.3 LEUPROLIDE 0.15 MG VS 0.5 – 1 – 2 - 4 MG

Evidence

There are no studies investigating the direct comparison of hCG with different dosages of GnRH agonist trigger with leuprolide. No controlled studies or RCT could be found comparing different dosages of Leuprolide for final oocyte maturation. Therefore, no recommendation can be formulated regarding optimal dosage.

15.4 DUAL TRIGGER

Evidence

A meta-analysis including 4 RCTs (527 women) compared the use of hCG with combined administration of hCG and GnRH agonist (dual trigger) for final oocyte maturation (Ding, et al., 2017). The meta-analysis found a significant higher pregnancy rate with dual trigger as compared to hCG trigger (2 RCT, RR, 1.55; 95% CI, 1.17–2.06, 320 women). There was no difference in the number of oocytes retrieved (4 RCT, WMD 0.47; 95% CI, -0.42 to 1.37, 527 women) (Ding, et al., 2017).

One RCT, not included in the meta-analysis, compared hCG 6500 IU with dual trigger (6500 IU hCG+0.2 mg GnRH agonist) in 192 normal responder women (Eftekhar, et al., 2017). There was no significant difference in ongoing pregnancy rate (22.9% (20/93) vs. 24.2% (24/99)) between hCG and dual trigger. However, significantly more oocytes with dual trigger compared to hCG trigger (10.85± 4.71 vs. 9.35 ±4.35) (Eftekhar, et al., 2017).

Recommendation

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 ⊕⊕○○

Justification

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.

Regarding patients with history of low fertilization rate or high number of immature oocytes, the existing literature is limited by its observational nature. In addition, large differences are observed in the definition of low maturity rate, low fertilization rate, dose of hCG administered and most importantly lack of LBR and OHSS rate as an outcome. The dual trigger in this subgroup of patients, cannot be recommended until data on its efficacy and safety from RCT's are available.

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16. Luteal phase support (LPS)

KEY QUESTION: WHAT IS THE EFFICACY AND SAFETY OF LUTEAL SUPPORT PROTOCOLS?

16.1 PROGESTERONE

Evidence

A Cochrane meta-analysis reported a higher live birth/ongoing pregnancy rate with progesterone compared to placebo/no treatment for luteal phase support (LPS) (5 RCT, OR 1.77, 95% CI 1.09-2.86, 642 women) (van der Linden, et al., 2015).

Dosing

The Cochrane meta-analysis also investigated the dosage of vaginal progesterone. Five studies compared a low dose (≤ 100 mg) with a high dose (≥ 100 mg) and reported no difference in live birth/ongoing pregnancy rate (5 RCT, OR 0.97, 95% CI 0.84-1.11, 3720 women) (van der Linden, et al., 2015). After the publication of the Cochrane review, a small pilot study was conducted including 146 women, investigating the effect of increasing the progesterone dosage in the mid-luteal phase in patients with progesterone levels below 15 ng/ml. There was no significant difference in live birth rate with increased progesterone dosage compared to original dosage (25% (9/36) vs. 17.1% (6/35)) (Aslih, et al., 2017). Another small RCT including 111 women compared 600 mg vaginal progesterone (capsules) with 90 mg vaginal progesterone (gel) and reported no difference in live birth rate (52.8% (28/53) vs. 42.6% (20/47)) (Michnova, et al., 2017).

Timing

Six RCTs investigated the timing of LPS initiation (Baruffi, et al., 2003, Fanchin, et al., 2001, Gao, et al., 2018, Mochtar, et al., 2006, Sohn, et al., 1999, Williams, et al., 2001). One RCT compared starting LPS with progesterone on the day of oocyte retrieval with the day after oocyte retrieval in 233 women and reported no significant difference in live birth rate (46.6% (48/103) vs. 45.7% (43/94)) (Gao, et al., 2018). Three RCTs compared starting LPS with progesterone on the evening of oocyte retrieval with starting on the evening of embryo transfer in respectively 103, 84 and 255 women and reported no significant difference in clinical pregnancy rate (respectively 27.4% vs. 28.8%; 42% vs. 29%; 28.1% (36/128) vs. 29.1% (37/127)) (Baruffi, et al., 2003, Fanchin, et al., 2001, Mochtar, et al., 2006). Only one study reported live birth rate and found no significant difference between groups (21.1% (27/128) vs. 20.5% (26/127); RR 0.97, 95% CI 0.60-1.56) (Mochtar, et al., 2006). Two RCTs (respectively 314 cycles and 385 women) compared starting LPS with progesterone before oocyte retrieval (respectively 12h before oocyte retrieval and at the evening of hCG trigger) with starting LPS after oocyte retrieval (Mochtar, et al., 2006, Sohn, et al., 1999). Mochtar et al. reported no significant difference in live birth (20% (26/130) vs. 21.1% (27/128); RR 0.94, 95% CI 0.58-1.52) or clinical pregnancy rate (23.1% (30/130) vs. 28.1% (36/128); RR 0.82, 95% CI 0.54-1.24) between groups (Mochtar, et al., 2006). However, Sohn et al. found a significantly lower clinical pregnancy rate when LPS was started before oocyte retrieval compared to after (12.9% vs. 24.6%) (Sohn, et al., 1999). One small RCT including 126 women compared starting LPS with progesterone on day 3 or day 6 after oocyte retrieval and found a significantly lower

clinical pregnancy rate when LPS was started on day 6 compared to day 3 (44.8% vs. 61.0%) (Williams, et al., 2001).

A meta-analysis including 6 RCTs compared stopping progesterone LPS at the time of pregnancy test with continuing progesterone until week 6/7 and found no significant difference in live birth rate (RR 0.95, 95% CI 0.86-1.05, 369 women) or ongoing pregnancy rate (RR 0.97, 95% CI 0.90-1.05, 1066 women) (Liu, et al., 2012).

Administration route

Several studies compared the efficacy of different administration routes for progesterone as LPS. An IPD meta-analysis compared the subcutaneous with the vaginal route (2 RCT, 1435 women) (Doblinger, et al., 2016). Live birth rate was 35.3% (252/714) with subcutaneous progesterone vs. 37.6% (271/721) with vaginal progesterone (risk difference -0.02, 95% CI -0.07-0.03). There was no difference in incidence of OHSS between both groups (27/714 vs. 26/721; OR 1.04, 95% CI 0.60-1.81) (Doblinger, et al., 2016). The Cochrane meta-analysis investigated vaginal/rectal compared to the oral route and reported no difference between groups for live birth/ongoing pregnancy rate (4 RCT, OR 1.19, 95% CI 0.83-1.69, 857 women) (van der Linden, et al., 2015). The Cochrane meta-analysis also investigated the vaginal/rectal compared to the intramuscular route and reported no difference in live birth/ongoing pregnancy rate (7 RCT, OR 1.37, 95% CI 0.94 to 1.99, 2039 women) (van der Linden, et al., 2015). A more recent RCT including 400 women also investigated the intramuscular compared to vaginal route and reported no difference in clinical pregnancy rate (26.5% (53/200) vs. 26.5% (53/200)) (Zargar, et al., 2016). One very small RCT including 40 women investigated the intramuscular compared to the oral route and reported no difference in live birth rate (OR 0.71, 95% CI 0.14-3.66) (Iwase, et al., 2008, van der Linden, et al., 2015).

Recommendations

Progesterone is recommended for luteal phase support after IVF/ICSI.	Strong ⊕○○○
Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.	GPP
The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg once daily for intramuscular progesterone 25 mg once daily for subcutaneous progesterone 90 mg once daily for vaginal progesterone gel 200 mg three times daily for micronized vaginal progesterone in-oil capsules	GPP

100 mg two or three times daily for micronized vaginal progesterone in starch suppositories 400 mg two times daily for vaginal pessary.	
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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
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Progesterone for luteal phase support should be administered at least until the day of the pregnancy test.	GPP
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Justification

Progesterone is recommended for luteal phase support for IVF/ICSI.

Start of luteal support has not been studied properly. More studies are necessary to investigate the need of luteal support and the correct timing to support endogenous progesterone levels. Until studies have been performed, luteal support should be provided in the window between the evening of the day of oocyte retrieval and D3 post oocyte retrieval.

With the current evidence available, no major differences in efficacy have been found comparing the different administration routes of progesterone or duration of progesterone LPS.

Long-term offspring health studies are currently lacking.

16.2 DYDROGESTERONE

Evidence

Daily dosages of 30 mg dydrogesterone are most frequently used for LPS.

A recent meta-analysis comparing the use of oral dydrogesterone and vaginal progesterone for LPS reported no difference in live birth/ongoing pregnancy rate (8 RCT, RR 1.08, 95% CI 0.92-1.26, 3386 women) (Barbosa, et al., 2018). An RCT, more recent than the meta-analysis, including 1034 women, compared dydrogesterone with vaginal progesterone gel and also reported no significant difference in live birth rate (34.4% (170/494) vs. 32.5% (159/489)) (Griesinger, et al., 2018).

A small RCT including 105 women compared the use of oral dydrogesterone with placebo for LPS and found no statistical difference in clinical pregnancy rate (29.6% (16/54) vs. 27.4% (14/51)) (Kupferminc, et al., 1990).

Recommendations

Dydrogesterone is probably recommended for luteal phase support.

Conditional ⊕⊕⊕○

Justification

When compared to progesterone, oral dydrogesterone has similar ongoing pregnancy rate. However, in the meta-analysis, results from frozen and fresh transfer cycles were pooled.

Additionally, 3 RCTs in the meta-analysis reported on patient dissatisfaction, the oral administration route was preferred over the vaginal route of progesterone in 2/3 RCTs (women in the 3rd RCT showed no difference in dissatisfaction) (Barbosa, et al., 2018). The studies by Tournaye et al. and Griesinger et al. reported similar safety and tolerability in both treatment groups (Griesinger, et al., 2018, Tournaye, et al., 2017).

As dydrogesterone is an orally-active progestogen different in structure from natural progesterone, there are some concerns regarding safety for the offspring. Evidence from 2 RCTs shows no difference in the rate of congenital anomalies as compared to natural progesterone (Griesinger, et al., 2018, Tournaye, et al., 2017), however, the GDG considers these data insufficient to make a firm statement and there is a lack of long-term offspring health studies.

Some disagreement within the guideline group regarding the strength of the recommendation was noted. One member considered that this should be a strong recommendation, based on the safety approval by ICH-GCP standard and the historical use of dydrogesterone for early miscarriage prevention.

16.3 OESTRADIOL SUPPLEMENTATION

Evidence

The Cochrane meta-analysis, mentioned before, reported no difference in live birth/ongoing pregnancy rate (9 RCT, OR 1.12, 95% CI 0.91-1.38, 1651 women) or OHSS (2 RCT, OR 0.58, 95% CI 0.20-1.68, 461 women) between progesterone with oestradiol supplementation and progesterone alone (van der Linden, et al., 2015). An RCT, more recent than the meta-analysis, including 220 women comparing progesterone and progesterone with oestradiol for LPS reported no significant difference in ongoing pregnancy rate (32.7% (36/110) vs. 36.3% (40/110)) (Ismail Madkour, et al., 2016).

In contrast, a RCT not included in the meta-analysis investigated the effect of adding oestradiol to a high dose of progesterone (200 mg vaginal capsules 3x/day + 100 mg intramuscular daily) for LPS in 240 women and reported a significant higher clinical pregnancy rate with oestradiol supplementation in women undergoing the long GnRH agonist and short flexible GnRH antagonist protocol (43.3% vs. 35% and 60% vs. 36.6% resp.), but not with the short GnRH agonist protocol (43.3% vs. 40%) (Gizzo, et al., 2014).

Two RCTs compared different dosages of oestradiol in addition to progesterone for LPS (Kutlusoy, et al., 2014, Tonguc, et al., 2011). Tonguc et al. compared vaginal progesterone with 3 different dosages

of oestradiol (2-4-6 mg) in 285 women and found no difference in clinical pregnancy rate between groups (31.6% (30/95) vs. 40% (38/95) vs. 32% (31/95) resp.) (Tonguc, et al., 2011). Kutlusoy et al. compared vaginal progesterone with 2 mg oestradiol and 6 mg oestradiol in 62 women and found no significant difference in live birth rate between dosages (37% (10/27) vs. 22.9% (8/35)) (Kutlusoy, et al., 2014).

Recommendation

The addition of oestradiol to progesterone for luteal phase support is probably not recommended.

Conditional ⊕⊕○○

Justification

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.

16.4 HUMAN CHORIONIC GONADOTROPHIN (HCG)

Evidence

The Cochrane meta-analysis, mentioned before, found a higher live birth/ongoing pregnancy rate with hCG for LPS compared to placebo/no treatment (3 RCT, OR 1.76, 95% CI 1.08-2.86, 527 women) (van der Linden, et al., 2015). However, the OHSS rate was increased with hCG for LPS (1 RCT, OR 4.28, 95% CI 1.91-9.60, 387 women) (Belaisch-Allart, et al., 1990, van der Linden, et al., 2015).

When compared to progesterone, hCG for LPS or supplementation of progesterone with hCG did not have a beneficial effect on live birth/ongoing pregnancy rate (5 RCT, OR 0.95, 95% CI 0.65-1.38, 833 women). Furthermore, progesterone was associated with lower rates of OHSS rates than hCG with or without progesterone (5 RCT, OR 0.46, 95% CI 0.30-0.71, 1293 women) (van der Linden, et al., 2015).

One small study including 91 women compared hCG with progesterone combined with oestradiol for LPS and found no difference in clinical pregnancy rate (RR 0.99, 95% CI 0.50-1.92) (Smitz, et al., 1988).

Recommendations

In hCG triggered ovarian stimulation cycles, hCG as luteal phase support in standard dosages of 1500 IU is probably not recommended.

Conditional ⊕⊕○○

Justification

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).

Studies comparing hCG and progesterone for luteal support have not been stratified according to ovarian response.

16.5 GNRH AGONIST

16.5.1 SINGLE GNRH AGONIST BOLUS SUPPLEMENTATION

Evidence

Most of the studies administered a single bolus of GnRH agonist for LPS on day 6 after oocyte pick-up at a dose of 0.1 mg for triptorelin 1 mg for leuprolide.

The Cochrane meta-analysis, mentioned before, reported that a bolus of GnRH agonist added to progesterone for LPS significantly increased live birth/ongoing pregnancy rate (5 RCT, OR 0.59, 95% CI 0.39-0.87, 1536 women) (van der Linden, et al., 2015). One RCT in the meta-analysis reported OHSS and showed no difference between the groups (OR 1.00, 95% CI 0.33-3.01, 300 women) (van der Linden, et al., 2015, Yildiz, et al., 2014).

An RCT which was not included in the meta-analysis, including 180 women, reported a significantly higher clinical pregnancy rate in women who received the bolus of GnRH agonist in addition to progesterone for LPS compared to progesterone alone (25.5% (23/90) vs. 10.0% (9/90)) (Razieh, et al., 2009).

Since the publication of the meta-analysis, another RCT has been conducted, (83 women) also reporting a beneficial effect of a GnRH agonist bolus in addition to progesterone for LPS compared to progesterone alone on the clinical pregnancy rate (27.9% (12/43) vs. 10% (4/40); OR 3.4, 95% CI 1.01-11.9) (Zafardoust, et al., 2015).

Recommendation

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

Justification

The use of GnRH agonist for LPS needs further evaluation in well-designed RCTs, available studies in the meta-analysis have been rated as of very low quality. Current evidence indicates higher live birth/pregnancy rates with GnRH agonist bolus in addition to progesterone for LPS. The evidence on safety of GnRH agonist for LPS is very limited (1 RCT), however, it does not seem to increase the risk of OHSS (Yildiz, et al., 2014). The evidence on GnRH agonist for LPS in GnRH antagonist cycles is also limited.

Long-term health effects in the new-born have not been studied. Until these data are available, the GDG recommends using GnRH agonist for LPS only in the context of clinical trials.

16.5.2 REPEATED GNRH AGONIST

Evidence

Most of the studies administered GnRH agonist for LPS at dosages of 0.1 mg for triptorelin 1 mg for leuprolide.

The Cochrane meta-analysis reported that multiple doses GnRH agonist added to progesterone for LPS significantly increased live birth/ongoing pregnancy rate compared to progesterone alone (5 RCT, OR 0.64, 95% CI 0.42-0.98, 1325 women) (van der Linden, et al., 2015). One RCT in the meta-analysis reported OHSS and showed no difference between the groups (OR 1.00, 95% CI 0.33-3.01, 300 women) (van der Linden, et al., 2015, Yildiz, et al., 2014).

Since the publication of the meta-analysis, a large retrospective cohort study, including 2529 women comparing GnRH agonist alone for LPS with progesterone was conducted. Live birth rate was significantly higher with GnRH agonist compared to progesterone for LPS (17.6% (254/1436) vs. 9.8% (108/1093)) (Bar Hava, et al., 2017).

Recommendation

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

Justification

Current evidence indicates higher live birth /pregnancy rates with GnRH agonist alone or in addition to progesterone for LPS. The evidence on safety of GnRH agonist for LPS is very limited (1 RCT), however, it does not seem to increase the risk of OHSS (Yildiz, et al., 2014). The evidence on GnRH agonist for LPS in GnRH antagonist cycles is also limited.

Long-term health effects in the new-born have not been studied. Until these data are available, the GDG recommends using GnRH agonist for LPS only in the context of clinical trials.

16.6 LH SUPPLEMENTATION

Evidence

One small RCT including 35 women reported no difference in live birth rate (22.2% (4/18) vs. 23.5% (4/17)) or number of oocytes retrieved (11.7±1.9 vs. 13.8±1.8) between the LH supplementation group and the progesterone alone group. No cases of OHSS were reported in either group (Papanikolaou, et al., 2011).

Recommendation

Addition of LH to progesterone for luteal phase support can only be used in the context of a clinical trial.

Research
only

Justification

The available evidence consists of 1 very small pilot study, which has investigated the effect of adding LH to progesterone for LPS. However, the study and control group received different triggers for final

oocyte maturation (rhCG compared to GnRH agonist). Therefore, no conclusions can be drawn on the effect of LH supplementation for LPS, and this intervention cannot be recommended.

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PART E: Prevention of OHSS

In previous sections, recommendations were formulated regarding the preferable protocol of ovarian stimulation for predicted high responders. In short, evidence indicates that GnRH antagonist protocol is as effective as the GnRH agonist protocol, and significantly reduces the risk of OHSS in PCOS women. Even though there is no specific evidence on predicted non-PCOS high responders or PCOM patients, consensus of the guideline group is that GnRH antagonist protocol should also be recommended in these patient groups (section 4A.1, page 42). Furthermore, evidence from one RCT indicated that in case an GnRH agonist protocol is used in high responders, a reduced gonadotropin dose may decrease the risk of OHSS (section 4A.2.3, page 44).

The GnRH antagonist protocol is recommended for PCOS women with regards to improved safety and equal efficacy.

Strong

⊕⊕○○

The GnRH antagonist protocol is recommended for predicted high responders with regards to improved safety and equal efficacy.

GPP

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

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17. GnRH agonist triggering

KEY QUESTION: WHICH GNRH AGONIST MEDICATION AS A METHOD OF TRIGGERING WILL ADD TO THE PREVENTION OF THE OVARIAN HYPERSTIMULATION SYNDROME ALSO WITH REGARDS TO OVERALL EFFICACY

17.1 GNRH AGONIST TRIGGER VS HCG TRIGGER IN (PREDICTED) HIGH RESPONDERS

Evidence

A Cochrane meta-analysis comparing GnRH agonist trigger with hCG trigger found that GnRH agonist trigger was associated with a significantly lower risk of moderate/severe OHSS when compared with hCG among women at high risk of OHSS (3 RCT, OR 0.09, 95%CI 0.02-0.52, 212 women) (Youssef, et al., 2014).

Due to technical limitations of the meta-analysis, all other outcomes were collected from individual studies. In an RCT including 28 PCO women, comparing GnRH agonist with hCG for final oocyte maturation, no significant difference was found for live birth rate (1/15 vs. 2/13) or number of oocytes retrieved (19.8 ± 2.5 vs. 19.5 ± 1.9) (Babayof, et al., 2006). Similarly, in an RCT including 66 women with PCOS or previous high response, no significant difference was found in ongoing pregnancy rate (53.3% (16/30) vs. 48.3% (14/29)) or number of oocytes retrieved (20.2 ± 9.9 vs. 18.8 ± 10.4) between GnRH agonist and hCG for final oocyte maturation (Engmann, et al., 2008). An RCT including 118 women at risk of OHSS comparing GnRH agonist trigger with hCG trigger reported no significant difference in ongoing pregnancy rate (28.3% (17/60) vs. 25.9% (15/58)) between GnRH agonist trigger and hCG trigger (Humaidan, et al., 2013).

Fresh transfer vs freeze-all

An RCT including 280 women at risk of OHSS (number of follicles ≥ 12 mm between 14 and 25 on the day of trigger) compared GnRH agonist trigger with or without freeze-all (Aflatoonian, et al., 2018). There was no significant difference in live birth rate (27.3% (33/121) vs. 26.9% (32/119); OR 1.02, 0.57-1.80) or moderate OHSS (5.8% (7/121) vs. 5.9% (7/119)) between GnRH agonist trigger with freeze-all or fresh transfer. No cases of severe OHSS were reported in either group (Aflatoonian, et al., 2018).

In a retrospective cohort study including 122 women at risk of OHSS also comparing GnRH agonist for final oocyte maturation and fresh transfer with freeze-all, no significant difference was found in live birth rate (40.5% (30/74) vs. 41.7% (20/48)), or moderate/severe OHSS (2.7% (2/74) vs. 0% (0/48)) (Karacan, et al., 2017).

GnRH agonist vs hCG non-10.000 IU trigger and fresh transfer

One RCT including 118 patients at risk of OHSS (between 14 and 25 follicles ≥ 11 mm diameter on trigger day) reported no difference in OHSS between GnRH agonist trigger (0% (0/60)) compared to reduced hCG dose (3.4% (2/58)) in a GnRH antagonist protocol. No severe OHSS was reported in either group. Ongoing pregnancy rates were similar for GnRH agonist trigger (28.3% (17/60))

compared to reduced-dose hCG trigger (25.9% (15/58)) and also a similar number of oocytes was retrieved in both groups (13.7±5.9 vs. 13.5±5.7) (Humaidan, et al., 2013).

Recommendation

A GnRH agonist trigger is recommended for final oocyte maturation in women at risk of OHSS.

Strong ⊕○○○

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

Justification

Triggering final oocyte maturation with GnRH agonist significantly reduces the risk of early-onset OHSS in patients at risk of OHSS.

Limited evidence suggests that GnRH agonist trigger with fresh transfer is as efficient and safe as GnRH agonist trigger with freeze-all in patients at risk of OHSS with number of follicles ≥ 12 mm between 14 and 25 on the day of trigger. Modified luteal support with LH-activity (hCG or LH) may overcome the reduction in clinical pregnancy rate after GnRH agonist trigger. However, its effectiveness of OHSS prevention is reduced.

Recommendation

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 ⊕○○○

Justification

Only one study addressed the question of comparing GnRH agonist trigger with hCG non-10.000 trigger and fresh transfer (Humaidan, et al., 2013) with a study population consisting of patients at moderate risk of OHSS (between 14 and 25 follicles ≥ 11 mm diameter on trigger day), and based on fresh replacement cycles, not taking into account the option of freeze-all. The study was underpowered to show a difference in the moderate and severe OHSS rate. A small non-significant difference in OHSS rates was 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.

17.2 GnRH AGONIST TRIGGER + FREEZE-ALL VS HCG TRIGGER+FREEZE-ALL

Evidence

A case-control study, including 248 women at risk of OHSS, compared hCG trigger and freeze-all with GnRH agonist trigger and freeze-all. There was no significant difference in cumulative pregnancy rate between hCG and GnRH agonist trigger with freeze-all (53.0% vs. 59.5%) (Borges, et al., 2016).

Similar results were found in a retrospective cohort study including 272 women at risk of OHSS, also comparing hCG trigger and freeze-all with GnRH agonist trigger and freeze-all. There was no difference in cumulative live birth rate between GnRH agonist and hCG for final oocyte maturation and freeze-all (48.15% vs. 48.08%) (Tannus, et al., 2017).

Recommendation

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 ⊕○○○
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Justification

Available evidence is derived from low-quality studies in patients at risk of OHSS. However, evidence from RCTs performed in oocyte donors indicates that GnRH agonist trigger is preferable over hCG when a freeze-all strategy is applied (Acevedo, et al., 2006, Galindo, et al., 2009, Melo, et al., 2009, Sismanoglu, et al., 2009). The guideline group thinks that the data can be extrapolated to GnRH agonist trigger compared to hCG with freeze-all in both arms for patients at risk of OHSS.

17.3 GnRH AGONIST TRIGGER VS COASTING+HCG TRIGGER

Evidence

A retrospective study including 94 women at risk of OHSS reported that 10/33 women in the coasting group had cycle cancellation because of the risk of development of OHSS vs. 0/61 in the GnRH agonist trigger group. No cases of OHSS occurred in either treatment group. Ongoing pregnancy rates (49.2% (30/61) vs. 24.2% (8/33)) and number of oocytes retrieved (26.9±9.5 vs. 17.7±9.3) were significantly higher in the GnRH agonist trigger group compared to the coasting group (DiLuigi, et al., 2010).

Another retrospective study including 248 women at risk of OHSS reported more cancelled cycles in the coasting group compared to the GnRH agonist trigger with freeze-all group (19.7% (30/152) vs. 8.3% (8/96) because of poor embryo quality or risk of OHSS. The clinical pregnancy rate in the coasting group was 29.5% (36/122), which was significantly lower than the GnRH agonist trigger with freeze-all (50% (44/88)) (Herrero et al., 2011).

Recommendation

A GnRH agonist trigger for final oocyte maturation with or without a freeze-all strategy is preferred over a coasting	GPP
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strategy in patients at risk of OHSS.	
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Justification

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 in patients at risk of OHSS.

17.4 GnRH AGONIST TRIGGER VS HCG TRIGGER+CABERGOLINE/ALBUMIN

Evidence

Regarding the research question posed above, no relevant studies could be identified. As such the research question cannot be answered.

Recommendation

Cabergoline or albumin as additional preventive measures for OHSS are not recommended when GnRH agonist is used for triggering final oocyte maturation.	
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GPP

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18. Freeze-all

KEY QUESTION: IS THE FREEZE-ALL PROTOCOL MEANINGFUL IN THE PREVENTION OF OVARIAN HYPER-STIMULATION SYNDROME ALSO WITH REGARD TO EFFICACY?

Ovarian hyperstimulation syndrome (OHSS) is a potential life-threatening condition. It implies hospitalization frequently, with health care additional costs and patient burden. However, it may be balanced to the possible negative effects of a freeze-all policy and the decline in live birth rates, due to eliminating the fresh transfer from the treatment scheme.

Evidence

A recent Cochrane meta-analysis combining 4 RCTs with 1892 women reported a lower Incidence of OHSS: 1-3% vs. 7% (2 RCT, OR 0.24, 95% CI 0.15-0.38, 1633 women) with the freeze-all strategy compared to fresh transfer. Furthermore, they found no difference in live birth rate cumulative for all embryo stages at transfer (4 RCT, OR 1.09, 95% CI 0.91-1.31, 1892 women), and no difference in ongoing pregnancy rate cumulative for all embryo stages at transfer (2 RCT, OR 1.05, 95% CI 0.64- 1.73) (Wong, et al., 2017).

Two RCTs were published after the meta-analysis. One RCT including 2157 women confirmed the findings of the meta-analysis, with no difference in live birth rate (48.7% (525/1077) vs. 50.2% (542/1080); RR 0.97, 95% CI 0.89-1.06) with frozen versus fresh embryo transfer, and a significant reduction in moderate and severe OHSS with frozen embryo transfer (0.6% (7/1077) vs. 2.0% (22/1080); RR 0.32, 95% CI 0.14-0.74) (Shi, et al., 2018). Another RCT including 782 women also reported no difference in live birth rate with frozen versus fresh embryo transfer (33.8% (132/391) vs. 31.5% (123/391); RR 1.07, 95% CI 0.88-1.31). However, there was no significant difference in moderate or severe OHSS between groups (0.8% (3/391) vs. 1.0% (4/391); RR 0.75, 95% CI 0.17-3.33) (Vuong, et al., 2018).

An earlier Cochrane meta-analysis compared freeze-all with intravenous albumin to prevent OHSS and reported no significant difference in moderate and/or severe OHSS (1 RCT, OR 5.33, 95% CI 0.51-56.24, 26 women) or clinical pregnancy rate (1 RCT, OR 0.06, 95% CI 0.00-1.17, 26 women) between groups (D'Angelo and Amso, 2007).

Recommendation

A freeze-all strategy is recommended to fully eliminate the risk of late-onset OHSS.

Strong ⊕⊕⊕○

Prior to start of ovarian stimulation, a risk assessment for high response is advised.

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Justification

The current evidence suggests that not performing a fresh embryo 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.

The conditions with a high prior risk of developing the OHSS comprise:

- patients with the PCOS syndrome,
- patients with an above average ovarian reserve status
- patients exhibiting a high ovarian response as indicated by follicle number at ultrasound, high oestradiol levels, or high number of oocytes obtained

Applying the freeze-all strategy implies the presence of a high-quality cryopreservation program.

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Glossary

Ovarian hyperstimulation syndrome (OHSS)	An exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It may be classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic complications.
Ovarian stimulation (OS)	Pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes: 1) for timed intercourse or insemination; 2) in ART, to obtain multiple oocytes at follicular aspiration.
Poor ovarian responder (POR) in assisted reproductive technology	A woman treated with ovarian stimulation for ART, in which at least two of the following features are present: (1) Advanced maternal age (≥ 40 years); (2) A previous poor ovarian response (≤ 3 oocytes with a conventional stimulation protocol aimed at obtaining more than three oocytes); and, (3) An abnormal ovarian reserve test (i.e. antral follicle count 5–7 follicles or anti-Mullerian hormone 0.5–1.1 ng/ml (Bologna criteria); or other reference values obtained from a standardized reference population.)
Poor ovarian response (POR) to ovarian stimulation	A condition in which fewer than four follicles and/or oocytes are developed/obtained following ovarian stimulation with the intention of obtaining more follicles and oocytes.
Mild ovarian stimulation	A protocol in which the ovaries are stimulated with gonadotropins, and/or other pharmacological compounds, with the intention of limiting the number of oocytes following stimulation for IVF.
Modified natural cycle	A procedure in which one or more oocytes are collected from the ovaries during a spontaneous menstrual cycle. Pharmacological compounds are administered with the sole purpose of blocking the spontaneous LH surge and/or inducing final oocyte maturation

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Annexes

Annex 1: Guideline development group

Annex 2: Summary of findings tables

Annex 3: Recommendations for research

Annex 4: Abbreviations

Annex 5: Methodology

Annex 6: Stakeholder consultation

Annex 7: Literature study: flowcharts, list of excluded studies

Annex 8: Evidence tables

Annex 1: Guideline development group

This guideline was developed by the ESHRE Reproductive Endocrinology Guideline Development Group (GDG). The GDG included gynaecologists with expertise in reproductive medicine and ovarian stimulation. We aimed for an equal distribution in gender, region and expertise.

Chair of the GDG

Frank Broekmans Department of Reproductive Medicine and Gynecology, University Medical Center Utrecht, Utrecht (The Netherlands)

GDG members

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Methodological support

Nathalie Le Clef European Society of Human Reproduction and Embryology (Belgium)

Nathalie Vermeulen

European Society of Human Reproduction and Embryology (Belgium)

DECLARATIONS OF INTEREST

All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms (see *ESHRE Manual for Guideline Development*).

Conflicts of interest	
Frank Broekmans	Research grants from Merck, Ferring Consulting fees from Ferring, Merck Speaker's fees from Merck
Nikolaos Polyzos	Research grants from Ferring, MSD, Roche and Besins Consulting fees from MSD, Ferring, IBSA Speaker's fees from Ferring, MSD, Merck, IBSA, Theramex, Besins Healthcare, Gedeon-Richter, Roche Diagnostics
Antonio La Marca	Research grants from Ferring, MSD, IBSA, Merck Serono, Gedeon-Richter, TEVA Consulting fees from Roche, Beckman-Coulter
Georg Griesinger	Consulting fees from MSD, Ferring, Merck Serono, IBSA, Theramex, Finox, TEVA, Gedeon-Richter, Glycotope, Abbott, Vitrolife, Biosilu, ReprodWissen, Obseva, PregLem Speaker's fees from MSD, Ferring, Merck Serono, IBSA, Finox, TEVA, Gedeon-Richter, Glycotope, Abbott, Vitrolife, Biosilu
Ernesto Bosch	Research grants from Gedeon-Richter Consulting fees from MSD, Ferring, Abbot, Gedeon-Richter, Merck, Roche Speaker's fees from MSD, Ferring, Abbot, Gedeon-Richter, Merck, Roche Ownership interest from IVI-RMS Valencia
Peter Humaidan	Research grants from Gedeon-Richter, Merck, IBSA, Ferring Speaker's fees from MSD, IBSA, Merck, Gedeon-Richter
Janos Urbancsek	Speaker's fees from IBSA, Ferring
Nathalie Massin	Research grants from MSD, Merck, IBSA Consulting fees from MSD, Merck, IBSA, Ferring Speaker's fees from MSD, Merck, IBSA, Gedeon-Richter, Theramex
Töyli Mira	None declared.
Michael Grynberg	Speaker's fees from Merck Serono, Ferring, Gedeon Richter, MSD
Sesh Kamal Sunkara	Speaker's fees from Merck, MSD, Ferring, Pharmasure
Simone Broer	None declared.
George Lainas	None declared.
Estratios Kolibianakis	Speaker's fees from Merck Serono, Angellini Pharma and MSD
Michal Kunicki	Speaker's fees from Ferring
Tanya Timeva	Speaker's fees from Merck, MSD, MLD
Sebastian Mastenbroek	None declared.
Nathalie Vermeulen	None declared.
Nathalie Le Clef	None declared.

Annex 3: Recommendations for research in OS for IVF/ICSI

From the literature and discussion of the available evidence, several topics were identified for which evidence is inconsistent, insufficient or non-existing. For the benefit of couples undergoing ovarian stimulation for IVF/ICSI, the GDG recommends that future research, where possible in well-designed RCTs, should focus on these research gaps.

Considered are:

- Gonadotropin dose reduction in predicted high responders as a tool for normalization of ovarian response (GnRH agonist or antagonist) compared to a standard dosage with option GnRH agonist trigger and/or a freeze-all strategy (in GnRH antagonist protocol).
- Pre-treatment options for scheduling in GnRH antagonist protocol compared to GnRH agonist protocol
- GnRH agonist LPS compared to progesterone LPS compared to low dose hCG LPS
- The efficacy and safety of a freeze-all strategy in cycles with routine embryo biopsy for PGD of PGS
- GnRH agonist trigger with adjusted luteal support compared to 10.000 hCG trigger with Freeze-all in observed high responders

Annex 4: Abbreviations

AFC	Antral follicle count
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technology
BMI	Body mass index
CC	Clomiphene citrate
CI	Confidence interval
COC	Cumulus-oocyte complex
COCP	Combined oral contraceptive pill
DHEA	Dehydroepiandrosterone
Duostim	Double stimulation, ovarian stimulation during the follicular and luteal phase of the same cycle
EFORT	Exogenous follicle stimulating hormone ovarian reserve test
EMT	Endometrial thickness
FSH	Follicle stimulating hormone
GDG	Guideline development group
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GPP	Good practice point
hCG	Human chorionic gonadotrophin
hMG	Human menopausal gonadotropin
hp-FSH	Highly purified follicle stimulating hormone
ICSI	Intracytoplasmic sperm injection
IPD	Individual patient data
IU	International unit
IUI	Intra-uterine insemination
IVF	In vitro fertilization
LBR	Live birth rate
LH	Luteinizing hormone
LPS	Luteal phase support
LR	Logistic regression
MD	Mean difference
MNC	Modified natural cycle
MPA	Medroxy progesterone acetate
OHSS	Ovarian hyperstimulation syndrome
OPU	Oocyte pick-up
OR	Odds ratio
OS	Ovarian stimulation
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
p-FSH	Purified follicle stimulating hormone
POI	Premature ovarian insufficiency
PR	Pregnancy rate
RCT	Randomized controlled trial
rFSH	Recombinant follicle stimulating hormone
rLH	Recombinant luteinizing hormone
ROC-AUC	Receiver operating characteristic – area under the curve
RR	Relative risk/risk ratio
SMD	Standardized mean difference
WMD	Weighted mean difference

Annex 5: Methodology

GUIDELINE DEVELOPMENT

European Society of Human Reproduction and Embryology (ESHRE) guidelines are developed based on the Manual for ESHRE guideline development (Vermeulen, et al., 2017), which can be consulted at the ESHRE website (www.eshre.eu/guidelines). The principal aim of this manual is to provide stepwise advice on ESHRE guideline development for members of ESHRE guideline development groups. The manual describes a 12-step procedure for writing clinical management guidelines by the guideline development group, supported by the ESHRE methodological expert:



The current guideline was developed and funded by ESHRE, which covered expenses associated with the guideline meetings (travel, hotel and catering expenses) associated with the literature searches (library costs, costs associated with the retrieval of papers) and with the implementation of the guideline (printing, publication costs). Except for reimbursement of their travel expenses, GDG members did not receive any payment for their participation in the guideline development process.

The scope of the guideline and first version of the key questions were drafted by the coordinator and deputies of the ESHRE Special Interest Group Reproductive Endocrinology. A call was launched for experts in the field interested in joining the guideline development group. All applications were reviewed, and experts were selected based on expertise and geographical location. We strived towards a balance in gender and location within Europe. A meeting of the guideline development group was organized to discuss the key questions and redefine them through the PICO process (patients – interventions – comparison – outcome). This resulted in a final list of 18 key questions. Based on the defined key words, literature searches were performed by the methodological expert (Dr. N. Le Clef). Key words were sorted to importance and used for searches in PUBMED/MEDLINE and the Cochrane library. We searched the databases from inception up to 8 November 2018.

Literature searches were performed as an iterative process. In a first step, systematic reviews and meta-analyses were collected. If no results were found, the search was extended to randomized controlled trials, and further to cohort studies and case reports, following the hierarchy of the levels of evidence. Reference were selected or excluded by the methodological expert and expert GDG member based on title and abstract and knowledge of the existing literature. If necessary, additional searches were performed in order to get the final list of papers. For interventional questions, focus was on prospective (randomized) controlled studies. The quality of the selected papers was assessed by means of the quality assessment checklist, defined in the ESHRE guideline manual. Furthermore, the evidence was collected and summarized in an evidence table according to GIN format (<http://www.g-i->

n.net/activities/etwg). The quality assessment and evidence tables were constructed by the expert GDG members.

Summary of findings tables (Annex 2) were prepared following the GRADE approach for randomized controlled intervention studies which reported pregnancy rates and/or safety data. Where available, summary of findings tables were based on existing up-to-date well-executed systematic reviews, if necessary supplemented with additional recent RCTs. When there was no recent valid systematic review available, we systematically searched for relevant studies, as described above, with focus on prospective (randomized) studies. Cumulative live birth rate, live birth rate and ovarian hyperstimulation syndrome (OHSS) were considered the critical outcomes.

GDG meetings were organized to discuss the draft recommendations and the supporting evidence and to reach consensus on the final formulation of the recommendations. In a final step, all evidence and recommendations were combined in the ESHRE guideline: “Ovarian stimulation for IVF/ICSI”.

FORMULATION OF RECOMMENDATIONS

We labelled the recommendations as either “strong” or “conditional” according to the GRADE approach. We used the words “we recommend” for strong recommendations and “we probably recommend” for conditional recommendations. Suggested interpretation of strong and conditional recommendations by patients, clinicians and health care policy makers is as follows:

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
Clinicians	Most individuals should receive the intervention Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences
Policy makers	The recommendation can be adopted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders

For each recommendation it is mentioned whether it is strong or conditional and what the quality of the supporting evidence was. In the justification section, more data are provided on the considerations taken into account when formulating the recommendations: balance between desirable and undesirable effects, certainty of the evidence of effects, certainty in how people value the outcome, acceptability and feasibility of the intervention. Impact on health equity and resource impact were only discussed where relevant.

STRATEGY FOR REVIEW OF THE GUIDELINE DRAFT

After finalization of the guideline draft, the review process was initiated. The draft guideline was published on the ESHRE website, accompanied by the reviewers' comments form and a short explanation of the review process. The guideline was open for review between 14 January and 10 February 2019.

To notify interested clinicians, we sent out an invitation to review the guideline by email to all members of the ESHRE SIG of Reproductive Endocrinology.

Selected reviewers were invited personally by email. These reviewers included:

- *Coordinators and deputies of the ESHRE SIG Reproductive Endocrinology and the ESHRE SIG Quality and Safety in ART.*
- *Contact persons of patient organizations across Europe.*
- *Contact persons of international and national societies focused on IVF/ICSI across Europe.*

All reviewers are listed in annex 6. The Reviewer comments processing report, including further information on the review and a list of all comments per reviewer with the response formulated by the GDG will be published on the ESHRE website.

GUIDELINE IMPLEMENTATION STRATEGY

The standard dissemination procedure for all ESHRE guidelines comprises publishing and announcement.

Each guideline is published on the ESHRE Website and in Human Reproduction Open. The announcement procedure includes a news item in "Focus on Reproduction", a newsflash on the ESHRE website homepage and a short presentation at the ESHRE Annual meeting. All participants in the annual ESHRE meeting will be informed about the development and release of new guidelines; all related national societies and patient organizations are informed about the guideline release. They are asked to encourage local implementation by, for instance, translations or condensed versions, but they are also offered a website link to the original document.

Patient versions of the guideline will be developed by a subgroup of the GDG together with patient representatives. The patient version is a translation of the recommendations in everyday language, with emphasis on questions important to patients. It aims to help patients understand the guideline's recommendations and facilitates clinical decision-making.

To further enhance implementation of the guideline, the members of the GDG, as experts in the field, will be asked to select recommendations for which they believe implementation will be difficult and make suggestions for tailor-made implementation interventions (e.g. option grids, flow-charts, additional recommendations, addition of graphic/visual material to the guideline).

SCHEDULE FOR UPDATING THE GUIDELINE

The current guideline will be considered for revision in 2023 (four years after publication). An intermediate search for new evidence will be performed two years after publication, which will inform the GDG of the necessity of an update.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found at www.eshre.eu/guidelines.

For more details on the methodology of ESHRE guidelines, visit www.eshre.eu/guidelines

Annex 6: Stakeholder consultation

As mentioned in the methodology, the guideline draft was open for review for 6 weeks, between 12 February and 26 March 2019. All reviewers, their comments and the reply of the guideline development group are summarized in the review report, which is published on the ESHRE website as supporting documentation to the guideline. The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representative	Organization
Raj Mathur	Brittish Fertility Society
Ferraretti A.P,	ESHRE, authors of "ESHRE definition on POR" (2011).
Richard Anderson, chair of GDG	ESHRE Fertility preservation guideline group

Reviewer	Country
Hans-Peter Steiner	Austria
Kris Poppe	Belgium
Pratip Chakraborty	India
Mariano Mascarenhas	UK
Arianna D'Angelo	UK
Juan A Garcia-Velasco	Spain
Carlos Calhaz-Jorge	Portugal
Riikka Leppänen	Finland
Ronit Beck Fruchter	Israel
Apostolos Tsironis	UK
Nick Macklon	UK
Klaus Bühler and co-workers	Germany
Hakan Yarali	Turkey
Li Rong	China
Ahmed Samy Saad	Egypt
Aboubakr Mohamed Elnashar	Egypt
Paolo Emanuele Levi-Setti	Italy
Corina Manolea	Romania
Julian Jenkins	Switzerland
Carlo Alviggi and co-workers	Italy and other countries
Thomas D'Hooghe	Belgium
Filippo Ubaldi and co-workers	Italy
Fei Gong	China
Yun Lin	China
Jan Olofsson	Switzerland
Aidong Gong	China
Pablo Diaz-Spindola	Mexico
Ahmet Turp	Turkey
Tamar Barbakadze	Georgia
Sandro C Esteves and co-workers	Brazil

Gemma Castellón Cortés	Spain
William Ledger	Australia
Yuan Li	China
Pedro Barri	Spain
Fabiola Beligotti	Switzerland
Julia Koloda	Russia
Ferraretti A.P.	Italy
Mochtar M., van Wely M., Braat D., Goddijn M.	Netherlands

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Vermeulen N, Le Clef N, D'Angelo A, Tillemans K, Veleva Z, Nelen WL. Manual for ESHRE guideline development. 2017.