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Controlled Ovarian Stimulation for IVF/ICSI

February 2019

ESHRE Reproductive Endocrinology Guideline Group

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Introduction to the guideline

Controlled ovarian stimulation for IVF/ICSI has not been addressed by existing evidence-based guidelines. Controlled 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).

A narrative review of evidence provided for WHO guidance on management of controlled 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 controlled 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 controlled 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 controlled 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 (GLOSSARY). The GDG decided to use the term controlled ovarian stimulation (COS) to confine to ovarian stimulation for IVF/ICSI.

Response after ovarian stimulation is usually classified as poor, normal and excessive response. 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 COS 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 19 follicles ≥11 mm in size on day of oocyte maturation trigger and/or 19 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.

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.

References

Farquhar C, Marjoribanks J, Brown J, Fauser B, Lethaby A, Mourad S, Rebar R, Showell M, van der Poel S. Management of ovarian stimulation for IVF: narrative review of evidence provided for World Health Organization guidance. *Reproductive biomedicine online* 2017;35: 3-16.

Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Human reproduction (Oxford, England)* 2011;26: 1616-1624.

279 Griesinger G, Verweij PJ, Gates D, Devroey P, Gordon K, Stegmann BJ, Tarlatzis BC. Prediction of
280 Ovarian Hyperstimulation Syndrome in Patients Treated with Corifollitropin alfa or rFSH in a GnRH
281 Antagonist Protocol. *PloS one* 2016;11: e0149615.

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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 of recombinant, high or low dosage of hCG, adding LH or LH like activity to the FSH as principal drug, management of high and low 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 (8-15 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. 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.

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 two months. 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 low 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 (Cantineau, et al., 2007, Lensen, et al., 2017, Ragni, et al., 2004, 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. Moreover, a few oocytes more may not make the desired difference in terms of live birth rates.

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.

References

Brandes M, Hamilton CJ, de Bruin JP, Nelen WL, Kremer JA. The relative contribution of IVF to the total ongoing pregnancy rate in a subfertile cohort. *Human reproduction (Oxford, England)* 2010;25: 118-126.

Brandes M, van der Steen JO, Bokdam SB, Hamilton CJ, de Bruin JP, Nelen WL, Kremer JA. When and why do subfertile couples discontinue their fertility care? A longitudinal cohort study in a secondary care subfertility population. *Human reproduction (Oxford, England)* 2009;24: 3127-3135.

Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. *The Cochrane database of systematic reviews* 2007: Cd005356.

Gameiro S, Finnigan A. Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. *Human reproduction update* 2017;23: 322-337.
Lensen SF, Wilkinson J, Mol BWJ, La MA, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI *Cochrane Database of Systematic Reviews*. 2017. John Wiley & Sons, Ltd.
McLernon DJ, Maheshwari A, Lee AJ, Bhattacharya S. Cumulative live birth rates after one or more complete cycles of IVF: a population-based study of linked cycle data from 178,898 women. *Human reproduction (Oxford, England)* 2016;31: 572-581.
Olivius K, Friden B, Lundin K, Bergh C. Cumulative probability of live birth after three in vitro fertilization/intracytoplasmic sperm injection cycles. *Fertility and sterility* 2002;77: 505-510.
Ragni G, Alagna F, Brigante C, Riccaboni A, Colombo M, Somigliana E, Crosignani PG. GnRH antagonists and mild ovarian stimulation for intrauterine insemination: a randomized study comparing different gonadotrophin dosages. *Human reproduction (Oxford, England)* 2004;19: 54-58.
Sterrenburg MD, Veltman-Verhulst SM, Eijkemans MJ, Hughes EG, Macklon NS, Broekmans FJ, Fauser BC. Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis. *Human reproduction update* 2011;17: 184-196.

List of all recommendations

Chapter	No.	Recommendation	Strength	Quality of evidence	Justification	Remarks
Pre-stimulation management						
1	1	For predicting high and low response to controlled ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests. *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.*	Conditional	⊕◯◯◯	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 controlled 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 controlled 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 GnRH agonist nor antagonist protocols.	SoF table 1
3	4	Pre-treatment with progesterone before controlled ovarian stimulation using 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 progesterone as pre-treatment in GnRH agonist nor GnRH antagonist protocols.	SoF table 2 a,b
3	5	The GDG acknowledges that oestrogen and 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 low 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 controlled 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 low responders is conflicting.	SoF table 4 a,b
LH suppression and ovarian stimulation						
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 COS 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 COS.	
4A	12	A reduced gonadotropin dose is recommended to decrease the risk of OHSS in predicted high responders if GnRH agonist protocols are used.	Strong	⊕◯◯◯	The recommendation is based on a subgroup analysis of one RCT. The guideline group would like to emphasize that clinicians are advised to use the GnRH antagonist protocol in expected high responders.	SoF table 6
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 antagonist protocol in regular IVF patients, the GnRH antagonist protocol is recommended in normal responder patients.	SoF table 7
4B	14	There is no evidence to recommend the use of Clomiphene Citrate in stimulation protocols for predicted normal responders.			The evidence was from studies performed in patients without predicted low 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	15	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 COS. The use of letrozole may reduce the risk of OHSS, however this was only shown in one small RCT.	SoF table 8
4B	16	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	17	GnRH antagonists and GnRH agonists are equally recommended for predicted low responders.	Conditional	⊕⊕◯◯	In women with low 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	18	Clomiphene citrate alone or in combination with gonadotrophins, and gonadotropin stimulation alone are equally recommended for predicted low responders.	Strong	⊕⊕◯◯	In women with low 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	19	The addition of letrozole to gonadotropins in stimulation protocols for predicted low responders is probably not recommended.	Conditional	⊕⊕◯◯	Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of COS	SoF table 12
4C	20	A higher gonadotropin dose of 300 IU is probably not recommended over the conventional dose of 150 IU for predicted low responders.	Conditional	⊕◯◯◯	A higher gonadotropin dose of 300 IU daily results in a higher number of oocytes in low responders, and more chances of having an embryo for transfer. There is unlikely to be significant benefit with doses > 300 IU daily.	SoF table 13
4C	21	A gonadotropin dose higher than 300 IU is not recommended for predicted low responders.	Strong	⊕◯◯◯		SoF table 14 a,b
4C	22	The use of modified natural cycle is probably not recommended over conventional ovarian stimulation for predicted low responders.	Conditional	⊕◯◯◯	There are no good quality studies available to support the use of Modified natural cycle or Natural cycle IVF in low responders.	SoF table 15
5	23	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	24	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	25	The use of progestin for LH peak suppression is probably not recommended. If applied, progestin can only be used in the	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	

		context of non-transfer cycles.			easy, cheap and patient friendly. However, the available evidence available is limited.	
6	26	The use of recombinant FSH (rFSH) and human menopausal gonadotropin (hMG) for controlled 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 an GnRH agonist cycle which was not considered clinically relevant, and with no difference in safety, the GDG concluded that hMG is probably not superior to rFSH. This conclusion is supported by the results of studies published after the meta-analysis.	SoF table 18
6	27	The use of recombinant FSH (rFSH) or purified FSH (p-FSH) for controlled ovarian stimulation 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	28	The use of either recombinant FSH (rFSH) and highly purified FSH (hp-FSH) for controlled ovarian stimulation 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	29	The addition of recombinant LH (rLH) to recombinant FSH (rFSH) is probably not recommended for controlled ovarian stimulation in the general IVF/ICSI population.	Conditional	⊕◯◯◯	According to the best available evidence, the additionof rLH to rFSH results in similar live birth rates compared to rFSH only.	SoF table 21
6	30	The addition of recombinant LH (rLH) to recombinant FSH (rFSH) is not recommended for controlled ovarian stimulation in low responders and women of advanced age.	Strong	⊕◯◯◯		SoF table 22 a,b
6	31	The use of highly purified FSH (hp-FSH) and human menopausal gonadotropin (hMG) for controlled ovarian stimulation in GnRH agonist protocols is equally recommended.	Conditional	⊕⊕◯◯	In patients undergoing COS 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 23
6	32	The use of recombinant LH + recombinant FSH (rFSH+rLH) for controlled 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 24
6	33	Letrozole is probably not recommended as a substitute for gonadotropins in low 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 25
6		There is no evidence available to recommend the substitution of FSH by Clomiphene Citrate in controlled ovarian stimulation.	/	/	/	Conclusion

6	34	The use of long-acting and daily recombinant FSH (rFSH) is equally recommended in GnRH antagonist cycles for normal responders.	Conditional	⊕⊕⊕◯	No differences have been observed in three large RCTs and in a small RCT in low responders regarding the probability of pregnancy or the number of COCs retrieved and the incidence of OHSS.	SoF table 26
7	35	Adjustment (increase or decrease) of the gonadotrophin dose beyond stimulation day 6 during controlled ovarian stimulation is probably not recommended.	Conditional	⊕◯◯◯	The current evidence does not support changing gonadotropin dose during COS beyond day 6.	
8	36	Routine use of adjuvant metformin before and/or during controlled 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 27
8	37	Use of adjuvant growth hormone before and/or during controlled ovarian stimulation is probably not recommended for low responders.	Conditional	⊕⊕◯◯	Despite the possible beneficial effects in low responders on live birth rate, the evidence is of too limited quality to recommend growth hormone during COS. The studies in the systematic review were generally underpowered and the definition of poor response very heterogeneous among studies.	SoF table 28 a,b
8	38	Use of testosterone before controlled ovarian stimulation is probably not recommended for low responders.	Conditional	⊕⊕⊕◯	Current evidence regarding adjuvant testosterone pre-treatment before COS 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 29
8	39	Use of DHEA before and/or during controlled ovarian stimulation is probably not recommended for low responders.	Conditional	⊕⊕⊕◯	There is currently inconsistent evidence that adjuvant DHEA use before and during COS improves ovarian response in terms of live birth/ongoing pregnancy rate in low responders following IVF treatment.	SoF table 30
8	40	Use of aspirin before and/or during controlled ovarian stimulation is not recommended in the general IVF/ICSI population and for low responders.	Strong	⊕⊕⊕◯	The existing evidence suggests that adjuvant aspirin before and/ or during controlled 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 31
8	41	Use of sildenafil before and/or during controlled ovarian stimulation is not recommended for low responders.	Strong	⊕◯◯◯	Current evidence from one low-quality, pseudo-randomized study involving women considered as low responders undergoing IVF showed no improvement in controlled ovarian response with adjuvant sildenafil use during controlled ovarian stimulation	
9	42	Random-start controlled 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	43	Late luteal phase start of gonadotropins is probably not recommended for low 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	44	Early luteal phase start of gonadotropins is probably not recommended for normal and low responders.	Conditional	⊕◯◯◯		
9	45	Luteal phase stimulation could be used in non-transfer cycles.	GPP			
9	46	Double stimulation in low 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 POR patients	
9	47	Double stimulation can be considered for urgent fertility preservation cycles.	GPP			
10	48	For controlled 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 COS, offer the possibility of triggering final oocyte maturation with GnRH agonist in case of high ovarian response, and reduce the risk of OHSS.	
10	49	In urgent (oncology) fertility preservation cycles, random-start ovarian stimulation is an option.	Conditional	⊕⊕◯◯	Evidence indicate that oocyte competence is probably not impacted by its luteal phase origin compared to follicular phase.	
10	50	In controlled ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, is probably recommended.	Conditional	⊕◯◯◯	The existing literature concerning controlled 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. Despite these limitations, both letrozole and tamoxifen protocols may be safe	
Monitoring						
11	51	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 32**
11	52	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 33**

12	53	Routine monitoring of endometrial thickness during controlled 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	54	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	55	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 34
13	56	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	57	It is not recommended to base timing of final oocyte maturation triggering on oestradiol levels.	Strong	⊕◯◯◯	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	58	It is not recommended to base timing of final oocyte maturation on oestradiol/follicle ratio.	Strong	⊕◯◯◯	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	59	A low response to controlled ovarian stimulation alone is not a reason to cancel a cycle.	Strong	⊕◯◯◯	For low 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	60	The physician should counsel the individual low responder regarding pregnancy prospects and decide individually whether to continue this and/or further cycles.	GPP			

14	61	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	62	The use of recombinant hCG and urinary hCG is equally recommended for triggering final oocyte maturation during controlled ovarian stimulation protocols.	Strong	⊕⊕◯◯	Cochrane review shows equal efficacy and safety for urinary and recombinant hCG.	**SoF table 35**
15	63	A reduced-dose of 5000 IU urinary hCG for final oocyte maturation is probably recommended over the conventional 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 36 a,b**
15	64	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 37**
15	65	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/ISCI population.	**SoF table 38**
15	66	The use of GnRH agonist for final oocyte maturation with luteal support with LH-activity and fresh transfer is probably not recommended for the predicted normal responder.	Conditional	⊕◯◯◯		**SoF table 39**
15	67	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	68	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 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.	**SoF table 40**
16	69	Progesterone is recommended for luteal phase support after IVF/ICSI.	Strong	⊕◯◯◯	Progesterone is recommended for luteal phase support for IVF/ICSI. Start of luteal support has not been studied in the	**SoF table 41**

16	70	The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg daily for intramuscular progesterone 25 mg daily for subcutaneous progesterone 90 mg daily for vaginal progesterone gel 600 mg daily at least for micronized vaginal progesterone capsules and 300 mg daily at least for micronized vaginal progesterone suppositories/capsules.	GPP		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 42
16	71	Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.	GPP			SoF table 43 a,b,c,d
16	72	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 44 a,b,c
16	73	Progesterone for luteal phase support should be administered at least until the day of the pregnancy test.	GPP			SoF table 45
16	74	Dydrogesterone is probably recommended for luteal phase support. Its efficacy and safety (OHSS) are equal to progesterone.	Conditional	⊕⊕⊕◯	The evidence suggests that when compared to progesterone, dydrogesterone has similar ongoing pregnancy rate. Additionally, patients prefer the oral administration route of dydrogesterone over the vaginal route of progesterone.	SoF table 46 a,b
16	75	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 47
16	76	In hCG triggered controlled 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 48 a,b,c
16	77	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 infections 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 49
16	78	Repeated GnRH agonist injections, alone or in addition to progesterone for luteal phase support in hCG triggered cycles can only be used in the context of a clinical trial.	Research only			SoF table 50

16	79	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 51
Prevention of OHSS						
17	80	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 52 a,b
17	81	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		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.	
17	82	If a freeze-all strategy is not used or not preferred in patients at risk of OHSS, the use of reduced-dose hCG trigger and GnRH agonist followed by luteal support with LH-activity is probably equally recommended in GnRH antagonist protocol.	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 53
17	83	In patients at risk of OHSS, the use of a GnRH agonist over hCG for final oocyte maturation is probably recommended 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	84	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	85	Cabergoline or albumin as additional preventive measures for OHSS are not recommended when GnRH agonist is used for triggering final oocyte maturation.	GPP			
18	86	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 54 a,b
18	87	Prior to start of controlled 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 CONTROLLED 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 controlled ovarian stimulation. Most of these studies have a limited number of patients, and the definition of low 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 low 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		High ovarian response		Low ovarian response		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
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 controlled 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 low 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		Low ovarian response		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**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 controlled ovarian stimulation. Most of these studies have a limited number of patients, and the definition of a low 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.

basal FSH		High ovarian response		Low ovarian response		
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**ROC-AUC**	**Remark**
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 controlled ovarian stimulation (COS). 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		High ovarian response		Low ovarian response		
Study	Cohort (n)	Criterium	ROC-AUC	Criterium	ROC-AUC	Remark
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 controlled 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		High ovarian response		Low ovarian response		
Study	Cohort (n)	Criterium	ROC-AUC	Criterium	ROC-AUC	Remark
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 controlled ovarian stimulation. Most of these studies have a limited number of patients, and the definition of low 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		**High ovarian response**		**Low ovarian response**	
Study	**Cohort (n)**	**Criterium**	**ROC-AUC**	**Criterium**	**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 controlled 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 low 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 low 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 low 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 low response to controlled ovarian stimulation, use of either antral follicle count (AFC) or anti-Müllerian hormone (AMH) is recommended over other ovarian reserve tests.	Strong	⊕○○○

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 low). 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 low 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).

REFERENCES

Andersen A, Witjes H, Gordon K, Mannaerts B. Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment *Human reproduction (Oxford, England)*. 2011, pp. 3413-3423.

Arce J, Marca A, Mirner KB, Nyboe AA, Fleming R. Antimüllerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients *Fertility and sterility*. 2013, pp. 1644-1653.

Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, te Velde ER. Predictors of poor ovarian response in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. *Fertility and sterility* 2002;77: 328-336.

Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Impact of repeated antral follicle counts on the prediction of poor ovarian response in women undergoing in vitro fertilization. *Fertility and sterility* 2004;81: 35-41.

Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Human reproduction update* 2006;12: 685-718.

Broer SL, Dolleman M, van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PM, Eijkemans MJ, Mol BW, Broekmans FJ. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis. *Fertility and sterility* 2013;100: 420-429.e427.

Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, Eijkemans MJ, Mol BW, Broekmans FJ. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. *Human reproduction update* 2013;19: 26-36.

Elgindy EA, El-Haieg DO, El-Sebaey A. Anti-Mullerian hormone: correlation of early follicular, ovulatory and midluteal levels with ovarian response and cycle outcome in intracytoplasmic sperm injection patients. *Fertility and sterility* 2008;89: 1670-1676.

Fawzy M, Lambert A, Harrison R, Knight P, Groome N, Hennelly B, Robertson W. Day 5 inhibin B levels in a treatment cycle are predictive of IVF outcome *Human reproduction (Oxford, England)*. 2002, pp. 1535-1543.

Heidar Z, Bakhtiyari M, Mirzamoradi M, Zadehmodarres S, Sarfjoo FS, Mansournia MA. Prediction of different ovarian responses using anti-Mullerian hormone following a long agonist treatment protocol for IVF. *Journal of endocrinological investigation* 2015;38: 1007-1015.

Hendriks DJ, Broekmans FJ, Bancsi LF, de Jong FH, Looman CW, Te Velde ER. Repeated clomiphene citrate challenge testing in the prediction of outcome in IVF: a comparison with basal markers for ovarian reserve. *Human reproduction (Oxford, England)* 2005;20: 163-169.

Jayaprakasan K, Al-Hasie H, Jayaprakasan R, Campbell B, Hopkisson J, Johnson I, Raine-Fenning N. The three-dimensional ultrasonographic ovarian vascularity of women developing poor ovarian response during assisted reproduction treatment and its predictive value. *Fertility and sterility* 2009;92: 1862-1869.

643 Jayaprakasan K, Campbell B, Hopkisson J, Johnson I, Raine-Fenning N. A prospective, comparative
644 analysis of anti-Mullerian hormone, inhibin-B, and three-dimensional ultrasound determinants of
645 ovarian reserve in the prediction of poor response to controlled ovarian stimulation. *Fertility and*
646 *sterility* 2010;93: 855-864.
647 Khairy M, Clough A, El-Toukhy T, Coomarasamy A, Khalaf Y. Antral follicle count at down-regulation
648 and prediction of poor ovarian response. *Reproductive biomedicine online* 2008;17: 508-514.
649 Kwee J, Elting ME, Schats R, McDonnell J, Lambalk CB. Ovarian volume and antral follicle count for the
650 prediction of low and hyper responders with in vitro fertilization. *Reproductive biology and*
651 *endocrinology : RB&E* 2007;5: 9.
652 Lan VT, Linh NK, Tuong HM, Wong PC, Howles CM. Anti-Mullerian hormone versus antral follicle count
653 for defining the starting dose of FSH. *Reproductive biomedicine online* 2013;27: 390-399.
654 Lensen SF, Wilkinson J, Mol BWJ, La MA, Torrance H, Broekmans FJ. Individualised gonadotropin dose
655 selection using markers of ovarian reserve for women undergoing IVF/ICSI *Cochrane Database of*
656 *Systematic Reviews*. 2017. John Wiley & Sons, Ltd.
657 Li R, Gong F, Zhu Y, Fang W, Yang J, Liu J, Hu L, Yang D, Liang X, Qiao J. Anti-Mullerian hormone for
658 prediction of ovarian response in Chinese infertile women undergoing IVF/ICSI cycles: a prospective,
659 multi-centre, observational study *Reproductive biomedicine online*. 2016, pp. 506-512.
660 Mutlu MF, Erdem M, Erdem A, Yildiz S, Mutlu I, Arisoy O, Oktem M. Antral follicle count determines
661 poor ovarian response better than anti-Mullerian hormone but age is the only predictor for live birth
662 in in vitro fertilization cycles. *Journal of assisted reproduction and genetics* 2013;30: 657-665.
663 Oehninger S, Nelson S, Verweij P, Stegmann B. Predictive factors for ovarian response in a
664 corifollitropin alfa/GnRH antagonist protocol for controlled ovarian stimulation in IVF/ICSI cycles
665 *Reproductive Biology and Endocrinology*. 2015.
666 Penarrubia J, Peralta S, Fabregues F, Carmona F, Casamitjana R, Balasch J. Day-5 inhibin B serum
667 concentrations and antral follicle count as predictors of ovarian response and live birth in assisted
668 reproduction cycles stimulated with gonadotropin after pituitary suppression. *Fertility and sterility*
669 2010;94: 2590-2595.
670 Soldevila PN, Carreras O, Tur R, Coroleu B, Barri PN. Sonographic assessment of ovarian reserve. Its
671 correlation with outcome of in vitro fertilization cycles. *Gynecological endocrinology : the official*
672 *journal of the International Society of Gynecological Endocrinology* 2007;23: 206-212.
673 Tolikas A, Tsakos E, Gerou S, Prapas Y, Loufopoulos A. Anti-Mullerian Hormone (AMH) levels in serum
674 and follicular fluid as predictors of ovarian response in stimulated (IVF and ICSI) cycles. *Human fertility*
675 *(Cambridge, England)* 2011;14: 246-253.
676 Tsakos E, Tolikas A, Daniilidis A, Asimakopoulos B. Predictive value of anti-mullerian hormone, follicle-
677 stimulating hormone and antral follicle count on the outcome of ovarian stimulation in women
678 following GnRH-antagonist protocol for IVF/ET. *Archives of gynecology and obstetrics* 2014;290: 1249-
679 1253.
680 van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, Themmen AP. Serum anti-
681 Mullerian hormone levels: a novel measure of ovarian reserve. *Human reproduction (Oxford, England)*
682 2002;17: 3065-3071.

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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 controlled 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 controlled 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 resp., in patients

with elevated (>1.5) levels at the start of controlled ovarian stimulation, compared to 33.8% in controls (progesterone <1.5 both at the start of COS 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 controlled ovarian stimulation is probably not recommended.	Conditional ⊕◯◯◯

Justification

Assessment of progesterone prior to initiation of stimulation on cycle day 2 in women undergoing controlled 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.

References

Blockeel C, Baumgarten M, De Vos M, Verheyen G, Devroey P. Administration of GnRH antagonists in case of elevated progesterone at initiation of the cycle: a prospective cohort study. *Current pharmaceutical biotechnology* 2011;12: 423-428.

Costello MF, Hughes GJ, Garrett DK, Steigrad SJ, Ekangaki A. Prognostic value of baseline serum oestradiol in controlled ovarian hyperstimulation of women with unexplained infertility. *The Australian & New Zealand journal of obstetrics & gynaecology* 2001;41: 69-74.

Faulisi S, Reschini M, Borroni R, Paffoni A, Busnelli A, Somigliana E. Clinical Value of Basal Serum Progesterone Prior to Initiate Ovarian Hyper-Stimulation with GnRH Antagonists: A Retrospective Cohort Study. *Gynecologic and obstetric investigation* 2017;82: 175-180.

Hamdine O, Macklon NS, Eijkemans MJ, Laven JS, Cohlen BJ, Verhoeff A, van Dop PA, Bernardus RE, Lambalk CB, Oosterhuis GJ *et al.* Elevated early follicular progesterone levels and in vitro fertilization outcomes: a prospective intervention study and meta-analysis. *Fertility and sterility* 2014;102: 448-454.e441.

Kolibianakis EM, Zikopoulos K, Smitz J, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Elevated progesterone at initiation of stimulation is associated with a lower ongoing pregnancy rate after IVF using GnRH antagonists. *Human reproduction (Oxford, England)* 2004;19: 1525-1529.

Panaino TR, Silva JB, Lima MA, Lira P, Areas PC, Mancebo AC, Souza MM, Antunes RA, Souza MD. High Progesterone levels in the beginning of ICSI antagonist cycles and clinical pregnancy: still a concern? *JBRA assisted reproduction* 2017;21: 11-14.

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3. Pre-treatment therapies

KEY QUESTION: DOES HORMONE PRE-TREATMENT IMPROVE EFFICACY AND SAFETY OF CONTROLLED 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 controlled 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 controlled 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 COS in 4 RCTs including 421 women. When progestogen pre-treatment was compared with no intervention, there was no difference between the groups in rates of 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 controlled ovarian stimulation using the GnRH antagonist protocol is probably not recommended for improving efficacy and safety.	Conditional ⊕⊕◯◯

The GDG acknowledges that oestrogen and 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, 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	⊕⊕◯◯

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 consecutives 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 on important impact on hormonal environment (Cedrin-Durnerin, et al., 2007, Griesinger, et al., 2015).

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 and 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 controlled 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 low 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.

References

Aflatoonian A, Hosseinisadat A, Baradaran R, Farid Mojtahedi M. Pregnancy outcome of "delayed start" GnRH antagonist protocol versus GnRH antagonist protocol in poor responders: A clinical trial study. *International journal of reproductive biomedicine (Yazd, Iran)* 2017;15: 231-238.

Blockeel C, Riva A, De Vos M, Haentjens P, Devroey P. Administration of a gonadotropin-releasing hormone antagonist during the 3 days before the initiation of the in vitro fertilization/intracytoplasmic sperm injection treatment cycle: impact on ovarian stimulation. A pilot study. *Fertility and sterility* 2011;95: 1714-1719.e1711-1712.

Cedrin-Durnerin I, Bstandig B, Parneix I, Bied-Damon V, Avril C, Decanter C, Hugues JN. Effects of oral contraceptive, synthetic progestogen or natural estrogen pre-treatments on the hormonal profile and the antral follicle cohort before GnRH antagonist protocol. *Human reproduction (Oxford, England)* 2007;22: 109-116.

DiLuigi A, Engmann L, Schmidt D, Benadiva C, Nulsen J. A randomized trial of microdose leuprolide acetate protocol versus luteal phase ganirelix protocol in predicted poor responders *Fertility and sterility*. 2011, pp. 2531-2533.

Farquhar C, Rombauts L, Kremer JA, Lethaby A, Ayeleke RO. Oral contraceptive pill, progestogen or oestrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques. *The Cochrane database of systematic reviews* 2017;5: Cd006109.

Griesinger G, Venetis CA, Tarlatzis B, Kolibianakis EM. To pill or not to pill in GnRH-antagonist cycles: the answer is in the data already! *Reproductive biomedicine online* 2015;31: 6-8.

Kim CH, You RM, Kang HJ, Ahn JW, Jeon I, Lee JW, Kim SH, Chae HD, Kang BM. GnRH antagonist multiple dose protocol with oral contraceptive pill pretreatment in poor responders undergoing IVF/ICSI. *Clinical and experimental reproductive medicine* 2011;38: 228-233.
Maged A, Nada A, Abohamila F, Hashem A, Mostafa W, Elzayat A. Delayed Start Versus Conventional GnRH Antagonist Protocol in Poor Responders Pretreated With Estradiol in Luteal Phase: a Randomized Controlled Trial *Reproductive sciences (Thousand Oaks, Calif)*. 2015, pp. 1627-1631.
Shahrokh Tehrani Nejad E, Bakhtiari Ghaleh F, Eslami B, Haghollahi F, Bagheri M, Masoumi M. Comparison of pre-treatment with OCPs or estradiol valerate vs. no pre-treatment prior to GnRH antagonist used for IVF cycles: An RCT. *International journal of reproductive biomedicine (Yazd, Iran)* 2018;16: 535-540.

PART B: LH suppression and ovarian stimulation

4. Controlled 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	⊕⊕◯◯

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 COS 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 COS 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 ⊕○○○

Conclusion

Clomiphene citrate, in addition to gonadotropin stimulation in COS 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 ⊕○○○

Justification

There is only limited evidence from non-randomised studies for the addition of letrozole to FSH for COS 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.

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

A reduced gonadotropin dose is recommended to decrease the risk of OHSS in predicted high responders if GnRH agonist protocols are used.	Strong	⊕○○○

Justification

The recommendation is based on insufficient evidence from a subgroup analysis of the RCT in GnRH agonist protocol. The mix of 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 reflects current clinical practice, questions the potential negative effects of conventional dosage stimulation in terms of cumulative pregnancy rate and OHSS rates.

The guideline group recommends that a GnRH antagonist protocol in predicted high responders should be used.

4A.3 Modified natural cycle

Modified natural cycle 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 COS 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 after the use of GnRH antagonists than after 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 regular IVF patients, 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 COS 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 and reported significantly less oocytes retrieved with 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 recommend the use of Clomiphene Citrate in stimulation protocols for predicted normal responders.

Justification

The evidence was from studies performed in patients without predicted low 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 COS (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 COS (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 ⊕○○○

Justification

Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of COS. 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 controlled ovarian stimulation.

4B.2.3 Reduced dose protocol

Evidence

A meta-analysis including 5 RCT (960 women) investigated the effect of 100 compared to 200 IU/day of rFSH for COS 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 ⊕⊕○○

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. Low 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 resp. 90 and 440 poor responders compared the microdose flare-up GnRH agonist with the GnRH antagonist protocol (Demirol and Gurgan, 2009, Merviel, et al., 2015). Demirol 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) (Demirol 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 low responders.	Conditional ⊕⊕◯◯

Justification

In women with low 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 (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, reported a significantly lower clinical pregnancy rate (5.9% vs. 14.1%) 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 low responders.	Strong	⊕⊕◯◯

Justification

In women with low ovarian response, no differences exist 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 an antagonist protocol did not differ as compared with 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)) (Eftekhar, et al., 2014).

Recommendation

The addition of letrozole to gonadotropins in stimulation protocols is probably not recommended for predicted low responders.	Conditional	⊕⊕◯◯

Justification

Addition of letrozole to FSH in an GnRH antagonist protocol does not improve efficacy of COS. 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 controlled ovarian stimulation.

4C.2.3 Reduced dose protocol

Evidence

No studies were found comparing a reduced FSH dose (<150 IU/day) to conventional FSH stimulation in low 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 150IU and 300/450IU dose of gonadotropins and no cases of moderate or severe OHSS in either group. However, significantly 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 300IU and 400/450IU 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 450IU and 600IU dose of gonadotropins and one case of moderate OHSS in the 600IU dose group (Lefebvre, et al., 2015, Lensen, et al., 2017).

Recommendation

A higher gonadotropin dose of 300 IU is probably not recommended over the conventional dose of 150 IU for predicted low responders.	Conditional	⊕○○○

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

Justification

A higher gonadotropin dose of 300 IU daily results in a higher number of oocytes in low responders, and more chances of having an embryo for transfer. However, 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, as comparisons with doses >300 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 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 low responders.	Conditional	⊕○○○

Justification

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

References

Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, Macklon NS, Fauser BC. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Human reproduction (Oxford, England)* 2007;22:980-988.

Bechtejew TN, Nadai MN, Nastri CO, Martins WP. Clomiphene citrate and letrozole to reduce follicle-stimulating hormone consumption during ovarian stimulation: systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2017;50: 315-323.

Blockeel C, Sterrenburg MD, Broekmans FJ, Eijkemans MJ, Smitz J, Devroey P, Fauser BC. Follicular phase endocrine characteristics during ovarian stimulation and GnRH antagonist cotreatment for IVF: RCT comparing recFSH initiated on cycle day 2 or 5. *The Journal of clinical endocrinology and metabolism* 2011;96: 1122-1128.

Chen Y, Yang T, Hao C, Zhao J. A Retrospective Study of Letrozole Treatment Prior to Human Chorionic Gonadotropin in Women with Polycystic Ovary Syndrome Undergoing In Vitro Fertilization at Risk of Ovarian Hyperstimulation Syndrome. *Medical science monitor : international medical journal of experimental and clinical research* 2018;24: 4248-4253.

Demirol A, Gurgan T. Comparison of microdose flare-up and antagonist multiple-dose protocols for poor-responder patients: a randomized study. *Fertility and sterility* 2009;92: 481-485.

Ebrahimi M, Akbari-Asbagh F, Ghalandar-Attar M. Letrozole+ GnRH antagonist stimulation protocol in poor ovarian responders undergoing intracytoplasmic sperm injection cycles: An RCT. *International journal of reproductive biomedicine (Yazd, Iran)* 2017;15: 101-108.

Eftekhar M, Mohammadian F, Davar R, Pourmasumi S. Comparison of pregnancy outcome after letrozole versus clomiphene treatment for mild ovarian stimulation protocol in poor responders. *Iranian journal of reproductive medicine* 2014;12: 725-730.

Hohmann F, Macklon N, Fauser B. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol *The Journal of clinical endocrinology and metabolism*. 2003, pp. 166-173.

Jiang S, Kuang Y. Clomiphene citrate is associated with favorable cycle characteristics but impaired outcomes of obese women with polycystic ovarian syndrome undergoing ovarian stimulation for in vitro fertilization. *Medicine* 2017;96: e7540.

Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, van der Veen F, van Wely M. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. *Human reproduction update* 2017;23: 560-579.

Lefebvre J, Antaki R, Kadoch IJ, Dean NL, Sylvestre C, Bissonnette F, Benoit J, Menard S, Lapensee L. 450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial. *Fertility and sterility* 2015;104: 1419-1425.

Lensen SF, Wilkinson J, Mol BWJ, La MA, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI *Cochrane Database of Systematic Reviews*. 2017. John Wiley & Sons, Ltd.

Lin YH, Seow KM, Hsieh BC, Huang LW, Chen HJ, Huang SC, Chen CY, Chen PH, Hwang JL, Tzeng CR. Application of GnRH antagonist in combination with clomiphene citrate and hMG for patients with exaggerated ovarian response in previous IVF/ICSI cycles. *Journal of assisted reproduction and genetics* 2007;24: 331-336.

Merviel P, Cabry-Goubet R, Lourdel E, Devaux A, Belhadri-Mansouri N, Copin H, Benkhalifa M. Comparative prospective study of 2 ovarian stimulation protocols in poor responders: effect on implantation rate and ongoing pregnancy. *Reproductive health* 2015;12: 52.

Morgia F, Sbracia M, Schimberni M, Giallonardo A, Piscitelli C, Giannini P, Aragona C. A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization. *Fertility and sterility* 2004;81: 1542-1547.

Mukherjee S, Sharma S, Chakravarty BN. Letrozole in a low-cost in vitro fertilization protocol in intracytoplasmic sperm injection cycles for male factor infertility: A randomized controlled trial. *Journal of human reproductive sciences* 2012;5: 170-174.

Oudshoorn SC, van Tilborg TC, Eijkemans MJC, Oosterhuis GJE, Friederich J, van Hooff MHA, van Santbrink EJP, Brinkhuis EA, Smeenk JMJ, Kwee J *et al.* Individualized versus standard FSH dosing in

women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder. *Human reproduction (Oxford, England)* 2017;32: 2506-2514.
Ragni G, Levi-Setti PE, Fadini R, Brigante C, Scarduelli C, Alagna F, Arfuso V, Mignini-Renzini M, Candiani M, Paffoni A *et al.* Clomiphene citrate versus high doses of gonadotropins for in vitro fertilisation in women with compromised ovarian reserve: a randomised controlled non-inferiority trial. *Reproductive biology and endocrinology : RB&E* 2012;10: 114.
Saleh S, Ismail M, Elshmaa N. The efficacy of converting high response - Ovulation induction cycles to in vitro fertilization in patients with PCOS *Middle East Fertility Society Journal*. 2014, pp. 51-56.
Schimberni M, Ciardo F, Schimberni M, Giallonardo A, De Pratti V, Sbracia M. Short gonadotropin-releasing hormone agonist versus flexible antagonist versus clomiphene citrate regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. *European review for medical and pharmacological sciences* 2016;20: 4354-4361.
Shin JJ, Park KE, Choi YM, Kim HO, Choi DH, Lee WS, Cho JH. Early gonadotropin-releasing hormone antagonist protocol in women with polycystic ovary syndrome: A preliminary randomized trial. *Clinical and experimental reproductive medicine* 2018;45: 135-142.
Sterrenburg MD, Veltman-Verhulst SM, Eijkemans MJ, Hughes EG, Macklon NS, Broekmans FJ, Fauser BC. Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis. *Human reproduction update* 2011;17: 184-196.
Trenkic M, Popovic J, Kopitovic V, Bjelica A, Zivadinovic R, Pop-Trajkovic S. Flexible GnRH antagonist protocol vs. long GnRH agonist protocol in patients with polycystic ovary syndrome treated for IVF: comparison of clinical outcome and embryo quality. *Ginekologia polska* 2016;87: 265-270.
Verpoest W, Kolibianakis E, Papanikolaou E, Smitz J, Steirteghem A, Devroey P. Aromatase inhibitors in ovarian stimulatio for IVF/ICSI: A pilot study *Reproductive biomedicine online*. 2006, pp. 166-172.
Xiao J, Chang S, Chen S. The effectiveness of gonadotropin-releasing hormone antagonist in poor ovarian responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertility and sterility* 2013;100: 1594-1601.e1591-1599.
Zander-Fox D, Lane M, Hamilton H, Tremellen K. Sequential clomiphene/corifollitrophin alpha as a technique for mild controlled ovarian hyperstimulation in IVF: a proof of concept study. *Journal of assisted reproduction and genetics* 2018;35: 1047-1052.

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 resp. 186 and 131 women also reported no significant difference in clinical pregnancy rate between the long and the short GnRH agonist protocol (resp. 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 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 GnRH agonist short protocol appeared as a modification of the classic long protocol with the aim of improving cycle outcome in low 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, and reported 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 resp. 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% resp. 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 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	⊕⊕⊕○

Justification

The introduction of GnRH antagonist allowed overcoming the significant undesirable effects of the 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 COS cycles in which a fresh embryo transfer is not scheduled, such as fertility preservation, oocyte donors, or freeze-all cycles.

References

Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. *The Cochrane database of systematic reviews* 2016;4: Cd001750.

1417 Berker B, Duvan CI, Kaya C, Aytac R, Satiroglu H. Comparison of the ultrashort gonadotropin-releasing
1418 hormone agonist-antagonist protocol with microdose flare -up protocol in poor responders: a
1419 preliminary study. *Journal of the Turkish German Gynecological Association* 2010;11: 187-193.
1420 Chen Q, Wang Y, Sun L, Zhang S, Chai W, Hong Q, Long H, Wang L, Lyu Q, Kuang Y. Controlled
1421 ovulation of the dominant follicle using progestin in minimal stimulation in poor responders.
1422 *Reproductive biology and endocrinology : RB&E* 2017;15: 71.
1423 Escudero E, Bosch E, Crespo J, Simon C, Remohi J, Pellicer A. Comparison of two different starting
1424 multiple dose gonadotropin-releasing hormone antagonist protocols in a selected group of in vitro
1425 fertilization-embryo transfer patients. *Fertility and sterility* 2004;81: 562-566.
1426 Friedler S, Gilboa S, Schachter M, Raziel A, Strassburger D, Ron El R. Luteal phase characteristics
1427 following GnRH antagonist or agonist treatment - a comparative study. *Reproductive biomedicine*
1428 *online* 2006;12: 27-32.
1429 Frydman R, Parneix I, Belaisch-Allart J, Forman R, Hazout A, Fernandez H, Testart J. LHRH agonists in
1430 IVF: different methods of utilization and comparison with previous ovulation stimulation treatments.
1431 *Human reproduction (Oxford, England)* 1988;3: 559-561.
1432 Gordts S, Van Turnhout C, Campo R, Puttemans P, Valkenburg M, Gordts S. A prospective randomised
1433 study comparing a GnRH-antagonist versus a GnRH-agonist short protocol for ovarian stimulation in
1434 patients referred for IVF. *Facts, views & vision in ObGyn* 2012;4: 82-87.
1435 Hamdi K, Farzadi L, Ghasemzadeh A, Navali N, Atashkhoei S, Pia H, Shahnazi V, Fattahi A, Bahrami-Asl
1436 Z, Sepasi F *et al.* Comparison of medroxyprogesterone acetate with cetrotide for prevention of
1437 premature luteinizing hormone surges in women undergoing in vitro fertilization. *International journal*
1438 *of women's health and reproduction sciences* 2018;6: 187-191.
1439 Kingsland C, Tan SL, Bickerton N, Mason B, Campbell S. The routine use of gonadotropin-releasing
1440 hormone agonists for all patients undergoing in vitro fertilization. Is there any medical advantage? A
1441 prospective randomized study. *Fertility and sterility* 1992;57: 804-809.
1442 Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q, Ai A, Shoham Z. Medroxyprogesterone acetate is an
1443 effective oral alternative for preventing premature luteinizing hormone surges in women undergoing
1444 controlled ovarian hyperstimulation for in vitro fertilization. *Fertility and sterility* 2015;104: 62-70.e63.
1445 Maldonado LG, Franco JG, Jr., Setti AS, Iaconelli A, Jr., Borges E, Jr. Cost-effectiveness comparison
1446 between pituitary down-regulation with a gonadotropin-releasing hormone agonist short regimen on
1447 alternate days and an antagonist protocol for assisted fertilization treatments. *Fertility and sterility*
1448 2013;99: 1615-1622.
1449 Ravhon A, Lawrie H, Ellenbogen A, Lavery S, Trew G, Winston R. A prospective, randomized controlled
1450 trial comparing the efficacy of recombinant follicle-stimulating hormone in three different in vitro
1451 fertilization protocols. *Fertility and sterility* 2000;73: 908-912.
1452 Sbracia M, Farina A, Poverini R, Morgia F, Schimberni M, Aragona C. Short versus long gonadotropin-
1453 releasing hormone analogue suppression protocols for superovulation in patients > or = 40 years old
1454 undergoing intracytoplasmic sperm injection. *Fertility and sterility* 2005;84: 644-648.
1455 Siristatidis CS, Gibreel A, Basios G, Maheshwari A, Bhattacharya S. Gonadotrophin-releasing hormone
1456 agonist protocols for pituitary suppression in assisted reproduction. *The Cochrane database of*
1457 *systematic reviews* 2015: Cd006919.
1458 Toftager M, Bogstad J, Bryndorf T, Lossl K, Roskaer J, Holland T, Praetorius L, Zedeler A, Nilas L,
1459 Pinborg A. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist
1460 protocol: RCT including 1050 first IVF/ICSI cycles. *Human reproduction (Oxford, England)* 2016;31:
1461 1253-1264.
1462 Toftager M, Bogstad J, Lossl K, Praetorius L, Zedeler A, Bryndorf T, Nilas L, Pinborg A. Cumulative live
1463 birth rates after one ART cycle including all subsequent frozen-thaw cycles in 1050 women: secondary
1464 outcome of an RCT comparing GnRH-antagonist and GnRH-agonist protocols. *Human reproduction*
1465 *(Oxford, England)* 2017;32: 556-567.

1466 Urbancsek J, Witthaus E. Midluteal buserelin is superior to early follicular phase buserelin in combined
1467 gonadotropin-releasing hormone analog and gonadotropin stimulation in in vitro fertilization. *Fertility*
1468 *and sterility* 1996;65: 966-971.
1469 Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in
1470 vitro fertilization outcome: a systematic review and meta-analysis. *Human reproduction (Oxford,*
1471 *England)* 2014;29: 964-977.
1472 Verpoest W, De Vos A, De Rycke M, Parikh S, Staessen C, Tournaye H, De Vos M, Vloeberghs V,
1473 Blockeel C. Gonadotropin Releasing Hormone Agonists or Antagonists for Preimplantation Genetic
1474 Diagnosis (PGD)? A Prospective Randomised Trial. *Current pharmaceutical biotechnology* 2017;18:
1475 622-627.
1476 Yu S, Long H, Chang HY, Liu Y, Gao H, Zhu J, Quan X, Lyu Q, Kuang Y, Ai A. New application of
1477 dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: a randomized
1478 controlled trial including 516 first IVF/ICSI cycles. *Human reproduction (Oxford, England)* 2018;33:
1479 229-237.

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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 controlled ovarian stimulation (COS) (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 COS (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 COS (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 controlled ovarian stimulation is equally recommended.	Strong	⊕⊕⊕○

Justification

The results from the meta-analysis suggest a slightly higher efficacy (LBR/PR) with hMG compared to rFSH in GnRH agonist cycles. However, the difference is not considered clinically relevant, and with no difference in safety, the GDG concluded that hMG is not superior to rFSH. This conclusion is supported by the results of studies published after the meta-analysis. An update of the Cochrane meta-analysis is expected.

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).

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 controlled ovarian stimulation is equally recommended.	Strong	⊕⊕◯◯

Justification

In patients undergoing controlled 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 resp. 70, 127 and 160 women reported no significant difference in live birth rate between rFSH and hp-FSH (resp. 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 (resp. 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 resp. 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 controlled ovarian stimulation is equally recommended.	Strong	⊕⊕◯◯

Justification

In patients undergoing controlled 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.

6.1.4 RECOMBINANT (RFSH) VS RECOMBINANT FSH + RECOMBINANT LH (RFSH+RLH)

Evidence

A Cochrane meta-analysis including 499 women found similar live birth rates 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), 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 low responders showed a beneficial effect of rLH supplementation 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 controlled 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 (203 vs. 236) or mature oocytes (164 vs. 191) (Rahman, et al., 2017).

Recommendation

The addition of recombinant LH (rLH) to recombinant FSH (rFSH) is probably not recommended for controlled ovarian stimulation in the general IVF/ICSI population.	Conditional	⊕◯◯◯

The addition of recombinant LH (rLH) to recombinant FSH (rFSH) is not recommended for controlled ovarian stimulation in low responders and women of advanced age.	Strong	⊕◯◯◯

Justification

According to the best available evidence, the addition of rLH to 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.

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 controlled 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 controlled ovarian stimulation in GnRH agonist protocols is equally recommended.	Conditional	⊕⊕◯◯

Justification

In patients undergoing COS 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 controlled ovarian stimulation with GnRH agonists, use of rFSH+LH 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+LH 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+LH) for controlled ovarian stimulation is probably not recommended over human menopausal gonadotropin (hMG) in GnRH agonist protocols with regards to safety.	Conditional ⊕◯◯◯

Justification

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. The recommendation is not applicable to GnRH antagonist cycles.

6.3 Aromatase inhibitors

The combining of the aromatase inhibitor letrozole with gonadotropin during COS 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 COS (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 COS.

Three RCTs, including resp. 70, 20 and 50 women, investigated the effect of FSH substitution with letrozole for COS (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 low 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 COS.

6.4 Clomiphene citrate

Evidence

There are no studies investigating the benefit of adding clomiphene citrate to gonadotropins for COS. 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 controlled 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 (3RCTs) (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 low 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	⊕⊕⊕◯

Justification

No differences have been observed in three large RCTs and in a small RCT in low 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.

References

Aboulghar M, Saber W, Amin Y, Aboulghar M, Mansour R, Serour G. Prospective, randomized study comparing highly purified urinary follicle-stimulating hormone (FSH) and recombinant FSH for in vitro fertilization/intracytoplasmic sperm injection in patients with polycystic ovary syndrome. *Fertility and sterility* 2010;94: 2332-2334.

Devroey P, Pellicer A, Nyboe Andersen A, Arce JC. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. *Fertility and sterility* 2012;97: 561-571.
Duijkers IJ, Vemer HM, Hollanders JM, Willemsen WN, Bastiaans LA, Hamilton CJ, Thomas CM, Borm GF. Different follicle stimulating hormone/luteinizing hormone ratios for ovarian stimulation. *Human reproduction (Oxford, England)* 1993;8: 1387-1391.
Ebrahimi M, Akbari-Asbagh F, Ghalandar-Attar M. Letrozole+ GnRH antagonist stimulation protocol in poor ovarian responders undergoing intracytoplasmic sperm injection cycles: An RCT. *International journal of reproductive biomedicine (Yazd, Iran)* 2017;15: 101-108.
Ferraretti AP, Gianaroli L, Motrenko T, Feliciani E, Tabanelli C, Magli MC. LH pretreatment as a novel strategy for poor responders. *BioMed research international* 2014;2014: 926172.
Figen Turkcapar A, Seckin B, Onalan G, Ozdener T, Batioglu S. Human Menopausal Gonadotropin versus Recombinant FSH in Polycystic Ovary Syndrome Patients Undergoing In Vitro Fertilization. *International journal of fertility & sterility* 2013;6: 238-243.
Gholami H, Vicari E, Molis M, La Vignera S, Papaleo E, Cappiello F. Pregnancy outcome following in vitro fertilization-embryo transfer (IVF-ET) in women aged < 37, undergoing ovulation induction with human FSH compared with recombinant FSH: a randomised controlled study. *European review for medical and pharmacological sciences* 2010;14: 97-102.
Goswami S, Das T, Chattopadhyay R, Sawhney V, Kumar J, Chaudhury K, Chakravarty B, Kabir S. A randomized single-blind controlled trial of letrozole as a low-cost IVF protocol in women with poor ovarian response: a preliminary report *Human reproduction (Oxford, England)*. 2004, pp. 2031-2035.
Griesinger G, Boostanfar R, Gordon K, Gates D, McCrary Sisk C, Stegmann BJ. Corifollitropin alfa versus recombinant follicle-stimulating hormone: an individual patient data meta-analysis. *Reproductive biomedicine online* 2016;33: 56-60.
Humaidan P, Chin W, Rogoff D, D'Hooghe T, Longobardi S, Hubbard J, Schertz J. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. *Human reproduction (Oxford, England)* 2017;32: 544-555.
Kolibianakis EM, Venetis CA, Bosdou JK, Zepiridis L, Chatzimeletiou K, Makedos A, Masouridou S, Triantafillidis S, Mitsoli A, Tarlatzis BC. Corifollitropin alfa compared with follitropin beta in poor responders undergoing ICSI: a randomized controlled trial. *Human reproduction (Oxford, England)* 2015;30: 432-440.
Lahoud R, Ryan J, Illingworth P, Quinn F, Costello M. Recombinant LH supplementation in patients with a relative reduction in LH levels during IVF/ICSI cycles: a prospective randomized controlled trial *European journal of obstetrics gynecology and reproductive biology*. 2017, pp. 300-305.
Mochtar MH, Danhof NA, Ayeleke RO, Van der Veen F, van Wely M. Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles. *The Cochrane database of systematic reviews* 2017;5: Cd005070.
Murber A, Fancsovits P, Ledo N, Szakacs M, Rigo J, Urbancsek J. Impact of highly purified versus recombinant follicle stimulating hormone on oocyte quality and embryo development in intracytoplasmic sperm injection cycles. *Acta biologica Hungarica* 2011;62: 255-264.
Pacchiarotti A, Sbracia M, Frega A, Selman H, Rinaldi L, Pacchiarotti A. Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial. *Fertility and sterility* 2010;94: 2467-2469.
Parsanezhad M, Jahromi B, Rezaee S, Kooshesh L, Alaee S. The effect of four different gonadotropin protocols on oocyte and embryo quality and pregnancy outcomes in IVF/ICSI cycles; a randomized controlled trial *Iranian journal of medical sciences*. 2017, pp. 57-65.
Rahman A, Francomano D, Sagnella F, Lisi F, Manna C. The effect on clinical results of adding recombinant LH in late phase of ovarian stimulation of patients with repeated implantation failure: a pilot study. *European review for medical and pharmacological sciences* 2017;21: 5485-5490.

1714 Selman H, Pacchiarotti A, El-Danasouri I. Ovarian stimulation protocols based on follicle-stimulating
1715 hormone glycosylation pattern: impact on oocyte quality and clinical outcome. *Fertility and sterility*
1716 2010;94: 1782-1786.
1717 Selman H, Pacchiarotti A, Rinaldi L, Crescenzi F, Lanzilotti G, Lofino S, El-Danasouri I. Simultaneous
1718 administration of human acidic and recombinant less acidic follicle-stimulating hormone for ovarian
1719 stimulation improves oocyte and embryo quality, and clinical outcome in patients with repeated IVF
1720 failures. *European review for medical and pharmacological sciences* 2013;17: 1814-1819.
1721 Sohrabvand F, Sheikhhassani S, Bagheri M, Haghollahi F, Shabihkhani M, Shariat M, Nasr Esfahani M.
1722 Comparison of highly purified urinary versus recombinant FSH: Effect on ART outcomes in polycystic
1723 ovary syndrome. *Iranian journal of reproductive medicine* 2012;10: 229-236.
1724 van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, Al-Inany HG. Recombinant versus
1725 urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. *The*
1726 *Cochrane database of systematic reviews* 2011: Cd005354.
1727 Verpoest W, Kolibianakis E, Papanikolaou E, Smitz J, Steirteghem A, Devroey P. Aromatase inhibitors in
1728 ovarian stimulatio for IVF/ICSI: A pilot study *Reproductive biomedicine online*. 2006, pp. 166-172.
1729 Vuong TN, Phung HT, Ho MT. Recombinant follicle-stimulating hormone and recombinant luteinizing
1730 hormone versus recombinant follicle-stimulating hormone alone during GnRH antagonist ovarian
1731 stimulation in patients aged >/=35 years: a randomized controlled trial. *Human reproduction (Oxford,*
1732 *England)* 2015;30: 1188-1195.
1733 Westergaard LG, Erb K, Laursen S, Rasmussen PE, Rex S. The effect of human menopausal
1734 gonadotrophin and highly purified, urine-derived follicle stimulating hormone on the outcome of in-
1735 vitro fertilization in down-regulated normogonadotrophic women. *Human reproduction (Oxford,*
1736 *England)* 1996;11: 1209-1213.
1737 Yasa C, Bastu E, Dural O, Celik E, Ergun B. Evaluation of low-dose letrozole addition to ovulation
1738 induction in IVF *Clinical and experimental obstetrics & gynecology*. 2013, pp. 98-100.
1739 Ye H, Huang G, Pei L, Zeng P, Luo X. Outcome of in vitro fertilization following stimulation with highly
1740 purified hMG or recombinant FSH in downregulated women of advanced reproductive age: a
1741 prospective, randomized and controlled trial. *Gynecological endocrinology : the official journal of the*
1742 *International Society of Gynecological Endocrinology* 2012;28: 540-544.

1743

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 75IU) 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 low responder patients. Van Hooff et al. investigated the effect of doubling hMG dose on day 6 of COS 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 COS 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 beyond stimulation day 6 during controlled ovarian stimulation is probably not recommended.	Conditional ⊕◯◯◯

Justification

The current evidence does not support changing gonadotropin dose during COS beyond day 6. Modification (higher or lower) of gonadotrophin dose during controlled ovarian stimulation for IVF/ICSI does not influence pregnancy rate. There is no evidence regarding dose modifications before day 6 during COS.

REFERENCES

Aboulghar MA, Mansour RT, Serour GI, Al-Inany HG, Amin YM, Aboulghar MM. Increasing the dose of human menopausal gonadotrophins on day of GnRH antagonist administration: randomized controlled trial. *Reproductive biomedicine online* 2004;8: 524-527.

Aboulghar MA, Mansour RT, Serour GI, Rhodes CA, Amin YM. Reduction of human menopausal gonadotropin dose before coasting prevents severe ovarian hyperstimulation syndrome with minimal cycle cancellation. *Journal of assisted reproduction and genetics* 2000;17: 298-301.

Cedrin-Durnerin I, Bstandig B, Herve F, Wolf J, Uzan M, Hugues J. A comparative study of high fixed-dose and decremental-dose regimens of gonadotropins in a minidose gonadotropin-releasing hormone agonist flare protocol for poor responders. *Fertility and sterility* 2000;73: 1055-1056.

Martin JR, Mahutte NG, Arici A, Sakkas D. Impact of duration and dose of gonadotrophins on IVF outcomes. *Reproductive biomedicine online* 2006;13: 645-650.

van Hooff MH, Alberda AT, Huisman GJ, Zeilmaker GH, Leerentveld RA. Doubling the human menopausal gonadotrophin dose in the course of an in-vitro fertilization treatment cycle in low responders: a randomized study. *Human reproduction (Oxford, England)* 1993;8: 369-373.

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 controlled 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 controlled 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 controlled 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 controlled 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 low 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 controlled ovarian stimulation is probably not recommended for low 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 controlled ovarian stimulation improves live birth rates in low 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, Kyrou, et al., 2009). Despite the possible beneficial effects in low responders on live birth rate, the evidence is of too limited quality to recommend GH during COS. The studies in the systematic review were generally underpowered and the definition of poor response very heterogenous among studies.

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 controlled ovarian stimulation in IVF/ICSI treatment. All studies addressing the role adjuvant testosterone were in predicted low 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 down regulation, or 2.5 mg testosterone patches for five days during pituitary down regulation 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 COS with the GnRH antagonist protocol (Kim, et al., 2014).

A Cochrane meta-analysis investigated the effect of testosterone pre-treatment before controlled 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 controlled ovarian stimulation is probably not recommended for low responders.	conditional ⊕⊕⊕◯

Justification

There is currently inconsistent evidence that adjuvant testosterone pre-treatment before controlled ovarian stimulation improves ovarian response in terms of number of oocytes retrieved and clinical outcomes of live birth rates in low 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 controlled 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 controlled ovarian stimulation and continued during controlled ovarian stimulation. Most studies started DHEA 12 weeks prior to controlled 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 controlled ovarian stimulation is probably not recommended for low responders	Conditional ⊕⊕⊕◯

Justification

There is currently inconsistent evidence that adjuvant DHEA use before and during controlled ovarian stimulation improves ovarian response in terms of live birth/ongoing pregnancy rate in low responders undergoing IVF treatment. The studies varied in duration of DHEA treatment, possibly contributing towards the inconsistence 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 controlled ovarian stimulation in IVF/ICSI treatment, studies were selected if aspirin was used before and/ or during controlled ovarian stimulation. Studies commencing aspirin after controlled 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 controlled 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 controlled ovarian stimulation is not recommended in the general IVF/ICSI population and for low responders.	Strong	⊕⊕⊕◯

Justification

The existing evidence suggests that adjuvant aspirin before and/ or during controlled 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 controlled ovarian stimulation in IVF treatment. Thus, there is no evidence to recommend the use of indomethacin during COS.

8.7 Sildenafil

Sildenafil is used in controlled 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 low 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 controlled ovarian stimulation is not recommended for low responders	Strong	⊕◯◯◯

Justification

Current evidence from one low-quality, pseudo-randomized study involving women considered as low responders undergoing IVF showed no improvement in ovarian response with adjuvant sildenafil use

during controlled 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).

REFERENCES

Abdalmageed OS, Farghaly TA, Abdelaleem AA, Abdelmagied AE, Ali MK, Abbas AM. Impact of Metformin on IVF Outcomes in Overweight and Obese Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Controlled Trial. *Reproductive sciences (Thousand Oaks, Calif)* 2018: 1933719118765985.

Ataalla W, Elhamid T, Elhalwagy A. Adjuvant sildenafil therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial *Middle east fertility society journal*. 2017, pp. 175-179.

Bosdou JK, Venetis CA, Dafopoulos K, Zepiridis L, Chatzimeletiou K, Anifandis G, Mitsoli A, Makedos A, Messinis IE, Tarlatzis BC *et al.* Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial. *Human reproduction (Oxford, England)* 2016;31: 977-985.

Choe SA, Kim MJ, Lee HJ, Kim J, Chang EM, Kim JW, Park HM, Lyu SW, Lee WS, Yoon TK *et al.* Increased proportion of mature oocytes with sustained-release growth hormone treatment in poor responders: a prospective randomized controlled study. *Archives of gynecology and obstetrics* 2018;297: 791-796.

Dirckx K, Cabri P, Merien A, Galajdova L, Gerris J, Dhont M, De Sutter P. Does low-dose aspirin improve pregnancy rate in IVF/ICSI? A randomized double-blind placebo controlled trial. *Human reproduction (Oxford, England)* 2009;24: 856-860.

Doldi N, Persico P, Di Sebastiano F, Marsiglio E, Ferrari A. Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing in vitro fertilization-embryo transfer. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2006;22: 235-238.

Duffy JM, Ahmad G, Mohiyiddeen L, Nardo LG, Watson A. Growth hormone for in vitro fertilization. *The Cochrane database of systematic reviews* 2010: Cd000099.

Ganzevoort W, Alfirevic Z, von Dadelszen P, Kenny L, Papageorghiou A, van Wassenaer-Leemhuis A, Gluud C, Mol BW, Baker PN. STRIDER: Sildenafil Therapy In Dismal prognosis Early-onset intrauterine growth Restriction--a protocol for a systematic review with individual participant data and aggregate data meta-analysis and trial sequential analysis. *Systematic reviews* 2014;3: 23.

Hawkes N. Trial of Viagra for fetal growth restriction is halted after baby deaths. *BMJ (Clinical research ed)* 2018;362: k3247.

Jacob SL, Brewer C, Tang T, Picton HM, Barth JH, Balen AH. A short course of metformin does not reduce OHSS in a GnRH antagonist cycle for women with PCOS undergoing IVF: a randomised placebo-controlled trial. *Human reproduction (Oxford, England)* 2016;31: 2756-2764.

Kim CH, Ahn JW, Moon JW, Kim SH, Chae HD, Kang BM. Ovarian Features after 2 Weeks, 3 Weeks and 4 Weeks Transdermal Testosterone Gel Treatment and Their Associated Effect on IVF Outcomes in Poor Responders. *Development & reproduction* 2014;18: 145-152.

Kolibianakis EM, Venetis CA, Diedrich K, Tarlatzis BC, Griesinger G. Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis. *Human reproduction update* 2009;15: 613-622.

Kotb MM, Hassan AM, AwadAllah AM. Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial. *European journal of obstetrics, gynecology, and reproductive biology* 2016;200: 11-15.

Kyrou D, Kolibianakis EM, Venetis CA, Papanikolaou EG, Bontis J, Tarlatzis BC. How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertility and sterility* 2009;91: 749-766.

Lambers MJ, Hoozemans DA, Schats R, Homburg R, Lambalk CB, Hompes PG. Low-dose aspirin in non-tubal IVF patients with previous failed conception: a prospective randomized double-blind placebo-controlled trial. *Fertility and sterility* 2009;92: 923-929.

Li XL, Wang L, Lv F, Huang XM, Wang LP, Pan Y, Zhang XM. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: A systematic review and meta-analysis. *Medicine* 2017;96: e6443.

Lok IH, Yip SK, Cheung LP, Yin Leung PH, Haines CJ. Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. *Fertility and sterility* 2004;81: 556-561.

Moini A, Zafarani F, Haddadian S, Ahmadi J, Honar H, Riazi K. Effect of low-dose aspirin therapy on implantation rate in women undergoing in-vitro fertilization cycles. *Saudi Med J* 2007;28: 732-736.

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. *The Cochrane database of systematic reviews* 2015: Cd009749.

Nargund G, Wei CC. Successful planned delay of ovulation for one week with indomethacin. *Journal of assisted reproduction and genetics* 1996;13: 683-684.

Narkwichean A, Maalouf W, Baumgarten M, Polanski L, Raine-Fenning N, Campbell B, Jayaprakasan K. Efficacy of Dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (DITTO): A proof of principle double blinded randomized placebo controlled trial. *European journal of obstetrics, gynecology, and reproductive biology* 2017;218: 39-48.

Pakkila M, Rasanen J, Heinonen S, Tinkanen H, Tuomivaara L, Makikallio K, Hippelainen M, Tapanainen JS, Martikainen H. Low-dose aspirin does not improve ovarian responsiveness or pregnancy rate in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. *Human reproduction (Oxford, England)* 2005;20: 2211-2214.

Rubinstein M, Marazzi A, Polak de Fried E. Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind placebo-controlled assay. *Fertility and sterility* 1999;71: 825-829.

Siristatidis CS, Basios G, Pergialiotis V, Vogiatzi P. Aspirin for in vitro fertilisation. *The Cochrane database of systematic reviews* 2016;11: Cd004832.

Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Macedo CR. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. *The Cochrane database of systematic reviews* 2014: Cd006105.

Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. *Fertility and sterility* 2010;93: 2281-2284.

Yeung T, Chai J, Li R, Lee V, Ho PC, Ng E. A double-blind randomised controlled trial on the effect of dehydroepiandrosterone on ovarian reserve markers, ovarian response and number of oocytes in anticipated normal ovarian responders. *BJOG: an international journal of obstetrics and gynaecology* 2016;123: 1097-1105.

9. Non-conventional start of controlled 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, and luteal start stimulation as compared to conventional start (day 2/3) (Pereira, et al., 2017).

Recommendation

Random-start controlled 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 low responders.	Conditional ⊕◯◯◯

Early luteal phase start of gonadotropins is probably not recommended for normal and low 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 low 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 specifics 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 low 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 low 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 low 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.

REFERENCES

Baerwald AR, Adams GP, Pierson RA. A new model for ovarian follicular development during the human menstrual cycle. *Fertility and sterility* 2003;80: 116-122.

Chen H, Wang Y, Lyu Q, Ai A, Fu Y, Tian H, Cai R, Hong Q, Chen Q, Shoham Z *et al.* Comparison of live-birth defects after luteal-phase ovarian stimulation vs. conventional ovarian stimulation for in vitro fertilization and vitrified embryo transfer cycles. *Fertility and sterility* 2015;103: 1194-1201.e1192.

Cimadomo D, Vaiarelli A, Colamaria S, Trabucco E, Alviggi C, Venturella R, Alviggi E, Carmelo R, Rienzi L, Ubaldi FM. Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle. *Human reproduction (Oxford, England)* 2018.

Kansal Kalra S, Ratcliffe S, Gracia CR, Martino L, Coutifaris C, Barnhart KT. Randomized controlled pilot trial of luteal phase recombinant FSH stimulation in poor responders. *Reproductive biomedicine online* 2008;17: 745-750.

Kuang Y, Chen Q, Hong Q, Lyu Q, Ai A, Fu Y, Shoham Z. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). *Reproductive biomedicine online* 2014;29: 684-691.

Kucuk T, Goktolga U, Sozen E. Efficiency of follicle-stimulating hormone, commenced in the luteal phase, for overcoming a poor response in assisted reproduction. *The journal of obstetrics and gynaecology research* 2008;34: 574-577.

Liu C, Jiang H, Zhang W, Yin H. Double ovarian stimulation during the follicular and luteal phase in women >/=38 years: a retrospective case-control study. *Reproductive biomedicine online* 2017.

Pereira N, Voskuilen-Gonzalez A, Hancock K, Lekovich JP, Schattman GL, Rosenwaks Z. Random-start ovarian stimulation in women desiring elective cryopreservation of oocytes. *Reproductive biomedicine online* 2017;35: 400-406.

Qin N, Chen Q, Hong Q, Cai R, Gao H, Wang Y, Sun L, Zhang S, Guo H, Fu Y *et al.* Flexibility in starting ovarian stimulation at different phases of the menstrual cycle for treatment of infertile women with the use of in vitro fertilization or intracytoplasmic sperm injection. *Fertility and sterility* 2016;106: 334-341.e331.

Rashtian J, Zhang J. Luteal-phase ovarian stimulation increases the number of mature oocytes in older women with severe diminished ovarian reserve. *Systems biology in reproductive medicine* 2018;64: 216-219.

Rombauts L, Suikkari AM, MacLachlan V, Trounson AO, Healy DL. Recruitment of follicles by recombinant human follicle-stimulating hormone commencing in the luteal phase of the ovarian cycle. *Fertility and sterility* 1998;69: 665-669.

Vaiarelli A, Cimadomo D, Trabucco E, Vallefuoco R, Buffo L, Dusi L, Fiorini F, Barnocchi N, Bulletti FM, Rienzi L *et al.* Double Stimulation in the Same Ovarian Cycle (DuoStim) to Maximize the Number of Oocytes Retrieved From Poor Prognosis Patients: A Multicenter Experience and SWOT Analysis. *Frontiers in endocrinology* 2018;9: 317.

Wu Y, Zhao FC, Sun Y, Liu PS. Luteal-phase protocol in poor ovarian response: a comparative study with an antagonist protocol. *The Journal of international medical research* 2017: 300060516669898.

Zhang Q, Guo XM, Li Y. Implantation rates subsequent to the transfer of embryos produced at different phases during double stimulation of poor ovarian responders. *Reproduction, fertility, and development* 2016.

Zhang W, Wang M, Wang S, Bao H, Qu Q, Zhang N, Hao C. Luteal phase ovarian stimulation for poor ovarian responders. *JBRA assisted reproduction* 2018;22: 193-198.

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). COS 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 COS 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.

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 controlled 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 controlled 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 COS, 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 controlled 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 follicular phase compared to the follicular phase (11.8 (±2.41) vs. 10.7 (±2.71) days) (Pereira, et al., 2016)

Recommendation

In urgent (oncology) fertility preservation cycles, random-start ovarian stimulation is an 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, controlled 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 controlled 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 controlled 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 COS without tamoxifen (Meirow, et al., 2014). One study in the systematic review compared COS with letrozole to COS 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±1.1 vs. 12.3±2.5) and (5.1±1.1 vs. 8.5±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 COS with letrozole in breast cancer patients with COS 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 controlled ovarian stimulation for fertility preservation in oestrogen sensitive diseases the concomitant use of anti-oestrogen therapy, such as letrozole or tamoxifen, is probably recommended.	Conditional ⊕◯◯◯

Justification

The quality of evidence is still low given the number and quality of studies available. The existing literature concerning controlled 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 COS 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 controlled 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. Despite these limitations, both letrozole and tamoxifen protocols may be safe. However, the use of letrozole is off-label for COS.

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

References

Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. *Human reproduction (Oxford, England)* 2016.

Ben-Haroush A, Farhi J, Ben-Aharon I, Sapir O, Pinkas H, Fisch B. High yield of oocytes without an increase in circulating estradiol levels in breast cancer patients treated with follicle-stimulating hormone and aromatase inhibitor in standard gonadotropin-releasing hormone analogue protocols. *The Israel Medical Association journal : IMAJ* 2011;13: 753-756.

Boots CE, Meister M, Cooper AR, Hardi A, Jungheim ES. Ovarian stimulation in the luteal phase: systematic review and meta-analysis. *Journal of assisted reproduction and genetics* 2016;33: 971-980.

Cardozo ER, Thomson AP, Karmon AE, Dickinson KA, Wright DL, Sabatini ME. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. *Journal of assisted reproduction and genetics* 2015;32: 587-596.

Chan JL, Johnson LN, Efymow BL, Sammel MD, Gracia CR. Outcomes of ovarian stimulation after treatment with chemotherapy. *Journal of assisted reproduction and genetics* 2015;32: 1537-1545.

Checa Vizcaino MA, Corchado AR, Cuadri ME, Comadran MG, Brassesco M, Carreras R. The effects of letrozole on ovarian stimulation for fertility preservation in cancer-affected women. *Reproductive biomedicine online* 2012;24: 606-610.

Das M, Shehata F, Moria A, Holzer H, Son WY, Tulandi T. Ovarian reserve, response to gonadotropins, and oocyte maturity in women with malignancy. *Fertility and sterility* 2011;96: 122-125.

Devesa M, Martinez F, Coroleu B, Rodriguez I, Gonzalez C, Barri PN. Ovarian response to controlled ovarian hyperstimulation in women with cancer is as expected according to an age-specific nomogram. *Journal of assisted reproduction and genetics* 2014;31: 583-588.

Domingo J, Guillen V, Ayllon Y, Martinez M, Munoz E, Pellicer A, Garcia-Velasco JA. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. *Fertility and sterility* 2012;97: 930-934.

Druckenmiller S, Goldman KN, Labella PA, Fino ME, Bazzocchi A, Noyes N. Successful Oocyte Cryopreservation in Reproductive-Aged Cancer Survivors. *Obstetrics and gynecology* 2016;127: 474-480.

Garcia-Velasco JA, Domingo J, Cobo A, Martinez M, Carmona L, Pellicer A. Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications. *Fertility and sterility* 2013;99: 1994-1999.

Johnson LN, Dillon KE, Sammel MD, Efymow BL, Mainigi MA, Dokras A, Gracia CR. Response to ovarian stimulation in patients facing gonadotoxic therapy. *Reproductive biomedicine online* 2013;26: 337-344.

Lawrenz B, Jauckus J, Kupka M, Strowitzki T, von Wolff M. Efficacy and safety of ovarian stimulation before chemotherapy in 205 cases. *Fertility and sterility* 2010;94: 2871-2873.

Lee S, Ozkavukcu S, Heytens E, Moy F, Oktay K. Value of early referral to fertility preservation in young women with breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010;28: 4683-4686.

Meirow D, Raanani H, Maman E, Paluch-Shimon S, Shapira M, Cohen Y, Kuchuk I, Hourvitz A, Levron J, Mozer-Mendel M *et al.* Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies. *Fertility and sterility* 2014;102: 488-495.e483.

Muteshi C, Child T, Ohuma E, Fatum M. Ovarian response and follow-up outcomes in women diagnosed with cancer having fertility preservation: Comparison of random start and early follicular phase stimulation - cohort study. *European journal of obstetrics, gynecology, and reproductive biology* 2018;230: 10-14.

Oktay K, Buyuk E, Davis O, Yermakova I, Veeck L, Rosenwaks Z. Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen. *Human reproduction (Oxford, England)* 2003;18: 90-95.

Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;23: 4347-4353.

Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, Bang H. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. *The Journal of clinical endocrinology and metabolism* 2006;91: 3885-3890.

Oktay K, Turkcuoglu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reproductive biomedicine online* 2010;20: 783-788.

Pereira N, Hancock K, Cordeiro CN, Lekovich JP, Schattman GL, Rosenwaks Z. Comparison of ovarian stimulation response in patients with breast cancer undergoing ovarian stimulation with letrozole and gonadotropins to patients undergoing ovarian stimulation with gonadotropins alone for elective cryopreservation of oocytesdagger. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2016: 1-4.

Reddy J, Turan V, Bedoschi G, Moy F, Oktay K. Triggering final oocyte maturation with gonadotropin-releasing hormone agonist (GnRHa) versus human chorionic gonadotropin (hCG) in breast cancer patients undergoing fertility preservation: an extended experience. *Journal of assisted reproduction and genetics* 2014;31: 927-932.

Revelli A, Porcu E, Levi Setti PE, Delle Piane L, Merlo DF, Anserini P. Is letrozole needed for controlled ovarian stimulation in patients with estrogen receptor-positive breast cancer? *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2013;29: 993-996.

Rodgers RJ, Reid GD, Koch J, Deans R, Ledger WL, Friedlander M, Gilchrist RB, Walters KA, Abbott JA. The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: a systematic review. *Human reproduction (Oxford, England)* 2017;32: 1033-1045.

Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, Brenghausen M, Geva-Lerner L, Friedman E, Levi-Lahad E *et al.* BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. *Fertility and sterility* 2015;104: 1162-1167.

PART C: Monitoring

11. Hormonal assessment during controlled 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 controlled ovarian stimulation in IVF/ICSI with ultrasound alone compared to ultrasound plus serum oestradiol concentration combined six 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 using 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 ⊕◯◯◯

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.

References

Golan A, Herman A, Soffer Y, Bukovsky I, Ron-El R. Ultrasonic control without hormone determination for ovulation induction in in-vitro fertilization/embryo transfer with gonadotrophin-releasing hormone analogue and human menopausal gonadotrophin. *Human reproduction (Oxford, England)* 1994;9: 1631-1633.

Kwan I, Bhattacharya S, Kang A, Woolner A. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). *The Cochrane database of systematic reviews* 2014: Cd005289.

Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Monitoring stimulated cycles during in vitro fertilization treatment with ultrasound only--preliminary results. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2012;28: 429-431.

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 controlled 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 <7mm 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 ~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 controlled 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.

REFERENCES

Aydin T, Kara M, Nurettin T. Relationship between Endometrial Thickness and In Vitro Fertilization-Intracytoplasmic Sperm Injection Outcome. *International journal of fertility & sterility* 2013;7: 29-34.

Coelho Neto MA, Martins WP, Lima ML, Barbosa MA, Nastri CO, Ferriani RA, Navarro PA. Ovarian response is a better predictor of clinical pregnancy rate following embryo transfer than is thin endometrium or presence of an endometrioma. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2015;46: 501-505.

Gallos ID, Khairy M, Chu J, Rajkhowa M, Tobias A, Campbell A, Dowell K, Fishel S, Coomarasamy A. Optimal endometrial thickness to maximize live births and minimize pregnancy losses: Analysis of 25,767 fresh embryo transfers. *Reproductive biomedicine online* 2018.

Griesinger G, Trevisan S, Cometti B. Endometrial thickness on the day of embryo transfer is a poor predictor of IVF treatment outcome. *Human Reproduction Open* 2018;2018: hox031-hox031.

Holden EC, Dodge LE, Sneeringer R, Moragianni VA, Penzias AS, Hacker MR. Thicker endometrial linings are associated with better IVF outcomes: a cohort of 6331 women. *Human fertility (Cambridge, England)* 2017: 1-6.

Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, Broekmans FJ. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. *Human reproduction update* 2014;20: 530-541.

Lamanna G, Scioscia M, Lorusso F, Serrati G, Selvaggi LE, Depalo R. Parabolic trend in endometrial thickness at embryo transfer in in vitro fertilization/intracytoplasmic sperm injection cases with clinical pregnancy evidence. *Fertility and sterility* 2008;90: 1272-1274.

Rehman R, Fatima SS, Hussain M, Khan R, Khan TA. Effect of endometrial thickness on pregnancy outcome after intracytoplasmic sperm injection. *JPMA The Journal of the Pakistan Medical Association* 2015;65: 448-451.

Ribeiro VC, Santos-Ribeiro S, De Munck N, Drakopoulos P, Polyzos NP, Schutyser V, Verheyen G, Tournaye H, Blockeel C. Should we continue to measure endometrial thickness in modern-day medicine? The effect on live birth rates and birth weight. *Reproductive biomedicine online* 2018.

Wu Y, Gao X, Lu X, Xi J, Jiang S, Sun Y, Xi X. Endometrial thickness affects the outcome of in vitro fertilization and embryo transfer in normal responders after GnRH antagonist administration. *Reproductive biology and endocrinology : RB&E* 2014;12: 96.

Yuan X, Saravelos SH, Wang Q, Xu Y, Li TC, Zhou C. Endometrial thickness as a predictor of pregnancy outcomes in 10787 fresh IVF-ICSI cycles. *Reproductive biomedicine online* 2016;33: 197-205.

Zhang T, He Y, Wang Y, Zhu Q, Yang J, Zhao X, Sun Y. The role of three-dimensional power Doppler ultrasound parameters measured on hCG day in the prediction of pregnancy during in vitro fertilization treatment. *European journal of obstetrics, gynecology, and reproductive biology* 2016;203: 66-71.

Zhao J, Zhang Q, Wang Y, Li Y. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. *Reproductive biomedicine online* 2014;29: 291-298.

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

It is not recommended to base timing of final oocyte maturation triggering on oestradiol levels.	Strong	⊕◯◯◯

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 controlled 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

It is not recommended to base timing of final oocyte maturation on oestradiol/follicle ratio.	Strong	⊕◯◯◯

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.

References

Chen Y, Zhang Y, Hu M, Liu X, Qi H. Timing of human chorionic gonadotropin (hCG) hormone administration in IVF/ICSI protocols using GnRH agonist or antagonists: a systematic review and meta-analysis. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2014;30: 431-437.

Mochtar MH, Custers IM, Koks CA, Bernardus RE, Verhoeve HR, Mol BW, van Wely M, van der Veen F. Timing oocyte collection in GnRH agonists down-regulated IVF and ICSI cycles: a randomized clinical trial. *Human reproduction (Oxford, England)* 2011;26: 1091-1096.

14. Criteria for cycle cancellation

KEY QUESTION: WHICH CRITERIA FOR CYCLE CANCELLATION ARE MEANINGFUL REGARDING PREDICTED LOW/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 low response was available and different definitions were used. In 2011, the European Society of Human Reproduction and Endocrinology (ESHRE) defined low 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

Low 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 low 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 low 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 low 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 COS 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 during COS 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 low response to controlled ovarian stimulation alone is not a reason to cancel a cycle.	Strong ⊕○○○

The physician should counsel the individual low 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 ⊕○○○

Justification

Reported pregnancy rates among low responders to controlled 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.

REFERENCES

Baka S, Makrakis E, Tzanakaki D, Konidaris S, Hassiakos D, Moustakarias T, Creatsas G. Poor responders in IVF: cancellation of a first cycle is not predictive of a subsequent failure. *Annals of the New York Academy of Sciences* 2006;1092: 418-425.

Broer SL, Dolleman M, van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PM, Eijkemans MJ, Mol BW, Broekmans FJ. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis. *Fertility and sterility* 2013;100: 420-429.e427.

Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Human reproduction (Oxford, England)* 2011;26: 1616-1624.

Garcia JE, Jones GS, Acosta AA, Wright G, Jr. Human menopausal gonadotropin/human chorionic gonadotropin follicular maturation for oocyte aspiration: phase II, 1981. *Fertility and sterility* 1983;39: 174-179.

Griesinger G, Verweij PJ, Gates D, Devroey P, Gordon K, Stegmann BJ, Tarlatzis BC. Prediction of Ovarian Hyperstimulation Syndrome in Patients Treated with Corifollitropin alfa or rFSH in a GnRH Antagonist Protocol. *PloS one* 2016;11: e0149615.

Jayaprakasan K, Chan Y, Islam R, Haoula Z, Hopkisson J, Coomarasamy A, Raine-Fenning N. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women. *Fertility and sterility* 2012;98: 657-663.

Mathur RS, Akande AV, Keay SD, Hunt LP, Jenkins JM. Distinction between early and late ovarian hyperstimulation syndrome. *Fertility and sterility* 2000;73: 901-907.

Nicopoullos JD, Abdalla H. Poor response cycles: when should we cancel? Comparison of outcome between egg collection, intrauterine insemination conversion, and follow-up cycles after abandonment. *Fertility and sterility* 2011;95: 68-71.

Oudendijk JF, Yarde F, Eijkemans MJ, Broekmans FJ, Broer SL. The poor responder in IVF: is the prognosis always poor?: a systematic review. *Human reproduction update* 2012;18: 1-11.

Papanikolaou EG, Pozzobon C, Kolibianakis EM, Camus M, Tournaye H, Fatemi HM, Van Steirteghem A, Devroey P. Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles. *Fertility and sterility* 2006;85: 112-120.

Steward RG, Lan L, Shah AA, Yeh JS, Price TM, Goldfarb JM, Muasher SJ. Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles. *Fertility and sterility* 2014;101: 967-973.

Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. *Human reproduction (Oxford, England)* 2011;26: 1768-1774.

Timeva T, Milachich T, Antonova I, Arabaji T, Shterev A, Omar HA. Correlation between number of retrieved oocytes and pregnancy rate after in vitro fertilization/intracytoplasmic sperm infection. *TheScientificWorldJournal* 2006;6: 686-690.

Toftager M, Bogstad J, Bryndorf T, Lossl K, Roskaer J, Holland T, Praetorius L, Zedeler A, Nilas L, Pinborg A. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist

protocol: RCT including 1050 first IVF/ICSI cycles. *Human reproduction (Oxford, England)* 2016;31: 1253-1264.

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 controlled ovarian stimulation protocols.	Strong	⊕⊕◯◯

A reduced-dose of 5.000 IU urinary hCG for final oocyte maturation is probably recommended over the conventional 10.000 IU dose in GnRH agonist protocols, as it may improve safety.	Conditional	⊕◯◯◯

Justification

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 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/ICSI population.

GnRH agonist triggering for (predicted) high responder is discussed further in the guideline (question 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 0.1-0.4mg 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 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.

References

Human recombinant luteinizing hormone is as effective as, but safer than, urinary human chorionic gonadotropin in inducing final follicular maturation and ovulation in in vitro fertilization procedures: results of a multicenter double-blind study. *The Journal of clinical endocrinology and metabolism* 2001;86: 2607-2618.

Ding N, Liu X, Jian Q, Liang Z, Wang F. Dual trigger of final oocyte maturation with a combination of GnRH agonist and hCG versus a hCG alone trigger in GnRH antagonist cycle for in vitro fertilization: A Systematic Review and Meta-analysis. *European journal of obstetrics, gynecology, and reproductive biology* 2017;218: 92-98.

Eftekhar M, Mojtahedi MF, Miraj S, Omid M. Final follicular maturation by administration of GnRH agonist plus HCG versus HCG in normal responders in ART cycles: An RCT. *International journal of reproductive biomedicine (Yazd, Iran)* 2017;15: 429-434.

Griesinger G, Diedrich K, Devroey P, Kolibianakis EM. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. *Human reproduction update* 2006;12: 159-168.

Humaidan P, Bungum L, Bungum M, Yding Andersen C. Rescue of corpus luteum function with peri-ovulatory HCG supplementation in IVF/ICSI GnRH antagonist cycles in which ovulation was triggered with a GnRH agonist: a pilot study. *Reproductive biomedicine online* 2006;13: 173-178.

2910 Humaidan P, Ejdrup Bredkjaer H, Westergaard LG, Yding Andersen C. 1,500 IU human chorionic
2911 gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing
2912 hormone agonist is used for ovulation induction: a prospective, randomized, controlled study. *Fertility*
2913 *and sterility* 2010;93: 847-854.
2914 Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, Papanikolaou EG, Andersen CY.
2915 GnRHa trigger and individualized luteal phase hCG support according to ovarian response to
2916 stimulation: two prospective randomized controlled multi-centre studies in IVF patients. *Human*
2917 *reproduction (Oxford, England)* 2013;28: 2511-2521.
2918 Kolibianakis EM, Papanikolaou EG, Tournaye H, Camus M, Van Steirteghem AC, Devroey P. Triggering
2919 final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot
2920 study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone
2921 antagonists and recombinant follicle-stimulating hormone. *Fertility and sterility* 2007;88: 1382-1388.
2922 Madani T, Mohammadi Yeganeh L, Ezabadi Z, Hasani F, Chehrazi M. Comparing the efficacy of urinary
2923 and recombinant hCG on oocyte/follicle ratio to trigger ovulation in women undergoing
2924 intracytoplasmic sperm injection cycles: a randomized controlled trial. *Journal of assisted*
2925 *reproduction and genetics* 2013;30: 239-245.
2926 Manau D, Fabregues F, Arroyo V, Jimenez W, Vanrell JA, Balasch J. Hemodynamic changes induced by
2927 urinary human chorionic gonadotropin and recombinant luteinizing hormone used for inducing final
2928 follicular maturation and luteinization. *Fertility and sterility* 2002;78: 1261-1267.
2929 Papanikolaou EG, Verpoest W, Fatemi H, Tarlatzis B, Devroey P, Tournaye H. A novel method of luteal
2930 supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone
2931 agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized
2932 prospective proof of concept study. *Fertility and sterility* 2011;95: 1174-1177.
2933 Shaltout A, Eid M, Shohayeb A. Does triggering ovulation by 5000 IU of uhCG affect ICSI outcome?
2934 *Middle East Fertility Society Journal*. 2006, pp. 99-103.
2935 Vuong TN, Ho MT, Ha TD, Phung HT, Huynh GB, Humaidan P. Gonadotropin-releasing hormone
2936 agonist trigger in oocyte donors co-treated with a gonadotropin-releasing hormone antagonist: a
2937 dose-finding study. *Fertility and sterility* 2016;105: 356-363.
2938 Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin
2939 for final oocyte maturation triggering in IVF and ICSI cycles. *The Cochrane database of systematic*
2940 *reviews* 2016;4: Cd003719.
2941 Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh
2942 I, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in
2943 antagonist-assisted reproductive technology. *The Cochrane database of systematic reviews* 2014:
2944 Cd008046.

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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 resp. 103, 84 and 255 women and reported no significant difference in clinical pregnancy rate (resp. 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 (resp. 314 cycles and 385 women) compared starting LPS with progesterone before oocyte retrieval (resp. 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	⊕◯◯◯

The dosing of natural progesterone has evolved empirically, usually dosages used include: 50 mg daily for intramuscular progesterone 25 mg daily for subcutaneous progesterone 90 mg daily for vaginal progesterone gel 600 mg daily at least for micronized vaginal progesterone capsules and 300 mg daily at least for micronized vaginal progesterone suppositories/capsules.	GPP

Any of the previously mentioned administration routes (non-oral) for natural progesterone as luteal phase support can be used.	GPP

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

Progesterone for luteal phase support should be administered at least until the day of the pregnancy test.	GPP

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. Its efficacy and safety (OHSS) are equal to progesterone.	Conditional ⊕⊕⊕◯

Justification

The evidence suggests that 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 study by Tournaye et al. reported similar safety and tolerability in both treatment groups (Tournaye, et al., 2017).

As dydrogesterone is a synthetic form of progesterone, there are some concerns regarding safety for the offspring. Currently, evidence shows no difference in the rate of congenital anomalies as compared to natural progesterone (Tournaye, et al., 2017). Long-term offspring health studies are currently lacking.

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 controlled 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.

REFERENCES

Aslih N, Ellenbogen A, Shavit T, Michaeli M, Yakobi D, Shalom-Paz E. Can we alter pregnancy outcome by adjusting progesterone treatment at mid-luteal phase: a randomized controlled trial. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2017;33: 602-606.

Bar Hava I, Blueshtein M, Ganer Herman H, Omer Y, Ben David G. Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles. *Fertility and sterility* 2017;107: 130-135.e131.

Barbosa MWP, Valadares NPB, Barbosa ACP, Amaral AS, Iglesias JR, Nastri CO, Martins WP, Nakagawa HM. Oral dydrogesterone vs. vaginal progesterone capsules for luteal-phase support in women undergoing embryo transfer: a systematic review and meta-analysis. *JBRA assisted reproduction* 2018;22: 148-156.

Baruffi R, Mauri AL, Petersen CG, Felipe V, Franco JG, Jr. Effects of vaginal progesterone administration starting on the day of oocyte retrieval on pregnancy rates. *Journal of assisted reproduction and genetics* 2003;20: 517-520.

Belaisch-Allart J, De Mouzon J, Lapousterle C, Mayer M. The effect of HCG supplementation after combined GnRH agonist/HMG treatment in an IVF programme. *Human reproduction (Oxford, England)* 1990;5: 163-166.

Doblinger J, Cometti B, Trevisan S, Griesinger G. Subcutaneous Progesterone Is Effective and Safe for Luteal Phase Support in IVF: An Individual Patient Data Meta-Analysis of the Phase III Trials. *PloS one* 2016;11: e0151388.

Fanchin R, Righini C, de Ziegler D, Olivennes F, Ledee N, Frydman R. Effects of vaginal progesterone administration on uterine contractility at the time of embryo transfer. *Fertility and sterility* 2001;75: 1136-1140.

Gao J, Gu F, Miao BY, Chen MH, Zhou CQ, Xu YW. Effect of the initiation of progesterone supplementation in in vitro fertilization-embryo transfer outcomes: a prospective randomized controlled trial. *Fertility and sterility* 2018;109: 97-103.

Gizzo S, Andrisani A, Esposito F, Noventa M, Di Gangi S, Angioni S, Litta P, Gangemi M, Nardelli GB. Which luteal phase support is better for each IVF stimulation protocol to achieve the highest pregnancy rate? A superiority randomized clinical trial. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2014;30: 902-908.

Griesinger G, Blockeel C, G TS, Patki A, Dhorepatil B, Yang DZ, Chen ZJ, Kahler E, Pexman-Fieth C, Tournaye H. Oral dydrogesterone versus intravaginal micronized progesterone gel for luteal phase support in IVF: a randomized clinical trial. *Human reproduction (Oxford, England)* 2018;33: 2212-2221.

Ismail Madkour WA, Noah B, Abdel Hamid AM, Zaheer H, Al-Bahr A, Shaeer M, Moawad A. Luteal phase support with estradiol and progesterone versus progesterone alone in GnRH antagonist ICSI cycles: a randomized controlled study. *Human fertility (Cambridge, England)* 2016;19: 142-149.

Iwase A, Ando H, Toda S, Ishimatsu S, Harata T, Kurotsuchi S, Shimomura Y, Goto M, Kikkawa F. Oral progestogen versus intramuscular progesterone for luteal support after assisted reproductive technology treatment: a prospective randomized study. *Archives of gynecology and obstetrics* 2008;277: 319-324.

Kupferminc MJ, Lessing JB, Amit A, Yovel I, David MP, Peyser MR. A prospective randomized trial of human chorionic gonadotrophin or dydrogesterone support following in-vitro fertilization and embryo transfer. *Human reproduction (Oxford, England)* 1990;5: 271-273.

Kutlusoy F, Guler I, Erdem M, Erdem A, Bozkurt N, Biberoglu EH, Biberoglu KO. Luteal phase support with estrogen in addition to progesterone increases pregnancy rates in in vitro fertilization cycles with poor response to gonadotropins. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2014;30: 363-366.

Liu XR, Mu HQ, Shi Q, Xiao XQ, Qi HB. The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a meta-analysis. *Reproductive biology and endocrinology : RB&E* 2012;10: 107.

Michnova L, Dostal J, Kudela M, Hamal P, Langova K. Vaginal use of micronized progesterone for luteal support. A randomized study comparing Utrogestan® and Crinone® 8. *Biomedical papers of the medical faculty of the university palacky, olomouc, czechoslovakia* 2017;161: 86-91.

Mochtar MH, Van Wely M, Van der Veen F. Timing luteal phase support in GnRH agonist down-regulated IVF/embryo transfer cycles. *Human reproduction (Oxford, England)* 2006;21: 905-908.

Papanikolaou EG, Verpoest W, Fatemi H, Tarlatzis B, Devroey P, Tournaye H. A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone

agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study. *Fertility and sterility* 2011;95: 1174-1177.
Razieh DF, Maryam AR, Nasim T. Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection. *Taiwanese journal of obstetrics & gynecology* 2009;48: 245-248.
Smitz J, Devroey P, Camus M, Deschacht J, Khan I, Staessen C, Van Waesberghe L, Wisanto A, Van Steirteghem AC. The luteal phase and early pregnancy after combined GnRH-agonist/HMG treatment for superovulation in IVF or GIFT. *Human reproduction (Oxford, England)* 1988;3: 585-590.
Sohn SH, Penzias AS, Emmi AM, Dubey AK, Layman LC, Reindollar RH, DeCherney AH. Administration of progesterone before oocyte retrieval negatively affects the implantation rate. *Fertility and sterility* 1999;71: 11-14.
Tonguc E, Var T, Ozyer S, Citil A, Dogan M. Estradiol supplementation during the luteal phase of in vitro fertilization cycles: a prospective randomised study. *European journal of obstetrics, gynecology, and reproductive biology* 2011;154: 172-176.
Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Human reproduction (Oxford, England)* 2017;32: 1019-1027.
van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *The Cochrane database of systematic reviews* 2015: Cd009154.
Williams SC, Oehninger S, Gibbons WE, Van Cleave WC, Muasher SJ. Delaying the initiation of progesterone supplementation results in decreased pregnancy rates after in vitro fertilization: a randomized, prospective study. *Fertility and sterility* 2001;76: 1140-1143.
Yildiz GA, Sukur YE, Ates C, Aytac R. The addition of gonadotrophin releasing hormone agonist to routine luteal phase support in intracytoplasmic sperm injection and embryo transfer cycles: a randomized clinical trial. *European journal of obstetrics, gynecology, and reproductive biology* 2014;182: 66-70.
Zafardoust S, Jeddi-Tehrani M, Akhondi MM, Sadeghi MR, Kamali K, Mokhtar S, Badehnoosh B, Arjmand-Teymouri F, Fatemi F, Mohammadzadeh A. Effect of Administration of Single Dose GnRH Agonist in Luteal Phase on Outcome of ICSI-ET Cycles in Women with Previous History of IVF/ICSI Failure: A Randomized Controlled Trial. *Journal of reproduction & infertility* 2015;16: 96-101.
Zargar M, Saadati N, Ejtahed M. Comparison the effectiveness of oral dydrogesterone, vaginal progesterone suppository and progesterone ampule for luteal phase support on pregnancy rate during ART cycles *International Journal of Pharmaceutical Research and Allied Sciences*. 2016, pp. 229-236.

PART E: Prevention of OHSS

In previous sections, recommendations were formulated regarding the preferable protocol of controlled 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

A reduced gonadotropin dose is recommended to decrease the risk of OHSS in predicted high responders if GnRH agonist protocols are used.	Strong	⊕◯◯◯

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).

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.

17.2 GnRH agonist vs hCG non-10.000 IU trigger

Evidence

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

If a freeze-all strategy is not used or not preferred in patients at risk of OHSS, the use of reduced-dose hCG trigger and GnRH agonist followed by luteal phase support with LH-activity is probably equally recommended in the GnRH antagonist protocol.	Conditional ⊕◯◯◯

Justification

Only one study addressed this question (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.

17.3 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 ⊕◯◯◯

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 (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.

17.4 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

strategy in patients at risk of OHSS.	

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.

17.5 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.	GPP

References

Acevedo B, Gomez-Palomares JL, Ricciarelli E, Hernandez ER. Triggering ovulation with gonadotropin-releasing hormone agonists does not compromise embryo implantation rates. *Fertility and sterility* 2006;86: 1682-1687.

Aflatoonian A, Mansoori-Torshizi M, Farid Mojtahedi M, Aflatoonian B, Khalili MA, Amir-Arjmand MH, Soleimani M, Aflatoonian N, Oskouian H, Tabibnejad N *et al.* Fresh versus frozen embryo transfer after gonadotropin-releasing hormone agonist trigger in gonadotropin-releasing hormone antagonist cycles among high responder women: A randomized, multi-center study. *International journal of reproductive biomedicine (Yazd, Iran)* 2018;16: 9-18.

Babayof R, Margalioth EJ, Huleihel M, Amash A, Zylber-Haran E, Gal M, Brooks B, Mimoni T, Eldar-Geva T. Serum inhibin A, VEGF and TNFalpha levels after triggering oocyte maturation with GnRH agonist compared with HCG in women with polycystic ovaries undergoing IVF treatment: a prospective randomized trial. *Human reproduction (Oxford, England)* 2006;21: 1260-1265.

Borges E, Jr., Braga DP, Setti AS, Vingris LS, Figueira RC, Iaconelli A, Jr. Strategies for the management of OHSS: Results from freezing-all cycles. *JBRA assisted reproduction* 2016;20: 8-12.

DiLuigi AJ, Engmann L, Schmidt DW, Maier DB, Nulsen JC, Benadiva CA. Gonadotropin-releasing hormone agonist to induce final oocyte maturation prevents the development of ovarian hyperstimulation syndrome in high-risk patients and leads to improved clinical outcomes compared with coasting. *Fertility and sterility* 2010;94: 1111-1114.

Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. *Fertility and sterility* 2008;89: 84-91.

Galindo A, Bodri D, Guillen JJ, Colodron M, Vernaeve V, Coll O. Triggering with HCG or GnRH agonist in GnRH antagonist treated oocyte donation cycles: a randomised clinical trial. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* 2009;25: 60-66.

Humaidan P, Polyzos NP, Alsbjerg B, Erb K, Mikkelsen AL, Elbaek HO, Papanikolaou EG, Andersen CY. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. *Human reproduction (Oxford, England)* 2013;28: 2511-2521.

Karacan M, Erdem E, Usta A, Arvas A, Cebi Z, Camlibel T. Gonadotropin-releasing hormone agonist triggering with concomitant administration of low doses of human chorionic gonadotropin or a freeze-all strategy in high responders. *Saudi Med J* 2017;38: 586-591.

Melo M, Busso CE, Bellver J, Alama P, Garrido N, Meseguer M, Pellicer A, Remohi J. GnRH agonist versus recombinant HCG in an oocyte donation programme: a randomized, prospective, controlled, assessor-blind study. *Reproductive biomedicine online* 2009;19: 486-492.

Sismanoglu A, Tekin HI, Erden HF, Ciray NH, Ulug U, Bahceci M. Ovulation triggering with GnRH agonist vs. hCG in the same egg donor population undergoing donor oocyte cycles with GnRH antagonist: a prospective randomized cross-over trial. *Journal of assisted reproduction and genetics* 2009;26: 251-256.

Tannus S, Turki R, Cohen Y, Son WY, Shavit T, Dahan MH. Reproductive outcomes after a single dose of gonadotropin-releasing hormone agonist compared with human chorionic gonadotropin for the induction of final oocyte maturation in hyper-responder women aged 35-40 years. *Fertility and sterility* 2017;107: 1323-1328.e1322.

Youssef MA, Van der Veen F, Al-Inany HG, Mochtar MH, Griesinger G, Nagi Mohesen M, Aboulfoutouh I, van Wely M. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *The Cochrane database of systematic reviews* 2014: Cd008046.

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 (0.6% (7/1077) vs. 2.0% (22/1080); RR 0.32, 95% CI 0.14-0.74) (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 controlled ovarian stimulation, a risk assessment for high response is advised.	GPP

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.

References

D'Angelo A, Amso N. Embryo freezing for preventing ovarian hyperstimulation syndrome. *The Cochrane database of systematic reviews* 2007: Cd002806.

Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, Zhu Y, Deng X, Qi X, Li H *et al.* Transfer of Fresh versus Frozen Embryos in Ovulatory Women. *The New England journal of medicine* 2018;378: 126-136.

Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, Nguyen LK, Norman RJ, Mol BW. IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries. *New England journal of medicine* 2018;378: 137-147.

Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. *The Cochrane database of systematic reviews* 2017;3: Cd011184.

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

REFERENCE

Zegers-Hochschild F, Adamson G D, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke I D *et al.* The International Glossary on Infertility and Fertility Care, 2017. *Human Reproduction* 2017; 32: 1786-1801.

Annexes

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 controlled ovarian stimulation. We aimed for an equal distribution in gender, region and expertise.

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Methodological support

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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
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, Finox, TEVA, Gedeon-Richter, Glycotope, Abbott, Vitrolife, Biosilu 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 MSD, 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
Sesh Kamal Sunkara	Speaker's fees from Merck, MSD, Ferring
Simone Broer	None declared.
George Lainas	None declared.
Stratis Kolibianakis	None declared.
Michal Kunicki	Speaker's fees from Ferring
Tanya Timeva	Speaker's fees from Merck, MSD, MLD
Sebastiaan Mastenbroek	None declared.
Nathalie Vermeulen	None declared.
Nathalie Le Clef	None declared.

Annex 3: Recommendations for research in COS 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 with RPL, 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
COS	Controlled ovarian stimulation
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
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 (N. Vermeulen, N. Le Clef, A. D'Angelo , K. Tilleman, Z. Veleva, W.L.D.M. Nelen, Manual for ESHRE guideline development, version 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: "Controlled 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 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

Reviewer	Country