First world conference on luteinizing hormone in ART: Landing in Asia Pacific
19-20 November, 2016 - Bangkok, Thailand
Overview
This conference will review and further enlighten the main topics discussed during the First world conference on luteinizing hormone (LH) in ART: A flight of discovery in Naples, Italy on 27-28 May 2016. The role of LH during folliculogenesis has heightened curiosity for at least three decades. In particular, the scientific community is still divided over recognizing the relevance of LH containing drugs during controlled ovarian stimulation (COS). Availability of recombinant drugs has offered, for the first time, the opportunity to explore the role of the follicle stimulating hormone (FSH) and LH separately. Despite this opportunity, the role of recombinant LH is still a matter of debate. This conference will show evidence from basic science to clinical practice regarding the use of recombinant LH and will illustrate its possible benefits as well as its physiopathological mechanism. Guided by experts, participants will grasp the rationale for using recombinant LH in assisted reproductive technology as well as understand the role of LH in human reproduction.

Learning objectives
By attending this conference, participants will be able to:
- Understand the physiology of LH and its role in ovulation induction
- Grasp the state of the art regarding the use of recombinant LH
- Individualise groups of patients that required LH during stimulation protocols
- Identify specific ovarian reserve markers and genotype polymorphisms useful for tailoring treatments and choosing the best approach

Target audience
This programme is intended for clinicians, embryologists, biologists and scientists working in ART.
CME Provider

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The CME conference "First world conference on luteinizing hormone in ART: Landing in Asia Pacific" held on 19-20 November 2016 in Bangkok, Thailand, is designated for a maximum of 6 [six] hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME® credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME® credit to AMA PRA category 1 credit, please contact the AMA.

EXCEMED adheres to the principles of the Good CME Practice group (gCMEp).
Venue
This educational conference will take place at the:

AVANI Riverside Bangkok Hotel
257 Charoennakorn Road, Thonburi
Bangkok 10600
Thailand

Language
The official language of this live educational conference is English.

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Visit
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**Saturday, 19 November 2016**

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**Legend**

- L: Lecture;
- 📜: Case studies;
- 🍂: Panel discussion
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- **Carlo Alviggi**: Declared receipt of honoraria or consultation fees from Merck
- **Sandro C. Esteves**: Declared receipt of honoraria or consultation fees from Merck and Besins
- **Robert Fischer**: Declared no potential conflict of interest
- **Peter Humaidan**: Declared receipt of unrestricted research grants from Merck and Ferring, of honoraria or consultation fees for lectures from Merck and MSD
SPEAKER BIOGRAPHIES
Carlo Alviggi obtained his MD degree (1994) with a specialty in Obstetrics and Gynaecology (1998), and a PhD in 2001 at the Faculty of Medicine, University of Naples “Federico II”, Italy. In 1998 he was a visiting fellow in the IVF Unit of the Imperial College of London– Hammersmith Campus, where he also collaborated with the Department of Immunology (Imperial College of London). Thereafter, he collaborated with the Laboratory of Immunology of the Italian National Research Council (Naples), the laboratory of Autoimmunity and Tolerance of the University of California (Los Angeles). This collaborative network resulted in various publications some of which concern new hypotheses on the pathogenesis of pelvic endometriosis. Over recent years, he has been working as associate professor in reproductive medicine at the Fertility Unit of the University of Naples “Federico II” (Department of Neuroscience, Reproductive Science and Odontostomatology). Dr Alviggi has published extensively and has been invited to lecture at over 100 international meetings dealing with reproductive medicine and gynaecological endocrinology. He has also served as adhoc reviewer for international journals in these fields. He has participated in several national and international (phase II-III) multicentric, prospective randomised trials. Dr Alviggi’s current research interests are the role of LH in folliculogenesis, the use of LH-containing drugs in patients undergoing ovarian controlled stimulation for IVF, the pathogenesis of pelvic endometriosis, oncology, reproduction endocrinology and the genetics of human reproduction.

Sandro C. Esteves is the Medical and Scientific Director of ANDROFERT - Andrology and Human Reproduction Clinic, a referral Fertility Center for male reproduction in Brazil. His Center was the first in Brazil to obtain full ISO 9001 certifications. Dr. Esteves obtained his MD in 1990 from the University of Campinas (UNICAMP), Brazil, where he did his residency training in Urology & Andrology. He completed his training in the United States (1995-1996) as a Fellow at the Cleveland Clinic’s Center for Reproductive Medicine. He was awarded his PhD in 2001 from the Federal University of São Paulo (UNIFESP), Brazil. Dr. Esteves is a Board-certified Urologist and Infertility Consultant with over 15 years of experience. He is a Collaborating Professor in the Department of Surgery (Division of Urology) at the University of Campinas [Brazil] and Research Collaborator at both the Cleveland Clinic’s Center for Reproductive Medicine [USA] and the Genetic Unit, Department of Biology, Universidad Autónoma de Madrid, [Spain]. He is holds an honorary title of Clinical Tutor in Urology at the University of Edinburgh [UK]. His research/clinical interests include male infertility, reproductive endocrinology, cleanroom technology and quality management. Dr. Esteves has published over 130 scientific papers and review articles in peer-reviewed scientific journals, authored over 60 book chapters, and presented over 150 papers at both national and international scientific meetings. His current Hirsch index (h-index) is 25 while his citation count is approximately 2,300. He has served as an editor of five textbooks related to reproductive medicine and assisted reproductive technology. He is the guest editor of three special issues in scientific journals on topics related to reproductive medicine. Sandro serves on the Editorial Board of several Journals and is Associate Editor of the International Brazilian Journal of Urology and Frontiers in Reproductive Medicine. Dr. Esteves has been invited as a guest speaker of many international meetings in over 30 countries. He is the recipient of the “Alumni of the Year” Award from the Cleveland Clinic Center for Reproductive Medicine, and the Star Award from the American Society for Reproductive Medicine for the last 4 years.
Robert Fischer
Fertility Centre Hamburg
Hamburg, Germany

Robert Fischer is founder and Medical Director of the IVF unit at the Fertility Center Hamburg - one of Germany’s largest and leading IVF centres. In July 1998 the Fertility Center Hamburg was one of the first centres in Germany, and worldwide, to introduce certified quality management according to the ISO 9001. In 2002, the IVF laboratory became ISO 17025 certified. Prior to these developments, in 1983 he pioneered and was medical director of the first outpatient IVF unit in Hamburg. Author of numerous publications in national and international scientific journals and books, as well as lecturer at conferences worldwide, he is also an active member of the American Society of Reproductive Medicine, founding member of the European Society of Human Reproduction and past member of its advisory committee as well as founding member of the German reproductive organisations, “AG Gynäkologische Endokrinologie und Fortpflanzungsmedizin” and “Berufsverband Reproduktionsmedizinischer Zentren”.

Peter Humaidan
Fertility Clinic
Skive Regional Hospital and Faculty of Health
Aarhus University
Aarhus, Denmark

Peter Humaidan is a specialist in reproductive endocrinology, Professor at The Fertility Clinic at Skive Regional Hospital, Aarhus University, Denmark, and Honorary Professor at Odense University, Denmark. He trained at the Sahlgrenska University Hospital, Gothenburg, Sweden. During his scientific work he has primarily focused on developing individualized treatment protocols for the infertile patient. His doctoral thesis [DMSc] explored the role of LH during the follicular and luteal phases in controlled ovarian stimulation. His main fields of interest are triggering ovulation with GnRH agonist, the use of GnRH antagonists, and OHSS prevention. He is the founder of the international society “The Copenhagen GnRHa Triggering Workshop Group” and board member of the ESHRE SIG Endocrinology Group. He has authored 100 + articles (H-index 26) in international peer reviewed journals as well as the Danish guidelines for OHSS prevention and chapters in textbooks. Peter Humaidan has a wide international scientific network and is frequently invited as a speaker at international conferences.
Poor ovarian responders (POR) are one of the most difficult patient categories to treat. Among the multiple challenges, including our limited understanding of the pathophysiology and the overall disappointing outcomes during ART, there is a large heterogeneity in its definition.

Until 2010, more than 40 clinical trials have been published, with a wide variation in the definition of poor responders. Among them, more than 90% of POR trials showed no statistical differences in their reported outcomes and almost 50% of trials have not performed sample size calculations. Moreover, heterogeneous definitions and designs have made it difficult to interpret results and draw valid conclusions. Not surprisingly, the Cochrane review published in 2010 on the "interventions for poor responders to controlled ovarian stimulation (COS) in IVF" concluded that there was insufficient evidence to support the routine use of any particular intervention either for pituitary down-regulation, ovarian stimulation or adjuvant therapy.

In 2011, the Bologna criteria for poor responders (ESHRE, 2011) was introduced with the main objective of selecting homogeneous groups of patients based on 'oocyte quantity' for testing in prospective randomized trials for different strategies. Until now, more than 70 clinical trials on POR have been published and an increasing number of trials have reported inclusion of patients according to the Bologna criteria.

Of note, among 44 trials on POR registered in clinicaltrials.gov, 23 trials (52%) applied the Bologna criteria. Notwithstanding, only 7 enrolled an adequate number of patients to avoid type II error; that is, the probability of the study not showing statistical difference in outcomes despite a difference truly exists. Among all trials, 8 have been completed and results published/presented, but only 1 reported a beneficial effect of a given intervention with regard to pregnancy outcome (Xu et al. PLoS One 2014). Although the Bologna criteria have fulfilled their intended goal, it seems little progress has been achieved with regard to the understanding of this enigmatic condition.

One problem with the Bologna criteria - and with all existing criteria - is that women with POR may comprise several subgroups with diverse baseline characteristics. Apart from the changes in follicle number across the female lifespan, there is high biological variability within same age groups. Furthermore, the Bologna criteria do not address the issue of oocyte quality. At present, it is not clear whether the Bologna criteria (or any other criteria) for POR eliminated clinical heterogeneity within the poor responder population. For instance, existing criteria for POR are not able to discriminate patients with reduced ovarian reserves from patients with different degrees of ovarian response to gonadotropins due to inherent ovarian resistance. In addition, oocyte number (or ovarian reserve) and oocyte quality should be distinguished. If the patient allocation is not fully balanced, bias can be introduced by studying groups with different baseline characteristics and, potentially, different prognoses. Analysis of whole populations may dilute effect size.

From the clinical practice standpoint, there seems to be a wide variation in the definition of POR. Unlike the common criteria used in published research, namely the number of oocytes retrieved, abnormal ovarian markers and a previous history of POR, the most used criterion is the "number of follicles produced" (79% responses; IVFonline). To complicate matters further, patients define POR as women who require large doses of medication and who make less than an optimal number of oocytes (RESOLVE), thus introducing a new element to the equation, namely, suboptimal response to stimulation. As it stands, it seems no one is fully satisfied with existing criteria for POR. Our efforts should be mainly focused on better stratifying poor responders, understanding their prognosis in IVF, and finding remedies to move a patient from a worse prognostic category to a better one. It is time to turn the page!
Variability in the infertile patient population excludes the possibility of a single approach to controlled ovarian stimulation (COS). Modern technology has led to the development of new drugs, treatment options and quantitative methods that allow an individualized patient approach to IVF. The personalization of treatments requires a comprehensive evaluation of several important aspects. Firstly, age still remains the best predictive factor of gamete euploidy rate. It was estimated that the percentage of abnormal embryos/oocytes dramatically increased in women over the age of 35. Strategies to improve the number of vital and euploid embryos in those women is currently the most intriguing challenge considering that more and more women seeking ART are in advanced age.

On the other hand, ovarian reserve markers, namely anti-Müllerian hormone (AMH) and antral follicle count (AFC), are also considered the most accurate predictors of ovarian reserve and could be used to successfully guide COS.

Finally, ovarian sensitivity to exogenous gonadotropin is also crucial in the management of infertile women. Several studies indicate that 10-15% of women who underwent COS require higher gonadotropin dosage during COS. There is emerging evidence that this “hypo-response” profile could be linked to specific genotype characteristics. If these data are confirmed, genetic screening may allow, in the future, better individualized COS on the basis of a pharmacogenomic approach. In conclusion, the correct management of infertility in women is a challenging drama requiring the interplay of three main actors: ovarian reserve, euploidy rates and ovarian sensitivity.
L3. From POR to low prognosis concept: a new proposed stratification by POSEIDON Working Group

Peter Humaidan
Fertility Clinic, Skive Regional Hospital and Faculty of Health, Aarhus University, Aarhus, Denmark

The incidence of poor response during ART has previously been reported to vary from 9 – 24 percent. Until the establishment of the ESHRE Bologna criteria for POR (2011), no strict criteria to define POR existed, which hampered conclusions made from previous clinical trials and meta-analyses. However, even the Bologna criteria have subsequently been criticized for being too strict, defining patients with low success rates who, in reality, are better off with oocyte donation. In this lecture a further attempt to define the poor responder patient will be made, taking into account ovarian reserve and age which are the two most important factors to predicting success after IVF treatment. Four different sub-groups of poor responder patients will be defined as well as the suggested matching protocols and regimens which, by definition, might increase the success rate of the patient. Moreover, a review of strategies and adjuvants as well as future therapeutical options for the poor responder patient will be presented. The impact of different stimulation protocols on the ovarian response to stimulation in the poor responding group of patients will be discussed, even if handling the poor responder patient is still a therapeutic challenge.
L4. How many oocytes are needed for one euploid embryo?

Sandro C. Esteves
ANDROFERT - Andrology & Human Reproduction Clinic, Campinas, Brazil

There is a strong relationship between the number of retrieved oocytes and female age in ART due to the inexorable depletion of the follicle pool with aging. Hereditable factors, genetic and medical conditions, as well as lifestyle and environmental chemicals not only impact on establishing the primordial follicle pool during fetal life but also on reproductive function in adult life, therefore contributing to interindividual variability.

Ovarian aging has a marked impact on oocyte quality. The age-related decrease in oocyte quality largely depends on chromosomal aneuploidy occurring prior to meiosis II. As a result, embryo euploid rates of about 60% are observed in younger women (<35 years of age) undergoing IVF, whereas these figures are 50% in women aged 35-39, and only 30% in those with 40-42 years-old. However, other biochemical processes may also be relevant, including mitochondrial dysfunction, oxidative stress and increased cumulus and granulosa cell apoptosis.

What would then be fair to offer an infertile couple planning IVF, especially in cases of advanced maternal age (>35) and poor ovarian reserve? The triad of (i) Evaluate properly; (ii) Provide a fair estimate of the outcome, and (iii) Develop a time-limited treatment plan has been proposed as a means to decreasing time to pregnancy. This strategy is aligned with the POSEIDON group’s proposal for a better stratification of low responders and establishing a new marker of successful outcome, namely, the ability to retrieve the number of oocytes necessary to obtain at least one euploid embryo for transfer in each patient.

The importance of estimating the number of oocytes needed for 1 euploid embryo relies on 3 main factors: 1. Oocyte quantity is different than oocyte quality; 2. A normal [euploid] embryo output varies in the populations undergoing IVF; and 3. Transfer of a euploid embryo practically eliminates the age-related decrease in implantation.

The number of oocytes needed for achieving 1 euploid embryo can easily be estimated by computing common IVF parameters, namely, i. %MII; ii. %2PN; iii. Cleavage (D3) or blastocyst formation rates, and iv. Embryo euploid rates. Maternal (and arguably paternal) age is an important qualifier because it not only affects euploid rates but may also impact fertilization and blastulation rates. Likewise, sperm source, sperm quality and the use of fresh or frozen gametes need to be taken into account. Ideally, fertility clinics should use their own databases to extract the aforementioned parameters. This will allow a more reliable estimate of the number of oocytes needed for one euploid embryo based on their specific conditions. However, a generalized estimate can be achieved by inputting literature data to the formula below.

\[
N_{oocytes} = \frac{1}{%MII \times %2PN \times %Blastulation \times \text{euploid embryos per age group}}
\]

For example, consider an infertile couple aged 36 (female) and 38 (male) with a history of failed IVF, which fits the POSEIDON group 2b criteria (adequate ovarian reserve parameters and unexpected suboptimal ovarian response in a previous cycle; n=6 oocytes retrieved) associated with severe male factor infertility in need of testicular sperm for ICSI. According to our own database, the following results are obtained in this given clinical scenario: MII rate = 77%, %2PN = 52%, %blastulation = 52%, and euploid rate = 40%. Applying the aforementioned formula, the number of oocytes needed to achieve one euploid blastocyst will be 12.

The POSEIDON stratification may serve as a guide to personalizing treatment and achieving the proposed measure of success. GnRH analogue regimens, gonadotropin dose and drug type, different trigger strategies, adjuvant therapy, combined strategies (eg. AccuVit; Duostim) as well as personalized application of laboratory technology and luteal phase support can be used to achieve this goal.

Combining quantitative and qualitative parameters may allow an individualized treatment strategy aimed at obtaining the necessary number of oocytes to obtain at least one euploid embryo for transfer. This strategy, which needs to be validated, will hopefully increase the chances of success and reduce time to pregnancy and also align with the expectations of patient and doctor.
The number of oocytes retrieved after ovarian stimulation to reproductive outcome of an IVF cycle is, without a doubt, extremely important. Therefore, the oocyte number predicts the chance of a live birth for patients of all ages. From this perspective, the oocyte number resulting in the highest chance of live birth was recently defined to be fifteen (Sunkara et al., 2011). Importantly, oocyte/embryo quality declines with age, but not with the number of oocytes/embryos obtained after stimulation. Therefore, the optimal ovarian stimulation protocol should result in the retrieval of a sufficient number of oocytes, leading to the transfer of one good (euploid) embryo, without increasing the risk of OHSS. As each follicle recruited during ovarian stimulation – like in the natural cycle - will produce progesterone, the more follicles obtained after ovarian stimulation, the higher the late follicular phase progesterone level (Requena et al., 2014). In this sense, the importance – or not - of late follicular phase progesterone rise ≥ 1.5 ng/ml for the reproductive outcome of an ART cycle has been debated intensively in recent years. However, the latest large analyses have corroborated the importance of distinguishing between the high responder patient with high late follicular progesterone levels and the low responder patient with high late follicular progesterone levels (Griesinger et al., 2013; Venetis et al., 2013). Whereas the former has an excellent reproductive outcome, the latter seems to have a poorer outcome. Whether the poor outcome in the low responder patient is the result of poor embryo quality rather than a reduced endometrial receptivity needs to be further clarified.
There is evidence that two or three follicular waves during the intra-ovulatory period of healthy women occur. It has also been suggested that follicles developing during the luteal phase (LP) may have the potential to ovulate in the presence of a luteinizing hormone (LH) surge, offering new possibilities for ovary stimulation. Double-stimulation approach (DuoStim) consists in both follicular phase (FP) and LP stimulations within a single menstrual cycle. Based on the limited available data, LP stimulation does not show differences in terms of fertilization, pregnancy, and implantation rates compared to FP stimulation.

In a recent prospective paired non-inferiority observational study, euploid blastocyst formation rates obtained after FP versus LP stimulation using DuoStim method were compared in patients with reduced ovarian reserve. Both FP and LP stimulations were carried out using follicle-stimulating hormone and luteinizing hormone starting on day 2 of the cycle and 5 days after the first oocyte retrieval. Gonadotropin-releasing hormone (GnRH) antagonist was used for preventing premature LH peak and GnRH agonist was used for ovulation triggering in both FP and LP. No statistically significant differences were found in the number of retrieved (5.1 ± 3.4 vs. 5.7 ± 3.3), MII oocytes (3.4 ± 1.9 vs. 4.1 ± 2.5), or biopsied blastocysts per stimulated cycle (1.2 ± 1.2 vs. 1.4 ± 1.7) from FP versus LP stimulation, respectively. Furthermore, no differences were observed in the euploid blastocyst rate calculated either per biopsied blastocyst (46.9% vs. 44.8%) or injected MII oocyte (16.2% vs. 15.0%).

In conclusion, this novel stimulation strategy could increase the number of available euploid blastocysts within a single menstrual cycle and, in turn, clinical outcomes. This strategy may be applied to those women who showed low prognosis to exogenous gonadotropin. Specifically, women who belong to Groups 3 and 4 according to the Poseidon Group (reduced ovarian reserve in terms of both antral follicles count and antimullerian hormone) could be optimal targets for this type of strategy.
Although exogenous FSH is the main regulator of follicular growth in controlled ovarian stimulation (COS), LH plays a key role in promoting steroidogenesis and follicle development. During the early follicular phase, LH stimulates the production of androgens by the theca cells. Androgens are then transferred to the granulosa cells (GC) and are transformed into estrogens via aromatization. Added to this, androgens act by increasing the responsiveness of GCs to FSH and may increase recruitability of pre-antral and antral follicles. From the mid-follicular phase onward, LH receptors are expressed in the GCs and LH has the direct effect of sustaining FSH-dependent granulosa cell activities, including aromatase production and growth factors release. LH receptor expression is at its maximum in GC of preovulatory follicles, but antral follicles with 3-10 mm in diameter express these receptors at approximately 10% of the maximum. LH is, therefore, important for follicular growth and final follicular maturation via its direct effects on the GC in the late follicular phase.

The “LH window” concept proposes that in the absence of a threshold level of serum LH of about 0.5 to 1.35 IU/L, estradiol production will be insufficient for follicular development, endometrial proliferation and corpus luteum formation. In fact, women with hypogonadotropic hypogonadism (HH) do not achieve adequate steroidogenesis by stimulation with FSH alone, which is resumed by LH supplementation. Apart from HH, normogonadotropic infertile women may also experience suboptimal outcomes in ovarian stimulation with FSH monotherapy. Regardless of the protocol used for suppressing the LH surge, COS induces a status of “relative” LH deficiency, which seems to be more detrimental to subgroups of susceptible patients, including older women and those with defective endogenous LH. Furthermore, serum androgen levels, particularly total testosterone (T), dehydroepiandrosterone sulfate, and androstenedione decline steeply with age, with the decline of each being greater in the early reproductive years than the later decades. As a result, a decrease in the number of oocytes retrieved, oocyte quality, fertilization rates, embryo quality, and pregnancy rates, and an increase in miscarriage rates can be observed. Several factors, alone or combined, may explain such effects, including a reduction of paracrine ovarian activity, a genetically determined reduced LH bioactivity, an impaired androgen secretory capacity, and a decreased number of functional LH receptors.

Currently, there are three available gonadotropin preparations containing LH activity: (i) hMG/HP-hMG, (ii) recombinant LH (lutropin alfa), and (iii) a combination of recombinant FSH (folitropin alfa) and LH (lutropin alfa) in a fixed ratio of 2:1. LH activity in recombinant LH preparations is derived from the pure LH glycoprotein unlike hMG/HP-hMG, in which hCG is concentrated during purification or added to achieve the desired amount of LH-like biological activity. LH and hCG differ in the composition of their carbohydrate moieties which, in turn, affect bioactivity and half-life. Although both LH and hCG act on the same receptor (LHCGR), LH exclusively stimulates the targeted LHCGR by cis-activation, whereas hCG is also capable of inducing trans-activation, thus affecting the kinetics of cAMP production and downstream ERK1/2- and AKT-pathway activation. Using equimolar concentrations of rec-LH and hCG in human granulosa cells (hGCs) obtained from women subjected to oocyte retrieval, Casarini and colleagues have shown that hCG is 5-fold more potent in vitro than rec-LH at the receptor level based on the measurement of intracellular cAMP. However, accumulation of intracellular cAMP by LH was significantly faster. On the contrary, rec-LH is more active than hCG to activate cell proliferation and survival mediators (pERK and pAKT). In addition, hGCs exposed to hCG show lower viability and higher expression of apoptosis markers (TP53, CASP3, XIAP) than rec-LH. Altogether, these studies confirm that rec-LH and hCG yield LH activity through different mechanisms. Whereas hCG is predominantly pro-stEROidogenic and potentially pro-apoptotic, rec-LH is predominantly a pro-growth, differentiation and survival factor.

In vivo, rec-LH has been associated with an increase in follicular fluid E2, T, and androstenedione levels in a dose-dependent manner (Bosch et al. 2012). Moreover, increased ovarian follicular angiogenesis via modulation of VEGF-A and its soluble receptor sFlt-1 expression (Gutman et al. 2008), improvement in follicular recruitment (Gómez-Palomares et al. 2005), and increased follicular maturation as shown by higher expression of maturation markers in cumulus cells (GF-beta, PTGS2 and HAS2; Barberi et al. 2012) have been observed when rec-LH is given during COS.

In conclusion, the use of LH during COS may offer a corrective measure for the ‘relative’ LH deficiency and impaired steroidogenesis, which could potentially benefit specific subgroups of women.
Recently, a group of experts (the Poseidon Group) proposed a more detailed stratification of low responders to ovarian stimulation that moves from the classical POR to a “low prognosis” concept. The definition of “low prognosis” patients introduces two new categories of impaired response to exogenous gonadotropin: (i) a “suboptimal response”, defined as the retrieval of four to nine oocytes, which is associated, at any given age, with a significantly lower live birth rate compared to normal responders; and (ii) a “hyporesponse” in which a higher dose of gonadotropins and more prolonged stimulation are required to obtain an adequate number of oocytes. Several lines of research reinforce, in detail, the hypothesis that a “hyporesponse” could be related to specific gene polymorphisms. The Poseidon Group proposed the following four groups of low prognosis patients:

Group 1: Young patients (<35 years) with sufficient pre-stimulation ovarian reserve parameters (AFC ≥ 5 and AMH ≥ 1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response. This group can be subdivided into: subgroup 1a, constituted by patients with fewer than four oocytes; and subgroup 1b, constituted by patients with four to nine oocytes retrieved after standard ovarian stimulation, who, at any given age, have a lower live birth rate than age-matched normal responders.

Group 2: Older patients (≥ 35 years) with sufficient pre-stimulation ovarian reserve parameters (AFC ≥ 5 and AMH ≥ 1.2 ng/mL) and with an unexpected poor or suboptimal ovarian response. This group can be subdivided into: subgroup 2a, constituted by patients with fewer than four oocytes; and subgroup 2b, constituted by patients with four to nine oocytes retrieved after standard ovarian stimulation, who, at any given age, have a lower live birth rate than age-matched normal responders.

Group 3: Young patients (<35 years) with poor pre-stimulation ovarian reserve parameters (AFC < 5 and AMH < 1.2 ng/mL).

Group 4: Older patients (≥ 35 years) with poor pre-stimulation ovarian reserve parameters (AFC < 5 and AMH < 1.2 ng/mL).

Based on this classification, we will propose how to determine the need for LH supplementation in the specific subgroups of low prognosis women. For instance, at least three randomized controlled trials (RCTs) and one meta-analysis have demonstrated that LH supplementation is effective in women with a hyporesponse profile who present features as patients belonging to our Group 1. In addition, LH administration has been associated with improvement in the outcome of IVF in women between 35 and 39 years of age, who would be classified in our Groups 2 and 4. Conversely, a recent RCT did not identify any benefit from LH administration in POR patients selected according to the Bologna criteria.

In conclusion, the stratification proposed by the Poseidon Group may serve as a guide to personalized treatment protocols by, for example, using different GnRH analogue regimens, detecting polymorphisms of gonadotropins and their receptors, tailoring the FSH starting dose and LH supplementation.
L9. What about personalized luteal phase support?

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The luteal phase of all stimulated IVF/ICSI cycles is abnormal. The reason for the luteal phase defect (LPD) is the multi-follicular development achieved during ovarian stimulation. This process leads to supra-physiological levels of steroids (progesterone and estradiol) secreted by a high number of corpora lutea during the early luteal phase, which directly inhibit the release of LH from the pituitary via feedback actions at the hypothalamic-pituitary axis level. The reduction in circulating endogenous LH has a detrimental effect on the early-mid luteal phase as LH plays a crucial role not only for the steroidogenic activity of the corpus luteum, but also for the up-regulation of growth factors and cytokines directly involved in the implantation process. Therefore, luteal phase support is mandatory after stimulation for IVF/ICSI. Even though a “standard luteal phase support” has been the gold standard until now, recent scientific evidence suggests using personalized luteal phase support in fresh as well as frozen embryo transfer cycles.
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