2013 CME Annual meeting in reproductive medicine

Improving success in ART: how to define it and key strategies to get the best outcomes

26-27 April 2013 - Athens, Greece

Different clinicians in different disciplines identify success differently, and the clinical definition may not be important to the patient. However, there is general agreement about the goal: an individual, healthy, full-term infant.

SESSION I
What is the most relevant standard of success in ART?

The first session started with an introduction from the scientific organisers regarding the flow of the meeting. Each lecture was preceded and followed by a question regarding the topic of the lecture in order to evaluate the knowledge of the participants. This first session was dedicated to defining the meaning of success starting from the physician’s point of view. G. Kovacs (Australia) explained that during 30 years of ART the technique of IVF has changed and so has the definition of success in ART. By 1983 he was able to report 309 pregnancies and 139 births through IVF, and pregnancy rates were expressed per cycle started, per laparoscopy or per transfer. He explained how pregnancy rates can be monitored according to various factors. “Life table analysis” was introduced in his centre and this method estimates what would happen to couples that have been followed up for further cycles. He stressed the importance of comparing “apples” with “apples” and not with “pears” and said that in the future the results would have to be standardise for patient population (especially age), and we should aim to perform SET (single embryo transfer) most of the time when possible.

In the second lecture K. Venees (UK) explained the patient point of view. She is a member of the “Infertility network” in the UK, and is spokeswoman for patients at IVF centres who have undergone the difficult treatment of IVF to achieve the dream of a child. She showed a movie about her family and explained the process involved before achieving the successful birth of a healthy daughter. After 12 months, she became naturally pregnant with her second child and she finally...
achieved the life she had dreamed of.

A.M. Olugi (USA) discussed the meaning of success from the viewpoint of the healthcare organisation. Between 1998 and 2008 the multiple birth ratio in the US increased nearly 14%, compared to singleton births. That means that 62% of twins and 97% of ART triplets were delivered preterm and the estimated relative cost of each preterm infant is about $51,600; the estimated annual financial burden of ART preterm deliveries is $1bn. He showed the strategies to reduce multiple pregnancies, starting from decreasing gonadotropin cycles for unexplained infertility or mild male factor infertility, educating consumers regarding the risks of a multiple gestation, including twins and promoting elective single embryo transfer (eSET).

The pediatrician’s point of view was discussed by M. Bonduelle (Belgium), who explored the topic of complications in babies born after ART. She explained that 1 in 25 babies in western countries are conceived through ART, and emphasised the importance of identifying in advance the complications mainly attributed to parental background, infertility per se, and to the high rate of multiple pregnancies. Regarding the perinatal outcome, most of the complications are due to pregnancy complications such as prematurity risk in singletons <37 weeks of gestation, low birth weight rate <2500g, 1500g. The most important causes of pregnancy complications are pre-eclampsia, premature rupture of membrane, placenta previa and gestational diabetes. Data regarding the neonatal outcome from twins born after ART and the general population is comparable, and there are no obvious differences between IVF and ICSI. Regarding chromosomal abnormalities, babies born after ICSI have a higher rate than the general population, mainly attributed to sex chromosomal abnormalities linked to sperm parameters. There are no significant data regarding congenital malformation between ICSI and IVF technique. There are studies of follow up after 18 years that show normal physical development compared to spontaneously conceived controls. She concluded that it is still important to monitor health and psychosocial parameters such as age, BMI, AFC, serum estradiol levels or number of developed follicles.

SESSION II
How to get the best results: stimulation protocols

This session started with an innovation: debates on controversial topics. The first debate was on stimulation protocols. F. Broeckmans (The Netherlands) argued for the use of the mild stimulation approach for all ART patients, showing how with reduction in the dosage of gonadotropins it is possible to reach the efficacy of the treatment, reducing the cost and enhancing the convenience, and he emphasised that this approach is safe for the mother and child. He showed data supporting that the reduction of FSH dosage leads to moderate ovarian response and there are no differences in pregnancy rate for started cycles; in addition, the OHSS rate may be halved. He concluded that mild stimulation for all ART patients does not influence the oocyte quality, and that it is cheap and convenient and, moreover, safe. A. Pellicer (Spain) argued for the role of controlled ovarian stimulation and (COS) and maximizing the success rate in ART with tailored stimulation protocols. He started with the definition of conventional or standard COS that means the use of 225-250 UI day gonadotropins in normal responders. The goal will be to obtain 15-20 oocytes avoiding OHSS. He showed how the antagonist protocol can avoid OHSS and maximize results. At the end of the debate Sunkara addressed burning questions to both debaters and the audience consensus was in favour of COS protocols as best the approach to ovarian stimulation.

C. Alviggi (Italy) showed how predictive biomarkers could be used to facilitate treatment decisions and to tailor therapy to increase the chances of achieving pregnancy. Among the hormonal biomarkers, anti-Müllerian hormone (AMH) has been shown to have the highest predictive value, and it also modulates the activity of follicle-stimulating hormone (FSH) in antral follicles during the FSH-dependent growth stage. Antral follicle count (AFC) is a well-known functional biomarker that is used to predict ovarian response to stimulation. It is also an important factor in determining the optimal starting dose of FSH for ART. Recent lines of research also reinforce the hypothesis that ovarian resistance (hyporesponsiveness) to exogenous FSH can be related to specific gene polymorphisms as receptor and LH polymorphism. These data support the idea of a tailored administration of gonadotropins based on a pharmagenomic approach.

The last lecture was focused on management of complications and new strategies to avoid OHSS. J.A. Garcia-Velasco (Spain) showed how OHSS in the 21st century remains an iatrogenic complication during COS. Prevention has relied on the awareness of the importance of clinical parameters such as age, BMI, AFC, serum estradiol levels or number of developed follicles. Different strategies have been evaluated for OHSS prevention including withholding human chorionic gonadotrophin (hCG) to coasting, and vitrification of the oocyte/embryo. More recently, dopamine agonist administration and the antagonist protocols provide the use of GnRH agonist to trigger final oocyte maturation.
SESSION III
How to get the best results: oocytes quality versus quantity

S.K.R. Sunkara [UK] showed data that demonstrated that there is strong association between the number of oocytes retrieved and live births following IVF. The optimum number of oocytes needed to maximize IVF outcomes is still controversial. COS should be tailored to the individual phenotype, maximizing the oocytes yield for poor responders and fine-tuning for hyper responders. She demonstrated how GnRH antagonist regimens optimise oocytes retrieved and maximise live births in all ART cycles. A. Sunde (Norway) explained the relationship between oocyte/embryo quality and stimulation protocols. Much data have demonstrated the relationship between observable oocyte/embryo parameters and outcomes in terms of pregnancies but none is particularly good in predicting oocyte/embryos quality. Several studies suggest a relationship between ovarian stimulation and oxygen consumption in oocytes, cumulus cell expression, implantation and delivery rates.

Genetic quality and the relationship with number of oocytes was the subject of S. Munné’s (USA) presentation. He explained how chromosome analysis of human embryos has evolved considerably in the last few years, from using fluorescence in situ hybridization (FISH) with 5-12 probes and mostly performing polar body or day-3 biopsy PGsV1 (preimplantation genetic screening) to analysing all chromosomes with arrays from blastocyst biopsies (PGsV2).

With the advent of the PGs technique the error rate of diagnoses has been reduced from 7.50%, depending on the laboratory, to 3%. Pregnancy outcomes have significantly improved. Data support that using PGsV2 there are no differences in chromosome aneuploidy rates, irrespective of the cohort size produced. Aneuploidy increases with maternal age and does not decrease with cohort size.

In contrast, F. Fiorentino (Italy) showed that higher oocyte yield is associated with an increased error rate and that this might be explained by unphysiological ovarian stimulation interfering with chromosome segregation behavior during maternal meiosis. Other studies have demonstrated that the incidence of aneuploidy in embryos may be affected by ovarian stimulation regimens employed in IVF, and that the mild stimulation is associated with a reduction in the number of oocytes retrieved and embryos generated compared with more intensive protocols. He presented data showing that an increased incidence of aneuploid embryos seems to be associated with a higher number of oocytes produced by ovarian stimulation.

The controversies section featured a debate between Munné and Fiorentino regarding embryo biopsy day-3 against day-5. Munné showed how blastocyst biopsy has more advantages with more DNA, lower error rate, and reduced impact on embryo biopsy, which means fewer embryos to process, because not all reach the blastocyst stage. He showed data regarding micro array CGH on day 3 and on day 5; the results of the study have shown that the implantation after embryo biopsy day 5 is 50% instead of 40% with day 3 biopsy, and pregnancy rate per transfer is 63% instead of 52% with biopsy day 3. Fiorentino remarked that embryo biopsy day 3 is still useful because at cleavage stage it is not detrimental for the embryo and is still useful for patient with a low embryo development rate to blastocysts stage. The debate outcome demonstrated that this topic remains controversial and emphasised the need for more data.

SESSION IV
How to define the best strategy and the technologies to make it happen

A. Sunde (Norway) explained how difficult it is to define strategies to achieve the results. Calculating the success of ART is far more complicated than just pregnancy rate per embryo replacement. Success criteria may also be different in different regulatory and financial environments. In states where the cost of ART is covered by the government or health insurance, the health provider will focus on total cost and can introduce economic incentives or regulations to increase the use of elective single embryo transfer (eSET). The role of embryo selection is dependent on the success criteria used. If the pregnancy rate after transfer is the most important success criterion, then a selection algorithm is needed that identifies the embryos with the highest developmental potential in a given cohort, but the algorithm will not influence cumulative delivery rates.

L. Rienzi (Italy) discussed how the use of technologies maximizes the success. One of the major hurdles to improving the overall efficiency of fertility treatments is the lack of objective tools to identify gametes with the highest viability and embryos with the highest implantation potential. The system commonly used in andrology and embryology laboratories is based mainly on subjective morphological criteria. She reviewed all techniques available in the laboratory to assess the quality of gametes and embryo from morphokinetics to embryo biopsy and suggested that the future will be an automation and technology combination from evaluation of cumulus cells of oocyte, IVF and ICSI procedures, followed by dynamic morphological evaluation until biopsy and evaluation of trophoderm cells.

N.G. Puchalt (Spain) showed recent data on sperm evaluation using mRNA microarray technology. Evidence suggests a requirement of sperm-delivered mRNA for adequate embryo formation, thus using a specific mRNA signature obtained from sperm samples from which a pregnancy was obtained to define male fertility could be useful as a gold standard. His research group initiated the Sperm Fertility Assay (SFA) project, which aims to determine the optimal transcriptomic signature in sperm for each ART. The aim is to develop a microarray-based sperm diagnostic tool to be clinically employed in counseling for couples and also to develop sperm selection strategies.

Uterine environment and endometrium receptivity was discussed by C. Simon (Spain). This period refers to a hormone-limited period in which the endometrial tissue acquires a functional and transient ovarian steroid-dependent status allowing blastocyst adhesion. Studies have demonstrated that endometrial receptivity is an active process involving up-and down-regulation of hundreds of genes. His group has developed the endometrial receptivity array (ERA) tool, a customized array of 238 genes. Preliminary data supporting the ERA method suggest that about 15% of all patients can be non-receptive. More data are needed to demonstrate and to support previous results.

SESSION V
Unsession

The unsession was dedicated to reinforcing the aim and the learning objectives of the meeting. All the speakers concluded with a take-home message summary of their point of view. This session was also important for reviewing the conclusions of the debates and the answers given by the participants during the real time survey to evaluate if their knowledge was enhanced after the meeting.
Timing of conception: no limits?

29-30 March 2013 - Moscow, Russian Federation

Satisfaction rate:
% Very Satisfied / Satisfied: 98%

The course was focused on the effect of advancing age on clinical infertility and how it is manifested in the pattern of ovarian response to controlled ovarian stimulation (COS). How female age reduces implantation efficiency and increases spontaneous abortion rate was also considered. The course was interactive and featured discussion sessions to focus participant attention and interest.

SESSION I
Maternal age and ovarian reserve

The first session was dedicated to maternal age and ovarian reserve. S.K. Sunkara (UK) explained how the demographics and the age of childbearing in women have been changing over the decades, although the physiology of female fertility remains unchanged. Human ovaries have a finite number of oocytes endowed before birth and there is a constant depletion of the oocyte pool from that time. This exponential decline in oocyte quantity and a parallel decline in oocyte quality has an impact in female fertility. Epidemiological observations in natural fertility populations have shown declining fecundity with maternal age. She showed different therapeutic approaches to stimulation protocols as GnRH agonist versus antagonist regimens and explained that published data show no significant different between agonist long protocol and antagonist regimens in poor responders. The antagonist regimen has the benefit of compliance and cost effectiveness.

S. Nelson (UK) focused his lecture on markers of ovarian reserve and the association with ovarian aging. Assessment of ovarian reserve includes measurement of serum follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH), and inhibin-B. Ultrasound determination of antral follicle count (AFC), ovarian vascularity and ovarian volume can also have a role. In infertile women, ovarian reserve markers can be used to predict low and high oocyte yield and treatment failure in women undergoing in vitro fertilization. The main objective of individualization of treatment in IVF is to offer every single woman the best treatment tailored to her own unique characteristics, thus maximizing the chances of success and avoiding wasted pregnancy attempts resulting from ovarian stimulation. The starting point is to identify whether a woman is likely to have a normal, poor or a hyper response and choose the ideal treatment protocol tailored to this prediction. The data shown from the literature demonstrated that AFC and AMH are the most sensitive markers of ovarian reserve, and are ideal in planning personalized COS protocols.

The role of LH supplementation in poor responders was presented by S. Nelson (UK). In younger women a poor response to ovarian stimulation may also be observed, but their overall success rates will be less adversely affected than in their older counterparts. Strategies to improve quality that contributes to their lower success rates. He showed studies that suggest that they will continue to have improved outcomes relative to their older counterparts even if they produce the same oocyte yield, suggesting that quantity and quality are independent determinants of outcome, with age being the principal determinant of quality. He emphasised that oocyte and embryo aneuploidy are age dependent, and that milder stimulation gives fewer oocytes to test and runs the risk of poor response. He explained that stimulation may alter aneuploidy, in fact GnRH antagonist cycles show similar aneuploidy to natural cycles.

SESSION II
Maternal age and oocyte/embryo quality

This session addressed oocytes and embryo quality. S. Nelson (UK) described how age relates to decline in oocyte quantity and quality, and is associated with the risk of a poor ovarian response and aneuploidy. He explored whether younger women with a reduced ovarian reserve also have a concomitant reduction in oocyte quality that contributes to their lower success rates in women with a reduced ovarian reserve have been limited, but LH supplementation would appear to be beneficial and easily achieved. He explained which patients benefit from LH supplementation in ART: patients with hypogonadotropic-hypogonadism, poor responders, and women older than 35 years. At the end of this session the participants were divided into groups to analyse the different therapeutic approaches with the help of case studies prepared by the speakers.

R. Fischer (Germany) introduced the topic of luteal phase support. He described the mechanism of the corpus luteum, which is an ovarian endocrine gland that develops after ovulation and characterizes the luteal phase following ovulation. It actively secretes steroid hormones, particularly progesterone, and is fundamental for the maintenance of early spontaneous abortion rate was also considered. The course was interactive and featured discussion sessions to focus participant attention and interest.

SESSION III
Maternal age and pregnancy after ART

The learners were extremely satisfied and demonstrated a high interest in the workshop format: they were extremely active during the working groups, speakers’ case studies presentation and discussions.
pregnancy. Progesterone prepares the endometrium for pregnancy by stimulating proliferation in response to human chorionic gonadotropin (hCG). Luteal-phase gonadotropin dependent dysfunction can lead to corpus luteum dysfunction and reduced female fertility. Hence changes in the endocrine pattern due to the gonadotrophins used for ovarian stimulation are thought to underlie the corpus luteum dysfunction associated with IVF cycles. In ART, progesterone production by the corpus luteum is reduced so that the luteal phase is supported, improving the implantation rate and thus pregnancy rates. The luteal support can be done with progesterone, hCG or gonadotropin releasing hormone (GnRH) agonists. He presented some recent systematic reviews that showed a significant effect in favour of progesterone for luteal phase support, and favouring synthetic progesterone over micronized progesterone.

S. Sunkara explained the process of implantation and how it is influenced by complex interactions involving maturational events in the embryo, synergism of the endometrium, maternal hormonal changes and immune responses. The advent of IVF has provided a unique opportunity to study factors affecting human embryo implantation. The negative impact of advanced female age on implantation has been demonstrated by IVF studies.Whilst, it was accepted that female age influences implantation it was initially debated whether this was a result of the embryonic or endometrial factors. Studies of oocyte donation involving young donors and older recipients confirmed that the former was the main contributory factor to reduced implantation with advanced female age. There is mounting evidence that the increased risk of miscarriage in older women, including women undergoing ART, is a result of chromosomal aneuploidy as a consequence of oocyte aneuploidy.

The management of pregnancy after ART was discussed by S. Sunkara. She suggested that success in ART should be defined as achieving a healthy live birth at term. However the advent of ART has brought complications in pregnancy due to a multiplicity of factors. ART carries the risk of late onset ovarian hyperstimulation syndrome (OHSS) in early pregnancy. It has been a matter of debate whether there is an increased incidence of early pregnancy complications such as early/late miscarriages and ectopic pregnancy following ART.

In recent years the combination of transvaginal sonography with advanced Doppler techniques (color/power) and three-dimensional (3D-US) approaches has made transvaginal ultrasound an indispensable tool in the diagnosis of gynecological diseases. The introduction into clinical practice of the modern high-frequency endovaginal probe has allowed gynecologists to achieve a high diagnostic accuracy in the study of ovarian cysts, both dysfunctional and physiological. The differential diagnosis between functional and organic ovarian cysts is crucial in choosing the most appropriate treatment. The dysfunctional ovarian cysts are caused by hormonal imbalances in the ovulatory cycle, probably as a result of an exaggerated ovarian response to hormones. They are benign, transitional and in any case susceptible to medical therapy. They are typical of reproductive age and they can be divided into follicular, luteal and hemorrhagic cysts. The polycystic ovarian syndrome (PCOS) is a common cause of anovulation and infertility, clinically manifested by hirsutism and acne. Ultrasound has a very important role in the diagnosis of this condition as this technique can identify the typical ovarian features representing one of the three criteria used to make the diagnosis.
This educational course was developed in collaboration with ALPHA: scientists in reproductive medicine. It focused on the impact of new laboratory technologies on success rates in IVF and delivered with three sessions and a final debate on “who is the most important in the IVF scenario between clinician and embryologist”. This challenging topic allowed active participation by the audience with the winner the embryologist. However it was recognised that the success of an IVF programme depends on the synergistic action of different professional figures, and on the high level of staff motivation.

**SESSION I**  
**New technologies in reproductive medicine**

In the first lecture, E. Borges (Brazil) highlighted the role of real-time high magnification observation of spermatozoa, called “motile sperm organelle morphology examination” MSOME. This system permits the identification of vacuoles in the sperm nucleus, whose role in sperm function is not completely clear. Furthermore, the incorporation of MSOME in ICSI procedures has allowed the introduction of IMSI (intracytoplasmic morphologically selected sperm injection). A positive correlation between IMSI and high quality embryos, implantation, pregnancy and live birth rates was observed mainly in cases of previous implantation failures, high sperm DNA fragmentation rates, male factor, advanced maternal age and unexplained infertility.

M. Bungum (Sweden) spoke about the controversial relationship between the sperm DNA fragmentation and miscarriages. Indeed, although male partners of couples experiencing recurrent pregnancy loss have increased sperm DNA fragmentation rates compared to controls, the evidence for a direct association is contradictory. Probably, it depends on the different methodologies used for detecting sperm DNA fragmentation and on the different aspects of DNA damage measured (single stranded or double stranded DNA breaks). New large-scale studies differentiating between the different types of DNA damage are needed, to improve counseling for patients with infertility and recurrent pregnancy loss.

J. Van Blerkom (USA) evaluated the mitochondrial activity during oocyte and embryo development. Mitochondria in the cell do not produce only ATP but have different pleiotropic and regulatory functions (such as macromolecular modifications, steroidogenesis, intracellular signaling and signal transduction). For blastocysts, the mitochondrial development is accompanied by increased capacity to generate ATP. Furthermore, it has been described that disproportionate segregation of mitochondria between blastomeres during early cleavage stages and abnormal regulation of free calcium homeostasis can determine reproductive failure. This could represent an important but unrecognized factor impacting on IVF success.

H. J. Leese (UK) highlighted the nutritional requirements for oocytes and pre-implantation embryos, demonstrating that the early stages of embryo development are quiescent in terms of nutrient and oxygen consumption. The blastocyst, instead, is characterized by a sharp increase in metabolic activity, in protein synthesis and Na+K+ ATPase activity, due to the high energy request for blastocoel formation. Interestingly, the turnover of amino acids has been correlated to embryo viability, showing that viable embryos have an amino acids depletion and appearance...
within a lower range than the arrested ones. The addition of creatine to embryo culture media may improve cytokinesis, a crucial process for embryo-cleavage but further research is needed to assess this topic.

N. Macklon (UK) spoke about the role of endometrial receptivity evaluated by a new approach called secretomics. This procedure, through the aspiration of endometrial fluids, may be performed immediately prior to embryo transfer in IVF cycles, with no detrimental effect on the implantation and pregnancy rates as already demonstrated. Some preliminary reports identify an “endometrial fingerprint”, constituted by pro-inflammatory and anti-inflammatory cytokines, chemokines, growth factors and signaling factors. Interesting in-vitro studies showed that the endometrial cell migration is directly related to the embryo viability, being more pronounced in good quality embryos and reduced in poor quality embryos. This selective capacity of the endometrium is absent in patients with recurrent miscarriages, opening new research possibilities on this topic. The endometrium seems to play an active role in implantation process.

SESSION II
From subjective to objective criteria in embryo selection: where are we?

P. Zsolt Nagy (USA) discussed the new technologies developed for assessing embryo viability in ART laboratories. The crucial objective of ART treatments is to provide the highest chance of pregnancy but, at the same time, to reduce the risks of multiple pregnancies. These aims can be achieved with the transfer of a single embryo with the highest implantation potential. Nevertheless, the identification of objective criteria for embryo viability assessment is certainly difficult. Different invasive and non-invasive procedures may have an important role for this objective. Concerning the invasive methods, the blastocyst-stage biopsy with array-CGH seems to be very promising but randomized controlled trials need to demonstrate its efficacy. Among the non-invasive methods, the “-omics” technologies (including the microarray analysis of the cumulus cells which surround the oocyte, metabolomics and proteomics) and the time-lapse technology may provide additional information for assessing embryo viability and improving the success rates in IVF.

The topic of Pre-implantation Genetic Screening (PGS) was discussed by D. Wells (UK). The rationale for proposing this procedure during an IVF cycle depends on the fact that oocytes and embryos are frequently chromosomally abnormal, with a direct correlation with the age of the woman (70% of blastocyst aneuploidies in women aged 40-42). Furthermore, the chromosome abnormalities have little effects on embryo morphology. Nevertheless, the clinical use of PGS has been controversial. New, more efficient technologies for comprehensive chromosomal analysis have been introduced in the last few years. Different randomized studies demonstrated that second-generation PGS improves pregnancy rates and reduces miscarriage rates. These results will certainly open new possibilities for a wider clinical application of PGS in IVF cycles.

K. Turner (UK) spoke about the Quality Management System which should be adopted by all IVF laboratories, following the 2006 European Tissue Directive. The Quality Management System (QMS) consists of quality assurance, risk management and quality improvement and describes a program for evaluating the quality of care using a variety of methodologies and techniques. Regarding IVF, QMS involves every clinical process in terms of best practice (medications, risk factors, technical procedures, team communication, educational staff assessment). It is crucial to control and measure the processes involving gametes and embryos within the laboratory, with audit if appropriate. In this way, the areas considered critical may be checked appropriately and eventually amended.

SESSION III
Success in IVF: debate on who is the most important?

In the final session, there was a debate on who is the most important between the clinician and the embryologist. L. Rienzi (Italy) spoke about the crucial role of the embryologist in determining the success rates in the IVF scenario, showing that all the most important changes in clinical activities in IVF during the last few years derived from embryology. She concluded that clinicians must recognize the importance of high-laboratory standards with highly qualified personnel and appropriate investment.

The counter view was taken by G. Grudzinskas (UK), who emphasized the role of the clinician in motivating staff, in having a general view of the problems, including legal ones and in leading the group in an organised way. He said that continued technical improvements in the lab are absolutely necessary for providing the best success rates for patients but are not sufficient without a clear vision of the overall complexity of the clinical problems.

The debate was won by the embryologist but all the participants realized that the success of an IVF programme depends on the synergistic action of clinicians and embryologists accompanied by a high level of staff motivation. In a definitive way, the most important actor in IVF scenario is the patient with her individual needs and hopes.
SESSION I
Controlled ovarian stimulation: a tailored approach

G. Kovacs (Australia) explained that during 30 years of ART the technique of IVF has changed and so has the definition of success in ART. He described the factors affecting success in the IVF cycle beginning with the patient preparation. The most important tools for individualization include measurement of biochemical-AMH, thyroid screening and ultrasound of the pelvis, with AFC (antral follicle count), and detection of fibroids, polyps, sinexia. It is important to identify cases that need laparoscopy or hysteroscopy, if pathology is suspected. Laparoscopy is requested if hydrosalpinges, endometrioma, or dermoids are present. He explained how stimulation regimens are based on these previously evaluated biomarkers and that the selection of appropriate COH protocol may be one of the most important steps to achieve success.

E. Papanikolaou (Greece) described the sources and effects of increase in P (progesterone) level, including the mechanisms and potential strategies to prevent its elevation during ovarian stimulation. The origin of production of P in the early follicular phase is adrenal, with a shift toward the ovaries prior to ovulation. Several factors contribute to the etiology of P level increase including the number of multiple follicles, the gonadotropins and poor ovarian response. Nowadays, the influence of the preovulatory P rise on IVF outcome remains controversial. Several authors have failed to demonstrate any negative impact, while others have reported a detrimental effect associated with the rise of P. To prevent a rise in P level it might be preferable to use an earlier trigger of ovulation, cryopreservation of all embryos and transfer in the natural cycle. He showed data from 26 different expression genes in the endometrium; the results from microarray analysis suggest a different capability of endometrial receptivity in the implantation window in patients with progesterone levels higher than normal patients. This may be one of the reasons for the lower pregnancy rate in elevated P patients in the day of HCG administration.

At the end of this session the participants used case studies to analyse these different therapeutic approaches.

SESSION II
Technologies and laboratory

M. Meseguer (Spain) in his lecture on embryo selection and laboratory techniques explained that single embryo replacement using a healthy embryo with the highest chance of implantation which results in a single healthy baby at term is the ultimate goal of ART treatment. This implies the ability to screen the embryos in the lab in order to ascertain which embryo has the highest chance of implantation. PGS has so far been employed for this purpose but, in the future, non-invasive methods of embryo screening could be preferred including time-lapse, oxygen consumption, proteomics or metabolomics with the ultimate goal of identifying a high-quality embryo. A tool has been developed and evaluated for the selection of viable embryos based on the exact timing of embryo development events together with morphological patterns by using an automatic time-lapse system to monitor embryo development.

G. Huszar (USA) explained how to select the best sperm. In the first approach, in his laboratory the sperm creatine kinase content is assessed, which reflects incomplete sperm cytoplasmic extrusion and surplus cytoplasm. His experiments provided three insights: (i) sperm that failed cytoplasmic extrusion show reduced...
binding in the zona pellucida, and incomplete cytoplasmic extrusion affects chromatid development, DNA integrity, and frequency of chromosomal aneuploidies; (ii) sperm-oocyte interaction is regulated primarily by the attributes of the spermatozoon; and (iii) there is a sperm plasma membrane remodeling in terminal spermiogenesis. This remodeling facilitates the formation of the zona pellucida and hyaluronic acid binding sites. Sperm-hyaluronic acid binding is the first objective assay in the andrology laboratory which provides an objective assessment that sperm in an ejaculate are able to bind to the zona pellucida. Another sperm biomarker is the chaperone protein HspA2, which is part of the synaptonemal complex, and also a key element of intracellular transport of DNA repair enzymes in the developing spermatozoa.

S. Muné (USA) described the advanced research into preimplantation genetic diagnosis (PGD). He explained how chromosome analysis of human embryos has evolved considerably in the last few years, from using fluorescence in situ hybridization (FISH) with 5-12 probes and mostly performing polar body or day-3 biopsy PGSv1 (preimplantation genetic screening) to analysing all chromosomes with arrays from blastocyst biopsies (PGS v2). With the advent of the PGS technique the error rate in diagnoses has been reduced from 7-50% to 3% depending on the laboratory. Pregnancy outcomes have significantly improved. Data support that using PGSv2 there are no differences in chromosome aneuploidy rates, irrespective of the cohort size produced. Aneuploidy increases with maternal age and does not decrease with cohort size.

**SESSION III**

**New milestones in ART**

C. Simon [Spain] discussed the topic of the endometrium and implantation. The endometrium is a hormonally regulated organ that is non-adhesive to embryos throughout most of the menstrual cycle in humans. Endometrial receptivity refers to a hormone-limited period in which the endometrial tissue acquires a functional and transient ovarian steroid-dependent status allowing blastocyst adhesion. Functional genomics studies of human endometrium in natural cycles have demonstrated that endometrial receptivity is an active process involving up- and down-regulation of hundreds of genes. He explained that, although personalized medicine is a well-accepted concept in reproductive medicine, the endometrial factor is still neglected. He showed data from his laboratory on ERA (endometrial receptivity array), a customized array of 238 genes coupled to a computational predictor capable of diagnosing a functionally receptive endometrium regardless of its histological appearance. The accuracy of the diagnostic tool ERA has been demonstrated to be superior to endometrial histology and results are completely reproducible 29 to 40 months later. The presentation focused on demonstrating the diagnostic and therapeutic efficiency of the ERA in patients with implantation failure (IF), through personalization of the day of embryo transfer (pET).

The role of vitrification and its application was discussed by Z. P. Nagy (USA). Cryopreservation of reproductive tissue and cells are essential components of assisted reproduction treatment. Historically, the slow-freezing procedure was used to cryopreserve ovarian tissue, oocyte and embryo. However, the efficiency of slow-freezing is low, especially for the cryopreservation of oocytes. Recently, vitrification has been introduced as an alternative technique that provides greatly improved success rates. Vitrification requires the use of higher concentrations of permeating and non-permeating cryoprotectants, as well as a very high speed of cooling – close to 20,000 Celsius per minute (in sharp contrast to the 0.3 Celsius per minute cooling rate for slow-freezing). As a consequence of the improved survival rates following vitrification, new options for patient treatment have emerged. Fertility preservation for both medical and social reasons is now possible by applying vitrification to eggs (or in some cases vitrification of the ovarian tissue). Vitrification today is also replacing slow-freezing inspection (examination for individuals) and confirmed by issuing a license; failure to comply with regulation results in penalties. Licensing is the process whereby an organization (or individual) is identified as being compliant with required regulations. Certification is the process whereby an organization (or individual) is identified as meeting one or more selected “standards”. Accreditation is a collegial process based on self- and peer-assessment, whereby an authoritative body (usually a non-government organization) gives formal recognition that an organization is in voluntary compliance with one or more standards set by the authoritative body.

C. Simon [Spain] discussed the topic of the endometrium and implantation. The endometrium is a hormonally regulated organ that is non-adhesive to embryos throughout most of the menstrual cycle in humans. Endometrial receptivity refers to a hormone-limited period in which the endometrial tissue acquires a functional and transient ovarian steroid-dependent status allowing blastocyst adhesion. Functional genomics studies of human endometrium in natural cycles have demonstrated that endometrial receptivity is an active process involving up- and down-regulation of hundreds of genes. He explained that, although personalized medicine is a well-accepted concept in reproductive medicine, the endometrial factor is still neglected. He showed data from his laboratory on ERA (endometrial receptivity array), a customized array of 238 genes coupled to a computational predictor capable of diagnosing a functionally receptive endometrium regardless of its histological appearance. The accuracy of the diagnostic tool ERA has been demonstrated to be superior to endometrial histology and results are completely reproducible 29 to 40 months later. The presentation focused on demonstrating the diagnostic and therapeutic efficiency of the ERA in patients with implantation failure (IF), through personalization of the day of embryo transfer (pET).

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Online activities

Predictors of IVF outcome
Faculty: C. Alviggi (Italy)

The pediatrician’s point of view: baby born after ART, complications and future
Faculty: M. Bonduelle (Belgium)

Producing more oocytes decreases genetic quality?
Faculty: F. Fiorentino (Italy)

Definition of successful treatments in ART
Faculty: G. Kovacs (Australia)

Producing more oocytes does not decrease genetic quality
Faculty: S. Munne (USA)

Sperm evaluation using mRNA microarray technology: future perspectives
Faculty: N. Garrido Puchalt (Spain)

Technologies needed to maximise success: the future ART laboratory
Faculty: L. Rienzi (Italy)

The uterine environment and endometrial receptivity: new frontiers of ART
Faculty: C. Simón (Spain)

Can different ovarian stimulation protocols affect oocyte and embryo morphology and quality?
Faculty: A. Sunde (Norway)

Management of complications: new strategy to avoid OHSS
Faculty: J.A. García Velasco, Spain

The patient’s point of view: a take-home baby
One patient’s personal experience of the IVF process
Faculty: K. Veness (UK)

Visit the reproductive medicine section of the new Serono Symposia International Foundation (SSIF) website.
www.reproductive-medicine.seronosymposia.org

Register to access free e-learning activities and receive updates on new events and resources.

Take a look at the SSIF reproductive medicine website

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Live educational events

E-learning programmes:
- Video interviews
- Online video lectures
- Online courses
- Video presentations
**IVF Preceptorship Istanbul**

12-13 September 2013 - Istanbul, Turkey  
Scientific organizer: R. Fischer (Germany)

This important conference looking at one of the most important causes of female infertility is being held by Serono Symposia International Foundation (SSIF). POR (poor ovarian response) occurs for several key reasons, including advanced maternal age, a previous POR or an abnormal ovarian reserve test. SSIF is collaborating with the American Hastanesi Hospital in Istanbul to provide new insights into a disease which produces symptoms in 5-10% of women of reproductive age.

In collaboration with the American Hospital Istanbul.

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**The top ten in reproductive medicine: Debating break-through basic and clinical papers with their authors**

20-21 September 2013 - Florence, Italy  
Scientific organizer: C. Simon (Spain)

This programme will focus on the presentation, discussion and follow-up of the top ten most important clinical and basic contributions in reproductive medicine during the last two years. The concept is to create a high quality meeting that will serve the key opinion leaders of the clinical and scientific community in reproductive medicine.

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**7th IVF Preceptorship: current practice in the 21st century**

26-27 September 2013 - Madrid and Valencia, Spain  
Scientific organizers: E. Bosch (Spain), J.A. García Velasco (Spain), A. Requena (Spain)

The two-day programme, focusing on infertility treatments and on new laboratory techniques, will be delivered using an innovative mix of traditional lectures, interactive working groups managed by young speakers and case studies submitted by participants.

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**International school of ultrasound in obstetrics and gynecology**  
In partnership with the University of Siena

28-29 September 2013 - Siena, Italy  
Scientific organizer: F.M. Severi (Italy)

Each course (lectures and practical sessions) is designed to improve the practical skills and interpretation of the operators who perform ultrasound for diagnostic purposes in the field of obstetrics and gynecology, by using latest generation ultrasound equipment. At the end of each course, trainees will be able to perform advanced ultrasound examinations, will be well oriented in the choice of the correct ultrasound approach to use in different clinical situations and will be able to correctly understand all the different sonographic features that they will have to face in the clinical practice.

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**IVF Preceptorship Madrid**

November 2013 - Madrid, Spain  
Scientific organizer: R. Fischer (Germany)  
Scientific co-organizers: J.A. Zafra (Spain), R.N. Calonge (Spain)

This live educational course offers an overview on ovarian stimulation and on new laboratory technologies for in vitro fertilization cycles. This meeting is dedicated to providing new insights on these topics, with an interactive programme where each lecture is followed by specific cases studies or working groups. The aim is to provide learners with both up-to-date knowledge and the possibility to share their experiences with each other and with the speakers.

In collaboration with the Tambre Clinic.
Welcome to the Serono Symposia International Foundation website!

IMPROVING THE PATIENT’S LIFE THROUGH MEDICAL EDUCATION

Welcome to the new SSIF website

Completely redesigned and much more functional, the new SSIF website can become your primary source of medical education.

Visit the RM section of the SSIF website www.reproductive-medicine.seronosymposia.org

Register for even more benefits:
- free e-learning activities
- a comprehensive library of abstracts, books, and slide presentations from leading academics in their fields
- follow up activities, extending SSIF teaching courses
- special interest groups to join – building on friendships made and knowledge gained at live events
- all that is new in accredited continuing medical education

... and if you cannot attend a live event use the SSIF website for video lectures and podcasts straight from the conference floor.

At Serono Symposia International Foundation we have a reputation for being at the forefront of continuing medical education. Our website is at the heart of all we do – promoting and supporting our live events and providing a gateway to online learning.

Our vision is to enable you to deliver better care and better outcomes for your patients. The SSIF website will help you to make that a reality.

Want to know more?

At SSIF we are always keen to talk to health professionals about the continuing medical education we provide. You can email us at info@seronosymposia.org

Improving the patient’s life through medical education

www.seronosymposia.org

Editors: Michèle Piraux, Michael Withers, Chloé Xiinas
Contributors: Angelo Marino, Irene Zerbetto

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