<table>
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<th>Madrid</th>
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**9th IVF Preceptorship:**
current practice in the 21st century

24-25 September 2015 - Madrid and Alicante, Spain
General information

Venue
This live educational course takes place at the:

- **IVI-MADRID**
  - Avenida del Talgo 68
  - Aravaca - Madrid, Spain

- **IVI-ALICANTE**
  - Avenida Denia, 111
  - 3015 Alicante, Spain

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

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Aims
For the 9th edition, this twin site live educational course will focus on the role of LH in controlled ovarian stimulation, recurrent implantation failure, SET (single embryo transfer) and new laboratory techniques and equipment for optimising IVF procedures. The programme will facilitate discussion about diverse experiences and address controversial issues as well as hot scientific and clinical topics to be discussed during interactive sessions. Each lecture is followed by case studies in working groups which will provide participants with up-to-date knowledge and an opportunity to share their experiences with peers and speakers. During the working groups, participants will propose specific take-home messages for each topic which will be compared and discussed during the plenary. A video session will enrich the proceedings by bringing the Madrid and Alicante participants together in discussion.

Learning objectives
By attending this live educational course participants will be able to:
• Identify current evidence-based recommendations to achieve optimal management of LH supplementation in stimulation protocols
• Learn the best embryo selection technique
• Understand the importance of luteal phase support and treatment possibilities
• Explore current tools in male infertility diagnosis and management
• Manage recurrent implantation failure

Target audience
This live educational course is designed for a small group of young clinicians, physicians and embryologists working in assisted reproductive medicine who want to acquire up-to-date information to improve their current clinical practice.

Format
This twin site event will run simultaneously at the two IVI Clinics of Madrid and Alicante. Participants will enjoy presentations from faculty members in person and via satellite link from the other centre. The faculty, composed mainly of local experts from both IVI Clinics - as well as some international experts - will be divided among the two venues. Advantages of a twin site event are the opportunity for exchange and debate with a larger group of young clinicians while also channeling expertise from two world-class IVI Clinics.
EXCEMED (www.excemed.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The CME course “9th IVF Preceptorship: current practice in the 21st century” held on 24-25 September 2015 in Madrid and Alicante, Spain, is designated for a maximum of 8 (eight) 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)
Scientific organisers

**Juan Antonio García-Velasco**
IVI Madrid
Rey Juan Carlos University
Madrid, Spain

**Manuel Muñoz Cantero**
IVI Alicante
Alicante, Spain

EXCEMED developed this programme in collaboration with the IVI Madrid and IVI Alicante clinics.
## Faculty members

### Live from Madrid IVI Clinic

- **Robert Fischer**  
  Fertility Centre Hamburg  
  Hamburg, Germany

- **Juan Antonio García-Velasco**  
  IVI Madrid  
  Rey Juan Carlos University  
  Madrid, Spain

- **Alberto Pacheco Castro**  
  IVI Madrid  
  Madrid, Spain

- **Tammie Roy**  
  Genea Biomedx  
  Sydney, Australia

- **Carmen Rubio**  
  IGENOMIX and  
  Valencian Infertility Institute Foundation (FIVI)/INCLIVA  
  Valencia, Spain

- **Hakan Yarali**  
  Anatolia IVF and Women’s Health Center  
  Department of Obstetrics and Gynecology  
  Hacettepe University, School of Medicine  
  Ankara, Turkey

### Live from Alicante IVI Clinic

- **Ernesto Bosch**  
  Human Reproduction Unit  
  Valencian Infertility Institute (IVI)  
  Valencia, Spain

- **María José De los Santos**  
  Valencian Infertility Institute (IVI)  
  Valencia, Spain

- **Mireia Florensa**  
  IVI Barcelona  
  Barcelona, Spain

- **Marcos Meseguer**  
  Valencian Infertility Institute (IVI)  
  Valencia, Spain

- **Manuel Muñoz Cantero**  
  IVI Alicante  
  Alicante, Spain

- **Felipe Vilella**  
  Valencian Infertility Institute Foundation (FIVI)  
  University Institute IVI/INCLIVA  
  Valencia University  
  Valencia, Spain
Scientific programme
Thursday, 24 September 2015

08.45 EXCEMED Opening
■ R. Fischer [Germany]

08.50 Welcome and introduction
■ J.A. García-Velasco [Spain] and
▲ M. Muñoz Cantero [Spain]

08.50 Welcome and introduction
■ J.A. García-Velasco [Spain] and
▲ M. Muñoz Cantero [Spain]

Chair: M. Muñoz Cantero [Spain]

09.00 L1: PCOS vs poor responders: the extremes of ovarian response
■ H. Yarali [Turkey]

09.20 L2: LH supplementation during controlled ovarian stimulation (COS): yes, no and for who?
▲ E. Bosch [Spain]

09.40 Question time

10.00 WG1: Case studies on L1 - L2
■ H. Yarali [Turkey]
▲ E. Bosch [Spain]

10.40 Coffee break

11.10 L3: Individualized controlled ovarian stimulation (iCOS): tools for matching patients and protocols
■ H. Yarali [Turkey]

11.30 L4: Oocyte quality: when should egg donation be applied?
▲ M. Florensa [Spain]

11.50 L5: Criteria for identifying the best sperm
■ A. Pacheco Castro [Spain]

12.10 Question time

12.30 WG2: Case studies on L3 - L4
■ H. Yarali [Turkey]
▲ M. Florensa [Spain]

13.10 Lunch

Controlled ovarian stimulation

Session I

Session II

Recurrent implantation failure and endometrial receptivity

Chairs: R. Fischer [Germany] and J.A. García-Velasco [Spain]

Chair: M. Muñoz Cantero [Spain]

14.10 L6: Why don’t all embryos implant?
Human endometrial receptivity bottleneck
▲ F. Vilella [Spain]

14.30 L7: The role of endometrium receptivity and the different possibilities of luteal phase support
■ J.A. García-Velasco [Spain]

14.50 Question time

15.10 WG3: Case studies on L6 - L7
■ F. Vilella [Spain]
▲ J.A. García-Velasco [Spain]

15.50 Visit at the IVI premises

16.50 End of the first day

Legend
■: Live from Madrid IVI Clinic; ▲: Live from Alicante IVI Clinic; L: Lecture; ✎: Question time; WG: Working Group; VS: Video session;
### Session III: Embryo selection strategy

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<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Chair</th>
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<tbody>
<tr>
<td>09.00</td>
<td>L8:</td>
<td>Time-lapse technology improves clinical outcomes</td>
<td>M. Meseguer (Spain)</td>
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<tr>
<td>09.20</td>
<td>L9:</td>
<td>Preimplantation genetic screening improves clinical outcomes</td>
<td>C. Rubio (Spain)</td>
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<tr>
<td>9.40</td>
<td></td>
<td>Question time</td>
<td></td>
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<tr>
<td>10.00</td>
<td>VS:</td>
<td>Video session on L8 - L9</td>
<td>M. Meseguer (Spain)</td>
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<tr>
<td>10.40</td>
<td></td>
<td>Coffee break</td>
<td>C. Rubio (Spain)</td>
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### Session IV: From the lab: embryo transfer and cryopreservation

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<th>Time</th>
<th>Session</th>
<th>Title</th>
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<tbody>
<tr>
<td>11.10</td>
<td>L10:</td>
<td>Role of the laboratory on clinical success</td>
<td>M.J. De los Santos (Spain)</td>
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<tr>
<td>11.30</td>
<td>L11:</td>
<td>Importance of cryopreservation in Assisted Reproductive Technology</td>
<td>T. Roy (Australia)</td>
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<tr>
<td>11.50</td>
<td>L12:</td>
<td>When should the “freeze-all” strategy be applied instead of fresh embryo transfer?</td>
<td>J.A. García-Velasco (Spain)</td>
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<tr>
<td>12.10</td>
<td>L13:</td>
<td>How to mother communicates with the preimplantation embryo and modifies its transcriptome. Good news for the ovum donation programme</td>
<td>F. Viella (Spain)</td>
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<tr>
<td>12.30</td>
<td></td>
<td>Question time</td>
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<tr>
<td>12.50</td>
<td>WG4:</td>
<td>Case studies on L10 - L11</td>
<td>M.J. De los Santos (Spain)</td>
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<td></td>
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<td>T. Roy (Australia)</td>
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<tr>
<td>13.30</td>
<td></td>
<td>Lunch</td>
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<tr>
<td>14.30</td>
<td></td>
<td>Visit of the IVI premises</td>
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<tr>
<td>15.30</td>
<td></td>
<td>End of the live educational course</td>
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Disclosure of faculty relationships

EXCEMED adheres to guidelines of the European Accreditation Council for Continuing Medical Education (EACCME®) and all other professional organizations, as applicable, which state that programmes awarding continuing education credits must be balanced, independent, objective, and scientifically rigorous. Investigative and other uses for pharmaceutical agents, medical devices, and other products (other than those uses indicated in approved product labeling/package insert for the product) may be presented in the programme (which may reflect clinical experience, the professional literature or other clinical sources known to the presenter). We ask all presenters to provide participants with information about relationships with pharmaceutical or medical equipment companies that may have relevance to their lectures. This policy is not intended to exclude faculty who have relationships with such companies; it is only intended to inform participants of any potential conflicts so that participants may form their own judgements, based on full disclosure of the facts. Further, all opinions and recommendations presented during the programme and all programme-related materials neither imply an endorsement nor a recommendation on the part of EXCEMED. All presentations represent solely the independent views of the presenters/authors.

The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

**Ernesto Bosch**
Declared no potential conflict of interest.

**Maria José De los Santos**
Declared receipt of honoraria or consultation fees from Ovascience.

**Robert Fischer**
Declared no potential conflict of interest.

**Mireia Florensa**
Declared no potential conflict of interest.

**Juan Antonio García-Velasco**
Declared receipt of grants and contracts from MSD, Merck Serono, Ferring.

**Marcos Meseguer**
Declared no potential conflict of interest.

**Manuel Muñoz Cantero**
Declared no potential conflict of interest.

**Alberto Pacheco Castro**
Declared no potential conflict of interest.

**Tammie Roy**
Declared to be stakeholder in Genea Biomedx.

**Carmen Rubio**
Declared no potential conflict of interest.

**Felipe Vilella**
Declared no potential conflict of interest.

**Hakan Yarali**
Declared receipt of honoraria or consultation fee from Merck Serono.
Biographies
Ernesto Bosch was born in Philadelphia, USA, in 1968. He completed Medicine School at the University of Valencia in 1992 and from 1993 to 1997, worked as a Specialist in Obstetrics and Gynaecology at Hospital La Fe, Valencia. Dr. Bosh trained in Human Reproduction at the Hospital of the University of Pennsylvania in 1997; and in 1999, he completed his doctoral thesis on the influence of LH in oocyte quality, with “cum laude” qualification, at the University of Valencia. In January 2000, he joined the team at the Human Reproduction Unit of the Instituto Valenciano de Infertilidad in Valencia; and in 2008 he obtained the title of Master in Research on Health Sciences, by the Autonomous University if Barcelona. Dr. Bosch has published 44 papers in PubMed indexed journals and written more than 50 book chapters in the field of IVF; has given over 150 lectures at international meetings around the world; He belongs to the Editorial Board of Fertility & Sterility, and Reproductive Biomedicine Online and is a regular reviewer for Human Reproduction, and Reproductive Biology and Endocrinology among others. He belongs to the Special Interest Group on Reproductive Endocrinology of the Spanish Fertility Society, and has received the Scientific Program Prize Paper Award at the 2008 Annual Meeting of the American Society for Reproductive Medicine. In May 2010, Dr. Bosch was appointed Medical Director of the Human Reproduction Unit of the Instituto Valenciano de Infertilidad in Valencia.

Maria J. De los Santos started her career in 1991 in the IVF laboratory of IVI Valencia. She received her PhD in Biology from University of Valencia in 1996, and from 1996-1999 she carried out her postdoctoral fellowship in Reproductive Immunology at Fearing Research Laboratory at Harvard Medical School. She also worked as embryologist at the Brigham and Women’s Hospital. Belong to the editorial board of two recently created scientific journals (MEDRES and Fertility Research and Practice). She is author of more than 50 scientific publications on peer-reviewed journals and of several book chapters. She has addressed her research in clinical embryology and reproductive biology.
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, he pioneered in 1983 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 lectures 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”.

Mireia Florensa
IVI Barcelona
Barcelona, Spain

Mireia Florensa, after achieving the Biology degree by the Universitat de Barcelona, has completed her training in embryology during the Masters in Assisted Reproduction held by Institut Universitari Dexeus also in Barcelona. Dr. Florensa first started working as junior embryologist at the IVF Laboratory of the Fertility Clinic of the Erasme Hospital in Brussels and then entered the IVF lab staff at IVI Valencia in 2002. She has been member of the IVF lab of IVI Barcelona since its opening in 2004 first as senior embryologist, then as lab manager and, since 2013, as lab Director. Her main field of interest has always been Preimplantation and Prenatal Diagnosis thus she has been in charge of the PGD program and the Prenatal Committee of IVI Barcelona since their foundation. Following this predilection she also completed a Master’s Degree on Prenatal Genetics and Fetal Medicine at University College of London in 2010.
Juan Antonio García-Velasco is Director of IVI Madrid as well as Director of the Masters Degree in Human Reproduction, Director of the Postgraduate course in Nursing in Human Reproduction, and Associate Professor of Obstetrics and Gynecology, Rey Juan Carlos University in Madrid. He is the author of more than 100 scientific articles as well as 22 book chapters and abstracts on human reproduction, especially on endometriosis and both hyper- and hypo- ovarian stimulation response. He has been a Principal Investigator for the Spanish Ministries of Health and Education. Dr Velasco has served on the editorial board of Fertility and Sterility and has been a member of ESHRE’s Advisory Committee.

Marcos Meseguer was born in November 1974, received his Biological Sciences Degree in 1997 from the University of Valencia in Spain. He performed a pre-doctoral fellowship in St Mary’s Hospital, Manchester University, United Kingdom. He received his Ph.D. Degree in Obstetrics and Gynecology in 2002 from the University of Valencia, Spain, and the European Doctor Degree form the same university. He has also a master degree in Research Methods, Design and Statistics from Universidad Autónoma de Barcelona, Spain. Actually is Scientific Supervisor and Senior Embriologist in the IVF unit of IVI Valencia. He was Co-Director of the Andrology Laboratory at the Instituto Valenciano de Infertilidad (IVI) from 2000 to 2004. Dr. Meseguer is a member of various scientific societies and has received the prize paper of the Society of Reproduction and Infertility (American Society of Reproductive Medicine). The Robert Edwards Prize paper award from RBMO on line, three times the Lalor Foundation International Award from the American Society of Andrology, four times the reasearch award from the Spanish Society of Fertility and three times the Spanish Society of Clinical Embryologist. The primary areas of his research are embryology and male infertility. Specifically he is focused on time-lapse research and sperm selection methods being author of patents related with embryo quality assessment. As Principal Investigator, his work has been funded through 8 projects sponsored by the Spanish Government and the Valencian Government, including two EUREKA projects [granted to high quality technological projects] supported by the European Community. He has published over 120 articles and 5 reviews or book chapters, made more than 350 presentations at national and international congresses. He has been the Director of 7 Doctoral Thesis all qualified with “Cum Laude”, and actually is directing 10 doctoral thesis. He is also currently Statistic Advisor in IVI Valencia the biggest infertility clinic in Spain and one of the most important in Europe, and associate professor of the Master in Biotechnology from Valencia University.
Biographies

Manuel Muñoz Cantero
IVI Alicante
Alicante, Spain

Manuel Muñoz Cantero, MD, PhD, is Director of IVI Alicante. He is also Professor of the Master’s Degree Programme in Human Reproduction at Rey Juan Carlos University, Madrid, Spain. Doctor Muñoz graduated from University Medical School, Alicante, in 1992 and received his Obstetrics and Gynaecology certification from Virgen de la Arrixaca Hospital, Murcia, in 1997. He performed his formation in Human Reproduction in IVI Valencia and IVI Murcia as Fellowship. He completed his PhD in Medicine from Valencia University, in 2012. His main research interests have been in IVF and Egg Donation and Ovarian Stimulation Protocols for IVF. He is the Principal Investigator of projects funded by the Ministry of Education and Ministry of Health, Spain. He has published over 14 peer-reviewed articles as well as 25 book chapters on Human Reproduction.

Alberto Pacheco Castro
IVI Madrid
Madrid, Spain

Alberto Pacheco received his Biological Sciences Ph.D in 1997 from the Complutense University of Madrid in Spain. He also has a Master degree in Reproductive Medicine since 2005. Since 2002, he is the Director of the Andrology Laboratory and Sperm Bank at the Instituto Valenciano de Infertilidad (IVI) in Madrid. Dr. Pacheco is a member of several scientific societies. The primary areas of his research are the molecular markers of male infertility and sperm survival after freezing/thawing, sperm DNA fragmentation, sperm oxidative stress and apoptosis, and sperm banking. Dr. Pacheco is the recipient of several grants from public and private organizations in Spain. He is professor, among others, of two post graduate Master in Human Reproduction from both Spanish Fertility Society, and Rey Juan Carlos University in Madrid. Dr. Pacheco is Professor of Immunology at Alfonso X El Sabio of Madrid since 2000. The main area in this field is peripheral and uterine NK characterization in cases of recurrent miscarriages and implantation failure. He has published over 60 articles and 30 reviews or book chapters, made almost 100 presentations at national and international congresses.
Tammie Roy is the Chief Scientific Officer at Genea Biomedx. She holds a PhD in Reproductive Biology from the University of Newcastle Australia. Tammie Roy joined Genea (formerly Sydney IVF) in May 2005, as a clinical embryologist. In 2009 she moved into their research group and worked on projects including oocyte vitrification and somatic cell nuclear transfer. She joined Genea Biomedx and has been a member since its inception. She has been involved in the conception, development and marketing of the current Genea product portfolio. As part of the original team that was responsible for the conception of Gavi (the automated vitrification instrument) Dr. Roy has extensive clinical and research experience in cryopreservation of embryos and oocytes.

Carmen Rubio trained in science in the University of Valencia and specialized in embryology and cytogenetic studies in human reproduction, at IVI and the University of Barcelona. Becoming interested in chromosomal abnormalities in human embryos, she completed her PhD in 2004 in Valencia in the field of Reproductive Genetics. Post-doctoral research includes a stage at the laboratory of Drs. Patricia Hunt and Terry Hassold at the School of Molecular Biosciences (Washington State University, USA) focused in male and female meiosis and the mechanism underlying human aneuploidy. At present, she is the Head of the Preimplantation Genetic Diagnosis program for chromosomal disorders at IGENOMIX.
Felipe Vilella

Valencian Infertility Institute Foundation (FIVI)
University Institute IVI/INCLIVA
Valencia University, Valencia, Spain

Felipe Vilella researches’ focus on endometrial receptivity, identifying molecular signals during the window of implantation. He was graduated in Biological Sciences in 2002 and in Biochemistry in 2004 he obtain his Ph. D. in Molecular Biology qualified with “Cum Laude” in 2006, he perform his postdoctoral position in the prestigious Medical Research Council of London (MRC) during 4 years. He has been a major member in about 10 international scientific projects. At ISI Web of Knowledge is author of 22 publications in international peer-review journals. He has delivered 20 oral communications in the international meetings and won several scientific prize. He has directed 2 European PhD Thesis.

Hakan Yarali, MD is a professor at Hacettepe University, School of Medicine, Department of Obstetrics and Gynecology and is the Clinical Director of Anatolia IVF Center, Ankara, Turkey. Following medical school and residency training in OB/GYN at Hacettepe University, he did his clinical fellowship at University of British Columbia, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Vancouver, Canada during 1991-1992. Dr. Yaralı has published over 90 original articles, reviews, and book chapters, and delivered several presentations, lectures and conferences worldwide. Dr. Yaralı is a reviewer for many international journals including Human Reproduction, Fertility & Sterility, RBM Online. Dr. Yaralı has received several national and international awards including the most promising young scientist in Turkey in 1998 by the Turkish Scientific Technical and Research Council, which is the most prestigious research council in Turkey. He was the former president of Turkish Society of Reproductive Medicine (TSRM); he is currently a member of the Executive Committee of TSRM. He has organized several national and international meetings. He is directing one of the busiest IVF centers in Turkey, Anatolia IVF, performing over 1800 cycles annually.
The two major challenges with controlled ovarian stimulation (COS) in in-vitro fertilization (IVF) are the extremes of ovarian response, poor and excessive ovarian response. Bologna criteria for defining poor ovarian responder (POR), while being a step forward, may not be perfect since various subgroup of patients fulfilling Bologna criteria may not be homogenous and associated with different live birth rates following IVF. GnRH-agonist and GnRH-antagonist protocols are associated with similar pregnancy outcome in PORs; however, GnRH-antagonist protocol may reduce treatment burden. Mild/modified natural cycle IVF may be cost-effective, patient friendly and may have pregnancy outcome comparable to traditional COS. Increasing FSH dose does not overcome POR. There is insufficient/weak evidence for most of the available adjuvants to improve live birth rates in PORs. Oocyte/embryo accumulation with conventional/minimal stimulation with an interval of at least one cycle or immediately after oocyte retrieval (double stimulation) may improve pregnancy rates and decrease dropout rates in PORs. Pre-implantation genetic screening (PGS) with trophoectoderm biopsy is valuable to select viable blastocysts to pool in women with advanced maternal age (AMA) and POR; however, the role of such an approach to improve outcome in younger women with POR needs to be studied with RCTs. In-vitro activation (IVA) may be a promising approach in selected cases with POR; 2 successful pregnancies and 1 healthy delivery have already been reported with this approach. As a conclusion, the currently available data suggest that insufficient evidence exists to recommend most of the treatment plans proposed to improve pregnancy rates, with the POR remaining one of the most challenging tasks in reproductive medicine.

Hyper-response may be defined as harvesting more than 15 oocytes, and is characterized by high AMH (>4 ng/ml) and high AFC (>20-24). GnRH-antagonist is the protocol of choice in this patient sub-group since it is associated with:

a) less severe OHSS compared with the long agonist protocol even with rhCG administration;

b) similar pregnancy rates compared with the long GnRH-agonist protocol;

c) most importantly, it permits the use of GnRH-agonist to trigger final oocyte maturation.

Co-administration of metformin does not improve live birth rates; however, it is associated with significant reduction of OHSS. Cabergoline, in patients with unexpected hyper-response, may significantly decrease the development of moderate-severe OHSS.
According to the classic "Two cells-two gonadotrophins concept", FSH and LH act in a synergic fashion on the follicular cells, to ensure proper follicular development and oocyte maturation for a successful ovulation; LH induces androgen synthesis by the follicular theca cells, which will be then aromatized to estrogens in the granulosa cells through the action of LH. However, the actions of both gonadotrophins are not independent, and theca and granulosa cells are not two isolated compartments, but they are subjected to auto-regulation one from the other: Thus, FSH stimulates the production of Insulin Growth factors and Inhibin by the granulosas cells that stimulate the synthesis of androgens by the theca cells, setting this way an intra-ovarian positive feed back which is maintained until the end of the follicular phase. In the meanwhile, the estrogens produced in the granulosa cells amplify the action of FSH at the autocrin level. As a result, the whole system works as a perfectly organized orchestra.

In the ovarian stimulation for in vitro fertilization (IVF) context, the role of FSH and LH is also defined. As in the natural cycle, their action is not independent one from the other. The onset of recombinant preparations has allowed understanding better the actions of both gonadotrophins. Clinical trials show that when stimulation is carried with FSH alone preparations, a larger number of follicles is developed, and more oocytes are obtained. However, in this FSH alone scenario, the overall estradiol production is lower, whilst the follicular phase progesterone production is higher. On the other hand, when LH activity is supplemented in ovarian stimulation for IVF, the number of oocytes obtained is lower, but the number of mature oocytes may not be compromised, while the estradiol production is higher, and progesterone levels are lower. These differences may have an impact on cycle outcome, especially in older women or those with diminished ovarian reserve, where LH administration has shown to obtain better results.

In conclusion, FSH and LH have different but interrelated roles in follicular development. The knowledge of these actions will allow the clinician to select in an individualized manner the best combination for a particular patient, in order to achieve the only final goal: a health baby.
The central paradigm for individualized controlled ovarian stimulation (iCOS) is to maximize live birth rates (LBRs), minimize/avoid risks and complications and offer the most cost-effective approach. Large population based cohorts in the UK and the USA demonstrated that an oocyte yield of 10 – 15 oocytes in all age groups resulted in the most optimal LBR, whereas retrieval of >15 oocytes significantly increased ovarian hyperstimulation syndrome (OHSS) risk without improving LBRs in fresh autologous in-vitro fertilization (IVF) cycles. Currently, anti-mullerian hormone (AMH) and antral follicle count (AFC) are the most valid biomarkers to predict excessive and hypo-response (AUC ≈ 0.80), both in GnRH-agonist and GnRH-antagonist cycles. However, both biomarkers are only weak predictors of implantation and LBRs. IVF should not be withheld based on abnormal ovarian reserve tests; reasonable ongoing pregnancy rates have been reported even with extremely low AMH levels (<0.2 ng/ml) in regularly cycling <42 yr-old women.

Despite AMH’s rapid adoption by many assisted-conception clinical laboratories, individual clinicians have had their confidence shaken, owing to issues with sample handling, complement interference, non-standardized reporting, and lack of reproducibility. With the introduction of new two automated assays, many of these issues have been overcome; however, values generated by these two automated assays can be markedly different from those of the two ELISA (enzyme-linked immunosorbent assay) based AMH assays, and hence assay-specific interpretation is required.

Hyper-response is defined as retrieving >15 oocytes and is characterized by AMH >4ng/ml, AFC>20, polycystic ovary syndrome (PCOS) and a history of OHSS/excessive number of oocytes harvested. The protocol of choice is GnRH-antagonist with 50-150 IU/d starting dose of rFSH; GnRH-agonist triggering for final oocyte maturation may be employed in selected cases. Poor ovarian response (POR) is characterized by harvesting ≤3 oocytes, AMH<1 ng/ml and AFC<5. The majority of the available therapeutic options cannot substantially alter the prognosis in PORs. Categorization of patients as normal responders is frequently based on the exclusion of a poor or an excessive response to iCOS, rather than by using specific inclusion criteria. However, women with 4-15 oocytes are not a homogenous group, and those with 4-9 oocytes (sub-optimal responder) and 10-15 oocytes (normo-responder) have different LBRs. In sub-optimal responders, specific single nucleotide polymorphisms (SNPs) in the FSH receptor (FSHR) or the β-subunit gene of LH may contribute to altered response to COS contrary to their predicted response based on ovarian reserve markers. Over the last two decades, the vast majority of randomized controlled trials (RCTs) and meta-analyses published in normo-responders failed to demonstrate meaningful differences in terms of pregnancy rates in their primary analysis, either when comparing GnRH agonist versus antagonist regimens or different gonadotropins and dosing schemes. However, the sub-optimal response group could be one of the few domains in which strategies could be tested, such as higher gonadotropin dosing, rLH co-administration or prolonged stimulation, to enhance clinical outcomes.
Switching to egg donation has both biological and emotional implications for the patients. Thus, clinicians and embryologists must be well aware about what can realistically be achieved, as well as which are the best approaches in order to maximize the results of an egg donation program before recommending it to the patients.

To understand the role of the oocyte in an In vitro Fertilization (IVF) cycle, we will explore its characteristics and the factors that can affect its quality during intraovarian development. Ovarian stimulation, advanced maternal age, polycystic ovaries and endometriosis are some of them.

Once the oocyte is in the laboratory, embryo culture system and embryo selection criteria are on the basis of good results; thus, a quick reminder of the old and new strategies will be included. We will also discuss some procedures such as mitochondrial transfer and Preimplantation Genetic Diagnosis (PGD) to overcome respectively poor cytoplasmic and nuclear nature.

Nevertheless, egg donation has its rightful indications that will also be exposed and debated. To improve egg donation program results, there are basic points that must be carefully covered. The donors’ selection criteria must be very strict when trying to improve recipients’ pregnancy. This selection will depend not only on the physical and genetic characteristics of the donor [properly matched with the ones of the recipients] but also on the donors’ ovarian stimulation and oocyte quality. To achieve both correct matching and good pregnancy results the expertise of the donation program team, the clinicians and the IVF laboratory will be needed. Moreover, each European country has a specific legislation related to gamete donation. According to Spanish law, donation must be anonymous and non-compensated so the details of how to develop a successful donation program in such conditions will also be described.

There are some other factors that can turn the results from acceptable into splendid; the day the transfer is performed, the origin of the oocytes [fresh or frozen] and the number of oocytes donated per cycle are among the most relevant. So hopefully, all the aspects related to egg donation will be discussed in order to give clinicians, nurses and embryologists a clear path to an excellent egg donation program.
The quality of gametes is a key factor to achieve a pregnancy. In natural conception, spermatozoa are selected in the female reproductive tract by many different and very strict processes based most of them in different functional characteristics, as DNA integrity, their oxidative status, the ability to induce acrosome reaction, capacity of binding to the zona pellucida, etc. Due to these selection processes, only a few hundreds of competent and functional sperm cells are finally able to reach the oocyte.

On the contrary, in assisted reproduction, only two traditional sperm selection techniques, described over 30 years ago, are currently performed in most of the centers, which are only based on the motile capacity (swim-up) or the ability to cross a given density of a compound (density gradient centrifugation) of sperm cells.

Therefore, to increase the success in assisted reproduction, especially in cases of male factor, it is first important improving the seminal study by analyzing functional features that help us to ascertain the origin of these defects. So, the study of chromosomal abnormalities (FISH or array-CHGH), sperm DNA damage, the ability to bind to the zona pellucida, or presence of apoptotic sperm could help us to identify the source of the male factor.

Once identified the defect, would then be useful to use new sperm selection techniques able to eliminate or reduce specifically the non-functional cells that present that defect. In this sense, in recent years, new techniques of sperm selection based on some functional characteristics have been developed in order to improve sperm selection.

Some of these techniques are based on the selection of a sperm population with a specific functional characteristic. For example, in the magnetic activated cell sorting (MACS) technique, apoptotic spermatozoa, which could prevent or diminish embryonic development, are removed from the sperm sample. Other methods (electrophoretic method and Zeta-potential) are focused on the selection of sperm cells with very strong negative charge on their plasma membranes, which is correlated with an optimal sperm maturation status. Finally, in the PICSI technique, there is an isolation of a sperm cell population able to bind to hyaluronic acid, as physiologically occur in the zona pellucida, previous to the conventional ICSI.

In contrast, other techniques are focused on the selection of individual spermatozoa, which is then used in ICSI treatment. One of them is the IMSI method, which is based on examination of the motile sperm organelles morphology (MSOME) at high magnifications to improve sperm selection with morphologically normal nuclei. Other recent developed technique is the Raman spectroscopy, which is based on the differentiation and isolation of sperm cells without DNA damage.

Thus, all of these techniques, and some others under development, are based on the selection of sperm with improved functional characteristics. Although many published works have shown promising results, especially in cases where the male factor is the sole or main cause of infertility, further studies are necessary to ascertain its clinical utility.
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 genomic 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.

Personalized medicine is a well-accepted concept in reproductive medicine except for the endometrial factor that is still neglected. Our group has developed the endometrial receptivity array (ERA), 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 aim of this presentation is to demonstrate the diagnostic and therapeutic efficiency of the ERA in patients with implantation failure (IF), through personalization of the day of embryo transfer (pET). A multicenter prospective clinical study analyzing the results of ERA in 116 IF patients (5.7 previous failed cycles), either with their own oocytes (IVF) (n=69) or ovum donation (OD) (n=47). In non-receptive, ERA was repeated on the day indicated by the predictor, and pET was guided according to ERA results.

Endometrial biopsies were collected at LH+7, or in HRT after 5 days of P impregnation. RNA was extracted and hybridized according to ERA technology. Data were analysed by the predictor using the SVM+KNN algorithm for the matrix of 238 genes and results were given as receptive (R) or non-receptive (NR).

We propose for the first time the concept of pET in patients with IF guided by ERA as they have a displacement of the endometrial window of receptivity. This concept can be extended to patients in their first visit to the fertility clinic. Preliminary data suggest that around 15% of all patients can be NR. We are conducting a RCT comparing ERA personalized embryo transfer versus routine embryo transfer in patients undergoing assisted reproductive technologies (ART).

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The restricted time-related period when the uterus is receptive to blastocyst implantation is known as endometrial receptivity. The window of implantation temporally frames this period of receptivity, and it requires an exquisite synchrony between embryo and endometrium. The spatial and temporal changes that the endometrium undergoes these days are crucial for a successful pregnancy, as embryos only attach under optimal conditions. It seems that only estrogens and progesterone are required to induce endometrial receptivity, but no clear preference exists on ideal dose, route of administration or duration.

On top of this, in the current era of personalized medicine, and very specially in reproductive medicine where we carefully customized protocols for our patients based on different predictors (i.e. age, BMI, AMH) or the number of embryos to be transferred based on their quality or availability, endometrial status at the time of embryo transfer is treated equally. May be due to the lack of knowledge, a customized approach is neglected. However, new technology is helping us to improve the accuracy, reproducibility and especially clinical utility of previous test to evaluate the endometrium. Transcriptomics is helping us to understand which genes are actively expressed at any given time within a specific cell population or tissue.
Traditionally, embryo incubation and assessment daily has been under a light microscope, these observations are inevitably restricted to specific times and considering that the development of the embryo is a dynamic process, several critical stages in between observations may go unnoticed. For this reason, the new technologies, time lapse monitoring, have focused on the research for additional markers of viability to supplement current criteria for embryo selection and thus, achieve a reduction in the number of embryos transferred and so multiple pregnancies, making the selection procedure even easier for the embryologist. However, for wide adoption of time-lapse technology in IVF practice, there are two key considerations. First, validation of the time-lapse technology is needed to demonstrate its safety and effectiveness by prospectively designed clinical trials in a multiple-clinic setting. Second, time-lapse technology must be compatible with the busy workflow of any standard IVF laboratory and practical-to-use for any embryologist.
Aneuploidies are common in early human embryos. Trisomic and monosomic embryos account for at least 10% of human pregnancies and, for women nearing the end of their reproductive lifespan the incidence may exceed 50%. Age-related defects result in higher aneuploidy rates in offspring. Aneuploidy may also be a contributing factor in other infertile populations. An abnormal embryonic karyotype was found to be the most frequent cause of recurrent miscarriage (RM). Repetitive implantation failure (RIF) remains a clinical challenge and embryonic aneuploidy has been proposed as one of the leading embryonic causes. In male factor (MF) infertility, an increase in sperm chromosomal abnormalities due to impairment of the meiotic process has been described. Preimplantation genetic screening (PGS) by fluorescence in situ hybridization (FISH) for a limited number of chromosomes was widely applied for almost two decades, but there was a clear need for a technique capable of comprehensive chromosome screening (CCS), which could also produce reliable and faithful results in a short period of time. Array-CGH (aCGH) was described as a robust and accessible diagnostic approach to assess 24-chromosome aneuploidy and hence IVF programs are moving towards PGS using aCGH.

In this course, we will present our current clinical experience of more than three years using aCGH for aneuploidy screening on cleavage stage and blastocyst biopsies as a co-adjuvant technique to improve reproductive outcomes in IVF patients with high aneuploidy risk. This retrospective study comprised a total of 2964 CCS, 2858 with cleavage stage biopsies and 106 with blastocyst biopsies. On cleavage stage biopsies aneuploidy rates were 67.2 in women <38 years and 86.3 in women ≥38 years. Clinical results showed that pregnancy rate per transfer and implantation rate in women <38 years were 59.0 and 49.0, respectively. In women ≥38 years, pregnancy rates per transfer and implantation rates stand as high as 51.1 and 46.2.

In blastocyst stage biopsies, aneuploidy rates were 49.5 in women <38 years and 69.4 in women ≥38 years. Clinical results, pregnancy rates per transfer and implantation rates in women <38 years were fairly close to those obtained in cleavage stage biopsies, 54.3 and 42.40. However, in women ≥38 years, pregnancy rates per transfer and implantation rates were higher than at cleavage stage, 70.3 and 64.1. In this subgroup of patients, the analysis of the characteristics of the patients undergoing cleavage stage or blastocyst biopsy showed better prognosis values for two parameters in blastocyst biopsies: mean female age and number of MII oocytes.

The efficiency of PGS has been assessed in several randomized controlled studies (RCTS) for different patient populations. In our group we are conducting two RCTs, in advanced maternal age and in severe male infertility with promising results in ongoing pregnancy rates when PGS by aCGH is performed.
Once gametes and embryos are removed from their in vivo situation, they are exposed to a new milieu that can be detrimental to their physiology. Many aspects of the embryo culture conditions have been claimed to potentially affect the viability of human embryos. Laboratory factors such as maintenance of temperature, light, air quality, osmolarity, pH, oxygen tension, may affect their in vitro developmental competence.

The scope of the present lecture will be related to culture media, pH issues as well as the existing two different philosophies behind the use of one step versus sequential embryo culture. The advantages and disadvantages of using one to another will be also discussed.

Keeping in mind that culture media is just one part of the overall culture system; the present lecture will address the following sections:

- Brief history of culture media
- Culture media composition
- Ways to measure the pH of the culture media and QC
- Culture systems: One step versus sequential embryo culture
- Optimization of embryo culture media to support blastocyst formation
Cryopreservation during assisted reproduction technologies (ART) is an essential practice for clinics to maximise cumulative pregnancy rates and minimise complications associated with multiple pregnancies. This presentation will summarise and present reviews of current literature covering cryopreservation techniques throughout ART including the preservation of gametes for both social and medical reasons and the preservation of embryos produced through IVF.

It is imperative that the cryopreservation protocol employed by the ART clinic has minimal impact on the gamete or embryo being preserved. The last decade has seen a shift from conventional controlled-rate (slow) freezing toward vitrification, which typically uses a high concentration of cryoprotectants and rapid cooling rates to minimize ice crystal formation. The presentation will analyse the key differences between the two methods and review clinical outcomes from each method. The review will also compare some of the vitrification devices that are currently available and the differences between open and closed systems as well as looking at some new technologies that are becoming available in the cryopreservation field.

Following this presentation it is envisaged that the participants will have a sound understanding of the reason why cryopreservation is so important for successful ART as well as have an understanding of the principles behind the two main cryopreservation techniques and what factors influence the success of each cryopreservation method.
The recent trend to freeze-all the oocytes/embryos after an IVF cycle and do the transfer in a subsequent embryo cycle is compelling: the concept of transferring in a more physiologic environment –either natural or HRT cycle- to avoid the elevated steroid levels, avoid the risks of developing OHSS –early and late- or the impact of progesterone accumulation during the late follicular phase, the great pregnancy rates obtained with the development of vitrification protocols –much better than 10 years ago-, the hypothetical decrease of maternal and perinatal morbidity, and even the possibility of genetic testing, all are highly attractive reasons, but still, not proven. In this presentation we will challenge the evidence in favor for a paradigm shift, to do all IVF cycles as freeze-all –treatment segmentation- and try to set the indications in which oocyte/embryo freezing might benefit the patient.
Objective
During implantation the blastocyst influences the endometrium, and the endometrial epithelium nurtures and regulates the preimplantation embryo. Our objective is to demonstrate that maternal miRNAs are transported through the endometrial fluid (EF) and uptaken by the embryo to induce modifications relevant for the establishment of pregnancy.

Design
To investigate the miRNA content of EF \( n=20 \) through the cycle identifying those differentially expressed in the window of implantation (WOI). To understand how endometrial miRNAs are secreted and taken up into the embryo where they induce adhesive modifications.

Materials and methods
miRNAs were identified using microarrays. Exosomes were isolated by ultracentrifugation of EF, and identified by TEM and western blot. Internalization studies of miRNAs were tested with fluorescent scramble and mimic syntethic miRNAs. Embryo transcriptomic modifications were assessed by expression microarrays and adhesive modifications by embryo adhesion assay. Student’s t test was used for comparisons.

Results
We detected 20 differentially expressed miRNAs in EF during the WOI in direct contact with the preimplantation embryo. The most represented was hsa-miR-30d. miRNAs are secreted by the endometrial epithelium both free and as exosome-associated molecules and are internalize by the embryo through the trophoectoderm. Also, miR-30d induced the overexpression of 10 genes related to cellular adhesion. Embryo adhesion was tested comparing control, scrambled miRNA, miR-30d mimic, and miR-30d inhibitor \( n=360 \). After 32h, miR-30d mimic increased adhesion vs scramble and this was abolished with miR-30d inhibitor \( (35.22\pm7.4\% \text{ vs } 53.44\pm6.4\% \text{ vs } 18.55\pm3.72\% ) \), respectively \( p=0.001 \).

Conclusions
Our results show a model in which endometrial maternal miRNAs function as transcriptomic regulators during early embryo development, offering a new perspective on the crosstalk during implantation, and as a potential mechanism for the developmental origins of certain adult diseases such as obesity and type II diabetes.
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