Pre-ESHRE advanced course in embryology
IVF today: is it possible to further improve the clinical outcomes?
2 July 2016 - Helsinki, Finland
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Overview
The first report of a human baby born using reproductive technology occurred in 1978. Since then, a lot of improvements in clinical and embryological procedures have been made. Despite that, the average clinical success rate reported in Europe is still quite unsatisfactory. This 2016 live educational course will focus on the state of the art concerning the actual medical and biological therapies available, with a look toward the future.

One important topic will focus on how to obtain and identify the embryo(s) with the higher implantation potential in order to achieve a single healthy live birth. There are many interconnected aspects that can have an influence on embryo development and genetic constitution that should be carefully evaluated. Therefore, this live event will look at embryo culture systems, culture media, culture conditions and embryo selection strategy.

In the last five years, a lot of papers have been published regarding the possibility of selecting the most viable embryo(s) by applying the time-lapse technology. This very promising topic will be examined during the meeting.

There is still a remarkable discussion regarding the opportunity to routinely perform preimplantation genetic diagnosis or only in some categories of patients. Some of the most skilled experts will debate this hot topic.

In addition, the best way to manage different categories of patients in order to give them a personalized treatment will be deeply analyzed.

Finally, the emerging technologies that could lead to better embryo culture and selection will also be featured.

The aim of the event is to update participants’ latest knowledge as well as take the opportunity to actively discuss their experiences with skilled embryologists and scientists.

Learning objectives
By attending this live educational course, participants will:

• Learn how optimize embryo culture and embryo selection strategy in order to obtain and select the best embryo
• Recapitulate the state of the art concerning preimplantation genetic techniques with a look to the future
• Enhance knowledge of management of patients who are infertile
• Acquire knowledge on latest news regarding embryo quality assessment

Target audience
This live educational course is aimed at embryologists, expert clinicians and scientists interested in understanding the latest advancements in the assisted reproductive medicine field.

Chairs
Robert Fischer
Fertility Center Hamburg
Hamburg, Germany

Zsolt Peter Nagy
Reproductive Biology Associates (RBA)
MEB-NA, Atlanta, Georgia, USA
ALPHA, Scientists in Reproductive Medicine

EXCEMED developed this programme in collaboration with: ALPHA, Scientists in Reproductive Medicine.
CME Provider

EXCEMED is a non profit foundation dedicated, since the last four decades, to the development of high-quality medical education programme all over the world.

EXCEMED adheres to the guidelines and standards of the European Accreditation Council for Continuing Medical Education (EACCME®) which states that continuing medical education must be balanced, independent, objective, and scientifically rigorous.

Continuing medical education

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The CME course “IVF today: is it possible to further improve the clinical outcomes?” held on 2 July 2016 in Helsinki, Finland, is designated for a maximum of 6 (six) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity.

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EXCEMED adheres to the principles of the Good CME Practice group (gCMEp).
GENERAL INFORMATION

This live educational course takes place at:

**Hilton Helsinki Kalastajatorppa**
Kalastajatorpantie 1
Helsinki, 00330, Finland

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

**CME Provider**
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**Format**
This live educational event is allowing participants to express their own views and opinions through debates, real-time surveys with voting system, questions cards and dedicated website.

**Dedicated website**
Access the dedicated website [www.16excemedpreeshre.org](http://www.16excemedpreeshre.org) to:
- View the agenda
- Get your certificate of attendance
- Get your EACCME® certificate
- Fill in the Post-event surveys

**Any question?**
You can post your questions on:
- Question card
PROGRAMME
SATURDAY, 2 JULY

8.00 Registration and welcome coffee
8.45 Opening and Introduction
   R. Fischer (Germany)

Real-time survey

Session I

Session Chairmen: R. Fischer (Germany) - Z.P. Nagy (USA)

9.00 L1: The importance of follicular environment in clinical treatment
   B.C.J.M. Fauser (The Netherlands)

9.20 L2: Comprehensive chromosome screening and embryo biopsy: advantages and difficulties
   A. Capalbo (Italy)

9.40 L3: Does time lapse technology improve success rate?
   T. Hardarson (Sweden)

10.00 L4: Automation and standardization in embryology lab
   T. Roy (Australia)

10.20 L5: Effect of laboratory and culture system on biological outcomes
   L. Rienzi (Italy)

10.40 Panel discussion
11.10 Coffee break

Session II

Session Chairman: Z.P. Nagy (USA)

11.30 Debate

D1: Genetic testing to improve clinical outcome - Pro
   D. Wells (UK)

VS

D2: Genetic testing to improve clinical outcome - Con
   S. Mastenbroek (The Netherlands)

12.10 Discussion
12.30 Lunch

Session III

Session Chairmen: R. Fischer (Germany) - Z.P. Nagy (USA)

13.40 L6: Consequences of sperm selection on embryo quality
   C.L.R. Barratt (UK)

14.00 L7: Gamete and embryo cryopreservation: when and how
   A. Cobo (Spain)

14.20 L8: Predictive value of embryonic mitochondrial DNA: reality or legend
   D. Wells (UK)

14.40 L9: From stem cells to artificial gametes: ready for the patient?
   E.E. Telfer (UK)

15.00 Panel discussion

Revisiting real time survey
15.30 Concluding remarks
   Z.P. Nagy (USA)
15.45 End of the live educational course

Legend:  L: Lecture  D: Debate
EXCEMED adheres to the 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:

**Christopher L.R. Barratt**  
Declared no potential conflict of interest

**Antonio Capalbo**  
Declared receipt of grants and contracts from Merck GFI 2013 and 2015; Receipt of honoraria or consultation fees from MSD; To be stakeholder in Genetyx srl

**Ana Cobo**  
Declared no potential conflict of interest

**Bart C.J.M. Fauser**  
Declared receipt of grants and contracts from Hartstichting, NGI, GFI; Receipt of honoraria or consultation fees from Ovascience, Ferring, Finox; To be member of Preglem and Euroscreen advisory boards and that his presentation will include discussion of off-labeled or otherwise non-approved uses of products

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

**Thorir Hardarson**  
Declared no potential conflict of interest

**Sebastiaan Mastenbroek**  
Declared no potential conflict of interest

**Zsolt Peter Nagy**  
Declared receipt of honoraria or consultation fees from Origio/Cooper-Surgical, Watermark; To be member of Cooper-Surgical and Recombine advisory boards; To be stakeholder in My Egg Bank and participation in Merck speaker’s bureau

**Laura Rienzi**  
Declared no potential conflict of interest

**Tammie Roy**  
Declared to be employee of Genea Biomedx

**Evelyn E. Telfer**  
Declared receipt of contract to carry out testing for OvaScience

**Dagan Wells**  
Declared to be member of Illumina advisory board and to be employed at Reprogenetics
BIOGRAPHIES
Christopher L.R. Barratt
School of Medicine
University of Dundee
Dundee, Scotland, UK

Christopher L.R. Barratt is Head of the Reproductive Medicine Group at the University of Dundee as well as a clinical scientist (Hon) with NHS Tayside. He graduated with an Honours degree in Zoology and then completed a Post Graduate Certificate in Education (University of Wales, Swansea). His PhD, also in Zoology, was under the supervision of Jack Cohen (of sperm selection fame) at the University of Birmingham. His formative post-doctoral studies and IVF experience was gained at the University of Sheffield (with Ian Cooke) where he specialized in natural cycle IVF. From 1997-2005 Prof Barratt was the Scientific Director of the ART Centre at the Birmingham Women’s Hospital. In 2002 he was awarded Young Andrologist of the Year (American Andrology Society) for outstanding contributions to the discipline. He is a regularly invited speaker at national and international scientific conferences/workshops. He was a member of the WHO Male Fertility Semen Analysis Taskforce (for both the 4th and 5th editions) and is now director of the new WHO (2012-2016) Male Fertility Expert Working Group which is devising a new system for the diagnosis and treatment of the infertile male. He was a member of the Human Fertilisation and Embryology Authority for 6 years. Prof Barratt has been on the Editorial Board of Human Reproduction, Human Fertility, Biology of Reproduction, Human Reproduction Update and Journal of Andrology. In 2014 Prof Barratt presented Professor Sir Robert Edwards’ keynote lecture at ESHRE. This presentation was based on the highest downloaded paper in Human Reproduction for 2013. Currently, he is Editor-in-Chief of Molecular Human Reproduction (Impact factor 5 year 3.9).

Antonio Capalbo
G.EN.E.R.A.
Centre for Reproductive Medicine
Rome, Italy

Antonio Capalbo received his Bachelor of Science Degree in Biotechnology from the University of Rome “La Sapienza” and a Ph.D. magna cum laude in Human Genetics at the Catholic University of the Sacred Heart of Rome in 2011. In the same year, he obtained a level II Master’s Degree in Epidemiology and statistical data analysis, also from the Catholic University of the Sacred Heart of Rome. He has been working as a clinical embryologist at G.EN.E.R.A., Reproductive Medicine Centers, Italy, since 2008. During this period, his research has focused on pre-implantation genetic diagnosis and screening and on the development of novel molecular methods to improve pregnancy and take-home baby rates in ART. In 2011 he worked as a research fellow at Reproductive Biology Associates, Atlanta, GA, USA and from 2012 he began collaborating as a consultant embryologist at the Embryonic Stem Cell Laboratories, Assisted Conception Unit of Guy’s Hospital, KCL, London, working on molecular profiling of human blastocyst differentiation. From 2012 he became a genetic consultant and PGD/PGS program coordinator at G.EN.E.R.A. He has also served as a Scientific and Laboratory Director at GENETYX, Reproductive Genetics Laboratory since 2014.
Ana Cobo has been part of the embryology staff at Instituto Valenciano de Infertilidad (IVI) since 1995. She obtained her Master’s of Biological Sciences Degree in Biology of Reproduction from the University of Chile in 1994, a Master’s Degree in Human Reproduction in 1998 and a PhD in 2003 from the University of Valencia, Spain. She currently leads the Cryobiology Unit at IVI-Valencia. Her major areas of interest are oocyte and embryo cryopreservation and oocyte morphology linked to embryo development. Dr. Cobo has been a member of ESHRE (European Society of Reproductive Medicine) since 1997, SEF (Sociedad Española de Fertilidad) from 1997, ASEBIR (Asociación para el estudio de la Biología de la Reproducción) since 2000, and ASRM (American Society for Reproductive Medicine) since 2007. She has recently joined the ALPHA executive board. Dr. Cobo has authored four textbooks, co-authored over 30 textbook chapters and has published over 60 articles for a variety of international journals. She has also made over 100 presentations at national and international symposia.

Bart C.J.M. Fauser teaches Reproductive Medicine at the University of Utrecht, former Chair of the Department of Reproductive Medicine & Gynecology, and former Head of the Woman & Baby Division, University Medical Center, Utrecht, the Netherlands. Professor Fauser also acts as Chief Editor of Reproductive Biomedicine Online (RBMO), as a member of the board of the Dutch Medical Research Council (ZonMW), and as chair of the World Health Organization steering committee on infertility guidelines. He is a visiting professor at Siena (Italy), Adelaide (Australia), and Southampton (UK), and a senior lecturer at the London Women’s Clinic (UK). Prof. Fauser previously held the following positions: Fulbright post-doctoral Scholar, University of California, San Diego, USA; Visiting Professor, Stanford School of Medicine, Palo Alto, California, USA; Saal van Zwannenberg Professor, Center of Reproductive Medicine, Free University, Brussels, Belgium; Professor of Reproductive Endocrinology and Director of the Center of Reproductive Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. Prof. Fauser is the former Editor-in-Chief of Human Reproduction Update. His major research interest is the pathophysiology of human ovarian function. He is the author of close to 400 PubMed publications, and his Hirsch Factor is 74. Prof. Fauser has served on many international editorial boards, has been active in many international societies, referees for all major journals, and his work has been widely covered in the national and international mainstream press.
Robert Fischer is founder and medical director of the IVF unit at the Fertility Center Hamburg - one of Germany’s largest and leading IVF centres. In July 1998 the Fertility Center Hamburg was one of the first centres in Germany, and worldwide, to introduce certified quality management according to the ISO 9001. In 2002, the IVF laboratory became ISO 17025 certified. Prior to these developments, in 1983 he pioneered and was medical director of the first outpatient IVF unit in Hamburg. As well as having authored numerous publications in national and international scientific journals and books, he also lectures at conferences worldwide, is 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”.

Thorir Hardarson is the Laboratory Director at Fertilitetscentrum, Gothenburg, and the Scientific Director for IVF Sverige, Sweden. He received his training at the University of Iceland where he earned his Bachelor’s Degree in biology and a Master’s Degree in physiology. After relocating to Sweden in 1997, he conducted research at Gothenburg University resulting in a PhD on human embryology. In the research for his PhD, he became a pioneer in 1999 on the use of time-lapse technology to study the dynamic development of embryos. His research interests have focused on new methods for identifying the best embryo to transfer, ranging from static and dynamic (time-lapse) morphological evaluation as well as metabolomics and PGS. He has been a member of the ALPHA executive committee since 2012. Dr. Hardarson has published over 60 scientific papers, book chapters and abstracts on embryology and human IVF. He is a reviewer of RBM Online and Human Reproduction.
Sebastiaan Mastenbroek is an Assistant Professor and Senior Clinical Embryologist at the Academic Medical Center of the University of Amsterdam, the Netherlands. An important focus of his research in past years has been Preimplantation Genetic Screening (PGS). In 2007, publication of his randomized controlled trial on PGS in the New England Journal of Medicine started a fiercely debated controversy on the use of PGS as it showed that the technique lowered rather than increased pregnancy rates after IVF. He then published research that provided technical as well as biological reasons for the inefficacy of the first generation of PGS methods. From a broader perspective he is interested in ovarian aging, early human development, implantation, assisted reproductive techniques and evidence based laboratory practice.

Sebastiaan Mastenbroek
Center for Reproductive Medicine
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Zsolt Peter Nagy is the Scientific and Laboratory Director at Reproductive Biology Associates (RBA), in Atlanta, USA. He obtained his MD (1986) and his Ob&Gyn specialty degrees (1996) at the Semmelweis Medical University in Budapest, Hungary. He obtained his PhD at the Free University of Brussels, Belgium [VUB] in 1997. Dr. Nagy has acquired a distinctive knowledge and experience in embryo science including novel viability assessment methods. He has also investigated the basic and clinical aspects of cryopreservation, particularly oocyte vitrification that has contributed to the development of the largest donor oocyte cryo-bank in North-America. Dr. Nagy is a member of several national and international professional societies, including the ASRM and ESHRE, as well as being an Alpha Scientist in Reproductive Medicine [ALPHA], and serving on various committees within these societies. He is also a member of the International Society for Fertility Preservation [ISFP] and of the Alliance for Fertility Preservation [AFP] and serves on the executive board of these two organizations. Dr. Nagy is a reviewer of several medical journals, and is currently a section editor of RBM Online. He has been an invited speaker and organizer at hundreds of medical and scientific meetings during his professional career. He has also authored or co-authored of over 200 publications, book chapters and books.

Zsolt Peter Nagy
Reproductive Biology Associates (RBA)
MEB-NA, Atlanta, Georgia, USA
ALPHA, Scientists in Reproductive Medicine
Laura Rienzi, Senior Clinical Embryologist, is Laboratory Director at the G.EN.E.R.A. Centres for Reproductive Medicine. With academic degrees in Biology and Reproductive Medicine, she is involved in many activities including educational, practice-based and editorial (having authored more than 110 articles, reviews and book chapters). Dr. Rienzi is internationally recognized for her expertise in human clinical embryology and research as evidenced by numerous invitations to speak at national and international scientific meetings. She is member of the editorial board for the 1st edition of the "WHO Infertility Guidelines". In 2008, she founded, together with Dr. Filippo Maria Ubaldi, the G.EN.E.R.A. Centres for Reproductive Medicine where she is Laboratory Director of the 4 Centres in Italy (Rome, Marostica, Umbertide, Naples). Her current areas of interest include in vitro fertilization, ICSI, human embryo culture, studies of gamete, zygote and embryo morphology in relation to their developmental ability and chromosomal constitution (PGD, PGS), as well as cryopreservation of embryos and oocytes. In 2014 she was nominated President of the Italian Society of Embryology, Reproduction and Research (SIERR).

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 then joined Genea Biomedx and has been a member since its inception. Dr. Roy has extensive clinical and research experience in cryopreservation of embryos and oocytes.
Evelyn E. Telfer holds a personal chair in Reproductive Biology at the University of Edinburgh. Evelyn was awarded her PhD in ovarian development from the University of Edinburgh in 1987 where she was supervised by Professor Roger Gosden. She was awarded a Rockefeller Foundation Fellowship to work with Professor John Eppig at the Jackson Laboratory, Bar Harbor Maine where she continued her work on developing in vitro systems to support oocyte development and also studied the role of the oocyte in directing follicle development. Prof. Telfer returned to the University of Edinburgh and now heads a research group in Ovarian Development within the Institute of Cell Biology and Centre for Integrative Physiology. Her group’s interests cover all aspects of follicle and oocyte development in mammals with particular interest in developing in vitro models to support oocyte development from primordial stages in domestic species and human. Her group is now using these models to study the potential of female germ line stem cells isolated from adult ovaries in a range of species. She has published widely in this area and is a regular invited speaker at International meetings. Prof. Telfer is also active in teaching and mentoring within the University. She introduced undergraduate teaching programmes in Reproductive Biology at the University of Edinburgh with the establishment of an Honours programme. She has been a visiting Professor at the Karolinska Institute, Stockholm, Sweden where she continues to contribute to postgraduate courses. Prof. Telfer has a wide network of basic science and clinical collaborations with groups in the U.K., Europe and the U.S.A. His research has been funded by BBSRC, Wellcome Trust and MRC.

Dagan Wells has been actively involved in preimplantation genetic diagnosis (PGD) and the study of human gametes and embryos for the last 25 years. He spent several years developing novel PGD tests at the University College London (UK), accomplishing the first comprehensive chromosome analysis of cells from human embryos in 1998, using a combination of whole genome amplification and comparative genomic hybridisation. In 1999 he moved to the United States and joined Reprogenetics, one of the world’s largest providers of PGD services. In 2003 he initiated Reprogenetics’ single gene PGD program, testing embryos for numerous serious inherited conditions. Dagan later joined the faculty of Yale University Medical School (New Haven, USA) where he set up a PGD and research laboratory before returning to the UK in 2007. He is now an Associate Professor at the University of Oxford, overseeing a research team based at the Nuffield Department of Obstetrics and Gynaecology. Dagan’s work has led to the publication of more than 150 peer-review publications and book chapters and has been recognized with the award of numerous prizes and grants. He is a Fellow of the Royal College of Pathologists and currently serves on the editorial boards of several international journals. Dagan also directs Reprogenetics-UK, a laboratory offering PGD services to IVF clinics in Europe, Africa and the Middle East.
Recruitment of resting primordial follicles at the beginning of the long trajectory of follicle development, along with single dominant follicle selection at the very end, are two fundamental processes regulating human ovarian function. Initial follicle recruitment being closely linked to diminished ovarian reserve resulting in decreased fertility with increasing female age. The single dominant follicle eventually releases the oocyte upon ovulation which may be fertilised and – under normal circumstances – give rise to a singleton pregnancy.

At present, the process of initial follicle recruitment cannot be influenced. During ovarian stimulation for IVF, all gonadotropin dependent follicles present at the beginning of the menstrual cycle are stimulated to ongoing development with the aim to eventually retrieve multiple oocytes for fertilisation in vitro. Currently used stimulation protocols are complex, time consuming, expensive, and may give rise to significant patient discomfort and complications, along with creating the need of frequent ovarian response monitoring.

Several good quality IVF centers reported recently that least 20 oocytes are required to generate a single live birth. It therefore seems justified to conclude that we have created a wasteful system, with on average 19 out of 20 oocytes not giving rise to a baby. Conditions exist known to affect oocyte quality such as advanced reproductive age, and women diagnosed with the polycystic ovary syndrome. Although not without controversy, evidence is accumulating that ovarian stimulation itself is directly linked to suboptimal oocyte quality and IVF outcome. Moreover, preliminary data suggest that growth factor concentrations in follicle fluid (especially GCSF) are linked to oocyte / embryo quality.

We need to appreciate that more is not always better as far as number of retrieved oocytes is concerned, and understand better what are the negative implications of ovarian stimulation in relation to oocyte quality, endometrial receptivity and luteal phase endocrinology.
The ultimate goal of emerging genetic testing technology for embryo selection is to increase the efficiency of each single treatment while reaching similar efficacy for standard IVF, defined as live birth rate per treatment. Currently, embryo selection criteria are still limited to morphology and/or morphokinetic assessment of preimplantation development, but they are still insufficient by themselves to improve embryo transfer policy toward a single replacement to all IVF patients as well as to minimize the risks of miscarriages and chromosomally abnormal children. In this presentation, a comprehensive overview of preimplantation genetic screening-based embryo selection, as well as current and emerging genetic testing technology for PGS application, will be provided. Considering the high impact of chromosome aneuploidies in human reproduction, Preimplantation Genetic Screening (PGS), a diagnostic technique aiming at the selection of euploid embryos to be transferred within a cohort of embryos produced by a couple during an IVF cycle, is currently exploited as the main genetic testing method for improving embryo selection. PGS version 1.0, including blastomere biopsy at da three of embryo development and FISH analysis for few chromosomes, failed to show enhanced embryo selection as demonstrated by several Randomized Control Trials (RCTs) and meta-analyses in recent years. Looking backwards in the preimplantation window, the polar bodies (PBs) approach has also been determined to be inappropriate since paternal and post-zygotic errors are not detectable and low accuracy in predicting female-derived aneuploidies was also claimed in recent publication. Looking forward in preimplantation development, blastocyst stage trophectoderm (TE) biopsy is bringing solid evidences and promising clinical outcomes. This stage, in fact, guarantees a more robust genetic analysis, no impact of biopsy and a low impact of chromosomal mosaicism on genetic testing. Several RCTs, systematic review and meta-analysis of the literature have recently been published suggesting blastocyst stage PGS as a validated method to improve embryo selection in IVF treatments. In this presentation, an overview of pros and cons of different timings for biopsy will be provided as well as a critical overview of available clinical evidences. For what concerns chromosomal testing methods, 9-chromosome FISH has been replaced by 24-chromosome screening methods, based on array technology (aCGH and aSNP) or on quantitative Real Time PCR (qPCR). All these platforms are suitable for an accurate comprehensive chromosome screening (CCS) analysis, but with different costs, accuracies, levels of validation and turnaround time of analysis. Here, the latest single-cell genomics methodologies based on DNA microarrays, single-nucleotide polymorphism arrays, quantitative real-time PCR or next-generation sequence analysis will be also discussed. We will focus on their strengths, their validation status, their weaknesses and the challenges for implementing them in IVF.
The use of time-lapse has rapidly increased in clinics all over the world since its recent introduction to IVF. Several benefits have been proposed through the use of time-lapse. First, taking a picture within incubators allows for an undisturbed culture that should therefore yield better culture conditions. Second, continuous observation allows for a more flexible laboratory: for example, making it possible to perform ICSI early in the morning while not missing fertilization in the middle of the night as well as not missing any other aberrant cell cleavages undetectable through traditional observation. Third, the unique information that can be extracted from time-lapse sequences could potentially allow for better prediction of which embryo to choose for transfer, thereby shortening time-to-pregnancy.

This last benefit is the most controversial as its associated instruments come with a high price tag. Several diversely designed studies have set out to address the question of costly treatment; results have indicated benefit and no benefit to time-lapse. As have the results been both showing benefits and no benefit of time-lapse.

In this presentation I will go through existing data on the possible benefits of time-lapse as a selection tool in IVF.
Following this presentation it is expected that participants will have a better understanding of how automation and standardization of processes within the embryology lab can help improve outcomes.

There are many processes involved in assisted reproduction technologies (ART); the majority of these processes are completed manually and are performed under different protocols that can vary from clinic to clinic -- and even from embryologist to embryologist. The result is that outcomes can also vary by clinic and embryologist by as much as 40%. The many processes of an In Vitro Fertilisation (IVF) cycle have numerous variables that can be difficult to control using standard manual methods. This presentation will summarize some of the variables, techniques and technologies used for standardizing and automating two common and very important IVF processes: culturing and cryopreservation.

Automation and standardization of culture and cryopreservation techniques create an opportunity to improve embryology outcomes in IVF. Automation and standardization offer clinics the capacity to complete manual tasks in a repeatable and measurable way to ensure consistency so as to achieve high-level outcomes across different labs and users.
Human pre-implantation embryo culture is a key element of assisted reproductive technologies (ART). Culture condition in the laboratory contributes substantially to the success of the procedures and its importance has increased over the past decade as extended in-vitro embryo culture, single blastocyst transfer and vitrification, have become essential approaches able to decrease the risks of multiple pregnancy while preserving the overall efficacy of the treatment.

However, a consensus is still missing as to the basic principles necessary to optimize and sustain in vitro embryo growth, including composition and exchange of media, the required physical and chemical environment and even the temperature of incubation.

Culture media is certainly one of the most important aspects of the embryo culture system, but its influence on embryo development has to be analysed together with other essential factors, both chemical and physical. These factors, such as temperature, pH and oxygen concentration, may have dramatic effects on embryo physiology and viability. Furthermore, a clear cumulative effect of these stressors has been documented. However, new technologies (such as benchtop incubators and time lapse systems) can help to better control potentially harmful chemical and physical factors during pre-implantation embryo culture; using these technologies is necessary to improve and standardize human embryo culture in the near future.

There is also a clear stage-specific correlation in the embryo resistance to stress. In particular, the oocyte (and the cleavage stage embryo) is much more susceptible to its environment than the embryo post-compaction. The success of blastocyst development is therefore likely associated with the quality of the in vitro condition used at earlier stages. However, the debate against extended culture in human IVF is still ongoing, although new evidence does not confirm any correlations between blastocyst culture and neonatal outcomes.

As clearly shown in animal models, in vitro culture may have a long-term effect on the embryo, but it is not yet clear which aspect of the ART cycle may be responsible in animals. Most likely it is a combination of in vitro and in vivo factors, including infertility factor, as well as age and weight of the parents. Keeping these potential risks in mind, the IVF laboratory must ensure an adequate control of the basic chemical and physical factors during the IVF cycle, independent of the duration of the in vitro culture.
Despite the fact that in vitro fertilisation treatment has been available for over 35 years, the process remains remarkably inefficient, with only about a third of treatment cycles resulting in a live birth. One of the most important factors affecting the probability of a pregnancy is the capacity to distinguish embryos with a high developmental potential from those that are non-viable. In order to achieve maximum pregnancy rates per transfer, it is essential to identify the embryo which is most likely to produce a successful pregnancy. However, current strategies for embryo evaluation, based on morphological appearance, are poorly predictive. It has been proposed that genetic testing might provide more definitive, less subjective insight into embryo potential. Multiple studies have shown that aneuploidy (an incorrect number of chromosomes) is extremely common in human gametes and, as a result, preimplantation embryos. Chromosomal abnormalities originating in meiosis are almost always lethal to the embryo and consequently it has been argued that screening for such aneuploidies would be helpful for embryo selection.

Despite the logic of chromosome screening as a strategy for embryo assessment, a series of clinical studies, carried out almost a decade ago, failed to demonstrate any improvement in IVF outcomes following aneuploidy detection. However, the introduction of new embryological and genetic methods since that time has utterly changed the landscape. Multiple randomised clinical trials, prospective studies and meta-analyses conducted in the last five years, clearly show that modern genetic techniques provide a superior guide to embryo potential than any other approach currently available. Identification and transfer of chromosomally normal embryos is unequivocally associated with improved pregnancy rates compared to the transfer of unscreened embryos. Additionally, the risk of miscarriage is greatly reduced, especially for female patients in their late thirties or forties, and aneuploid disorders [e.g. Down syndrome] are rarely observed. The number of fruitless embryo transfers are greatly reduced and cryopreservation and storage of non-viable embryos is minimised. Furthermore, in cycles where multiple embryos are produced, the chance that the very first embryo transfer will be successful is significantly increased, shortening the time to pregnancy compared with strategies involving cryopreservation followed by multiple sequential transfers of unscreened embryos.

The technology used for the detection of genetically abnormal embryos is evolving extremely rapidly and in the coming years we can look to further advances that will lower the costs of embryo testing and bring unprecedented benefits to patients, forever changing genetic diagnostics and the treatment of infertility.
Preimplantation genetic screening (PGS) consists of: the biopsy of one or more cells from a preimplantation embryo, the analysis of these cells and the transfer of embryos which are determined to be euploid. The goal of PGS has always been to improve IVF success rates. After its clinical introduction in 1995 it took more than a decade before the first properly designed randomised controlled trials (RCTs) on PGS were published. These did not indicate a benefit of PGS, but instead a decreased chance of ongoing pregnancy when compared to IVF without PGS. Currently, it is widely recognized that PGS, as it had been applied, with FISH analysis of blastomeres aspirated on day three of embryo development, did not benefit women in achieving pregnancy. The disappointing results of the first generation of PGS methodology led to the development of new PGS methods. These new forms of PGS are again rapidly being introduced into routine clinical practice, just as in the 1990s with the first wave of the procedure. In contrast to the 1990s, however, the use of PGS now seems justified as RCTs report positive results on the effectiveness of these new PGS methods. But careful analysis of the current trials on PGS, following basic principles of evidence based medicine (EBM), shows that there is actually insufficient evidence to justify the current use of PGS in routine clinical practice. It also seems that the rationale of PGS, i.e. to discard aneuploid embryos as they are not viable, is no longer self-evident. Embryos determined to be aneuploid by PGS were shown to result in healthy live births, albeit with lower efficiency. Proper evaluation of effectiveness and cost-effectiveness should precede routine application of an invasive and costly procedure such as PGS – a view that seems to have been pushed aside once again.
Sperm dysfunction is the single most common cause of infertility and affects approximately 1:15 men. Studies using semen assessment as the criteria for sub fertility (sperm concentration <20x10^6/ml) show that 1:5 18-year-olds are classed as sub-fertile. Therefore, male sub-fertility is a significant global problem and, worryingly, recent reports suggest its prevalence is increasing.

There are a plethora of studies demonstrating that sperm quality is important for embryo quality (e.g. damage to the paternal genome affects embryo development and implantation.) However, the degree of this effect and how to accurately assess it is strongly debated. This has also led to a number of studies attempting to examine new sperm selection techniques. It is possible we are looking at this in the wrong way. For example, highly defective sperm (extra chromosome 21) can still fertilise an egg and form a viable pregnancy. The presentation will discuss the current evidence and what we can do in the future.
The use of vitrified oocytes -- either in autologous or donation cycles -- has greatly increased in the last few years. It has been reported that the rise in the quantity of cryo-transfers has lead to an increased number of babies born from cryopreserved embryos when compared to births achieved from fresh embryo transfers. The reason for the increased use of cryopreservation in ART can be attributed to the availability of highly efficient vitrification programs. This ice-free cryopreservation technology is dependent on the application of very high cooling and warming rates, combined with the use of high cryoprotectant concentrations and minimum volumes for loading the samples. The different devices currently available are designed to meet these requirements, including the open and closed systems classified according to whether or not samples should be subjected to direct contact with liquid nitrogen during the vitrification procedure and/or storage.

Vitrification has become the standard approach for oocyte cryopreservation. This strategy is useful in a wide range of clinical or social indications, including ovum donation and for women seeking fertility preservation. Oocyte cryo-storage brings additional advantages to ART programs as it is helpful in solving different clinical situations such as low responder patients, unpredictable unavailability of semen sample collection from the male partner, or other cases in which embryo transfer is not advised. The efficiency of the approach has been demonstrated by its similar results in terms of survival and clinical outcomes when compared to fresh oocytes in both donated or own oocyte scenarios. We have compiled a large body of evidence regarding the use of egg-banking in ovum donation programs confirming the efficacy of the approach.

However, there is less information on the use of vitrified oocytes in autologous (nondonor) cycles, especially in the elective fertility preservation population, or in cancer patients, mainly because of delay between oocyte storage and subsequent use. Nonetheless, recent reports indicate that the strategy also proven effective in this population. The current data indicate that success after vitrification can be affected by several factors, including the type of patient, age, and number of oocytes vitrified. The rate at which vitrified oocytes develop into live-born children is highly relevant in order to establish the complete efficiency of egg-banking. Information on how all these factors impact the final outcome will improve our understanding of what possibilities the approach can offer – information which is of great value when counselling patients.

Although three decades of successful results have been achieved from slow freezing embryos, with the addition of vitrification, we have managed to not only significantly improve survival rates, but also clinical results. Accordingly, a growing number of IVF clinics worldwide have switched to this technique for embryo cryopreservation. High survival and delivery rates can be achieved at all embryo developmental stages after vitrification/warming. Consequently, improved and more efficient cryopreservation programs are accessible, allowing a safe approach to certain strategies that require optimal results after cryo-storage. Among these strategies are the delay of fresh embryo transfers, also known as “freeze all”. Embryo vitrification has also been revealed as an efficient co-adjuvant technique when comprehensive chromosome screening is required. Accumulation of embryos is helpful in order to build up a larger cohort, therefore rendering more embryos to analyze, when the patient requiring the PGS analysis responds poorly to Controlled Ovarian Stimulation (COS). Additionally, the usefulness of this technique has also been evidenced by the survival and clinical outcomes achieved subsequent to the vitrification of the biopsied blastocysts in order to allow timing for obtaining genetic results.
The viability of embryos created using assisted reproductive technologies varies greatly -- even within a single cohort created from the gametes of a single couple. It is estimated that less than one-fifth of all embryos generated using IVF are capable of producing a pregnancy. In order to maximize the likelihood of a successful embryo transfer, there is a need for accurate assessment methods for embryo potential, guiding doctors and embryologists to the embryo most likely to produce a baby. Over the years, many different strategies for evaluating embryos have been proposed, including multiple morphological grading strategies, screening for chromosomal abnormalities, morphokinetics and metabolomics.

Today, it is widely accepted that chromosome abnormality is the principal cause of implantation failure and pregnancy loss, leading some clinics to advocate preimplantation genetic screening (PGS) to distinguish aneuploid and euploid embryos. However, approximately one-third of chromosomally normal blastocysts of high morphological grade still fail to implant after transfer to the uterus. Clearly, there are other factors influencing embryo viability. A recent proposal has focused on mitochondria, or more specifically the small amount of DNA (mtDNA) that they contain, claiming that abnormal quantities are associated with failure of implantation. Mitochondria fulfill a variety of essential functions within cells, the most well-known of which relates to their role in energy production. Thus, it is conceivable that mitochondrial abnormalities could be associated with embryo viability.

The first studies to report a potential link between mtDNA and the viability of human blastocysts were those of Fragouli and colleagues. In detailed studies, Fragouli reported that subtle increases in levels of mtDNA are associated with advancing female age and also, independently, with aneuploidy (Fragouli et al., 2013; Fragouli et al., 2015). While these findings raise interesting biological questions, a more important clinical finding was that embryos with significantly elevated levels of mtDNA never seem to implant. Following an initial retrospective study, during which the relationship with implantation was first noted, a prospective study was undertaken and confirmed the original results. Subsequently, a study from Diez-Juan also provided data strongly suggesting that mtDNA levels with respect to blastocyst viability. These authors also suggested that mtDNA might have predictive value at earlier embryonic stages. They also proposed that embryos could be divided into several distinct grades with differing implantation potential depending on the level of mtDNA, in contrast to the single definitive cut-off used by Fragouli.

Most recently, Fragouli and colleagues have conducted a prospective blinded, clinical, non-selection study, in which mtDNA levels were tested in hundreds of trophectoderm biopsy specimens from embryos that were selected for transfer to the uterus based upon PGS and morphological criteria - i.e. all embryos were euploid, but mtDNA results were not known at the time of transfer (Fragouli et al., 2016). Results were compared to pregnancy outcome data and, again, no pregnancies were observed for embryos that had levels of mtDNA above the critical threshold. Ongoing pregnancy rates for chromosomally normal blastocysts with appropriate levels of mtDNA were approximately 10% higher than for the cohort as a whole.

The data supporting the use of mtDNA as a biomarker of embryo viability are increasingly strong, yet some uncertainty remains. Although no peer-reviewed publications exist at this time, some authors have reported difficulties detecting an mtDNA threshold predictive of viability. The reasons for this are unknown, but might be related to technological issues. For example, standard next generation sequencing methods, used for PGS, may be suboptimal for the quantification of mtDNA due to problems mapping a sufficient number of sequence reads to the mitochondrial genome. Additionally, the relative rarity of affected embryos (incidence of approximately 10%) means that relatively large numbers of embryos must be assessed in order to have meaningful data. Another area of uncertainty is the underlying reason for expanded mtDNA levels in non-viable embryos. Do the greater amounts reflect a deficiency of function, embryos increasing their number of mitochondria to compensate for malfunctioning organelles? Alternatively, are higher levels of mtDNA a consequence of elevated metabolism and the associated increase in energy requirements? This latter possibility may be of relevance to Henry Leese's “quite embryo” hypothesis, which proposes that embryos with higher metabolic activity may display reduced viability. Clearly, more research will be needed to answer these interesting and important questions.
For the past 60 years, management of ovarian insufficiency and failure, including infertility caused by aging or insults, has been governed by the belief that the entire germ cell (oocyte) pool is endowed at birth, after which ovaries lose capacity for oocyte renewal (oogenesis). In 2004, studies with mice challenged the idea of a fixed ovarian reserve, and the controversy of whether postnatal oogenesis occurs in mammals was re-ignited. Almost a decade later, a body of evidence has emerged which supports the idea that a rare population of germ line cells with oocyte-forming potential can be isolated from ovaries of adult mice and women. These cells, termed female germ line stem cells (fGSCs) or oogonial stem cells (OSCs), are characterised by expression of primitive germ cell-specific markers and high levels of telomerase. When isolated and subsequently cultured in vitro, OSCs maintain a germ line profile while actively dividing. In addition, OSCs when combined with somatic cells form what appear to be oocytes/follicles. However, the physiological relevance of these cells to adult ovarian function and fertility remains to be determined.

While there is still controversy over the biological significance of these cells, it must be acknowledged that their identification and isolation is a significant advance with the potential to change infertility treatments -- and possibly even non-reproductive consequences of the loss of ovarian function in the future. Many practical and conceptual obstacles remain before clinical application of OSC-based technologies could be fully realised, but it is important to move on from scepticism towards solid testing to determine the potential utility of these cells. This presentation will focus on the relevance of these putative OSCs and data will be presented to show their utility in vitro. Evidence supporting their physiological relevance and potential function will also be discussed.
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