VITROLIFE SCIENTIFIC SYMPOSIUM 2016
“REDUCING TIME TO LIVE BIRTH AND ENSURING THE DELIVERY OF A HEALTHY BABY”

ABSTRACT BOOK
Tuesday 5 July, 10.00 - 11.00
ESHRE 2016, Helsinki, Finland
Chairman: Prof. David K. Gardner
Welcome:
Reducing time to live birth and ensuring the delivery of a healthy baby
Chairman Prof. David K Gardner, University of Melbourne, Australia

Reducing time to live birth by optimising culture conditions – a practical-based holistic view
Prof. Markus Montag, ilabcomm GmbH, Germany

Time-lapse technology in a PGS world – is there room for both?
Prof. Simon Fishel, Founder & President, CARE Fertility Group, UK

How a physiologically based embryo transfer medium facilitates increased live birth rate
Prof. Bulent Urman, American Hospital-Istanbul
WELCOME:
REDUCING TIME TO LIVE BIRTH AND 
ENSURING THE DELIVERY OF A HEALTHY 
BABY

Chairman Prof. David K Gardner, University of Melbourne, 
Australia

With the establishment of reliable and effective culture systems, made possible by the continual improvement of culture media and laboratory conditions, the move to Single Embryo Transfer (SET) is now a reality for all IVF programs. By employing a holistic approach to establishing and running a clinical laboratory, it is not only possible to optimize performance, but also to ensure the functioning of the laboratory remains at its highest level.

With the advent of time-lapse microscopy systems we have entered an era whereby we can visualise embryos throughout development at a frequency otherwise impossible, while also being able to score embryos at times not feasible in working hours. Consequently, it has become possible to detect key morphological events, and to assign distinct temporal weightings to embryo development, making analysis of embryo development significantly more quantifiable, thereby providing the means to deselect clearly abnormal embryos. Furthermore, with the development of suitable algorithms, morphokinetic analysis can now be applied to all patients in an IVF program, making time lapse technology of value in assisting in the selection of embryo for transfer.

A concern for patients, who are typically of advanced reproductive age, is the age-related increase in chromosomal abnormalities in their resultant embryos. Through the implementation of preimplantation genetic screening (PGS), through either blastomere or trophectoderm biopsy, and subsequent molecular analysis, one can not only ensure the transfer of euploid embryos, but also the selection of such embryos for cryopreservation. Combining PGS with time lapse technologies will lead to a greater ability to identify euploid embryos with the highest developmental potential, while the use of morphokinetics data could be used to deselect clearly aberrant embryos that would not benefit from PGS.

All the optimization of laboratory conditions and embryo analysis will be in vain however, lest we are able to successfully transfer the resultant embryo to the uterus and establish high levels of implantation and a healthy pregnancy.
The development of a transfer medium based on maternal physiology, and containing elevated levels of the glycosaminoglycan hyaluronan, has proven to be a valuable means to ensure an excellent outcome at transfer. This has translated not only in higher implantation rates, but in significantly higher take home baby rates.

In this symposium we are delighted to have three international experts in the field of assisted human reproduction who will consider the impact of laboratory conditions, time-lapse microscopy and PGS, and embryo transfer conditions on transfer outcomes. They will demonstrate how together they are helping to reduce the time to pregnancy whilst focusing on the health of the child conceived through ART.

Professor David Gardner did his undergraduate and postgraduate training at the University of York in the UK in the laboratory of Professor Henry Leese. He then spent time as a Fellow at Harvard Medical School with Professor John Biggers, before moving to Monash University in the late 1980’s to work with Professor Alan Trounson. At Monash David worked on methods for the successful culture and diagnosis of human embryos. In 1997 he moved back to the USA where he became the Scientific Director of the Colorado Centre for Reproductive Medicine, established a large research team and was an adjunct Professor at Colorado State University. In 2007 David returned to Australia to take up the position of Chair of Zoology at the University of Melbourne and from 2008 to 2014 he was Head of Department. He is currently a Research Professor in the newly formed School of Biosciences. David has published over 250 scientific papers and chapters, and edited 14 books on embryology and Human IVF.
Reducing time to live birth by optimising culture conditions — a practical-based holistic view

Prof. Markus Montag, ilabcomm GmbH, Germany

Optimising culture conditions requires a thorough understanding of oocyte and embryo physiology as well as insight into good laboratory practice. Oocytes and embryos are considered to show a certain degree of plasticity and to be able to adapt to various environmental conditions. However, problems in the laboratory can accumulate, which will increase the stress factor. Cumulative stress in the laboratory may sometimes be reflected by impaired embryo development. It can equally result in high biochemical pregnancy rates that do not translate into comparable high ongoing clinical pregnancy rates. Consequently, increased early pregnancy loss rates will delay the time to live birth. The importance of optimised culture conditions in the laboratory is relevant for patients as well as for the entire clinical and embryology team. Minimising stress and facilitating an optimal embryo development is the primary tasks of human clinical embryology. Optimisation involves each single step and all aspects that are part of the procedure chain: from dish preparation to retrieval through culture up to transfer as well as temperature, osmolality and pH. The most vulnerable stage in the entire laboratory workflow is follicle puncture, oocyte isolation and insemination. Temperature control and speed of handling is of uttermost importance.

Stress reduction can be achieved by using culture media that are adapted for the specific culture system used and by having a culture system that avoids that embryos have to be removed from the incubator. Rigorous quality control is a must in today’s IVF and this applies to consumables and devices at all stages. The same holds true for monitoring the parameters to which oocytes and embryos are exposed from the very beginning at gamete collection until the final stage of embryo transfer. Last but not least the human factor is important, too. Awareness of the responsibility is required from every team member, as is the recognition, that the success of any IVF program is based on many shoulders.

Dr. Markus Montag started his career at the German Cancer Research Centre in Heidelberg, Germany, where he initially worked in developmental biology. He obtained his PhD in 1992 and then worked as a Post-doc at the National University Hospital in Singapore with Prof SC Ng, the father of the first SUZI baby.

Back in Germany he then joined a private IVF unit as laboratory director before becoming Director of the Reproductive Biology Laboratory at the University Clinics of Bonn in 1995. He was appointed Appl. Professor for Experimental Reproductive Medicine in 2009 and in 2011 he became head of the IVF Laboratory at the University Clinics of Heidelberg. In 2011 he also founded his own company to perform consulting in reproductive biology and medicine on a global scale. Markus left University end of June 2013 and since then works as CEO for his private enterprise, ilabcomm GmbH.

Markus’ research interest is focused on gamete and embryo viability including time-lapse imaging and ovarian tissue banking. He has published more than 200 papers, including over 130 peer reviewed articles and 20 book chapters.
Advances in embryo culture and tools to select embryos appear to have improved the incidence of live birth after IVF. Most scientists now believe that PGS for comprehensive chromosome screening and time-lapse technology with morphokinetic analysis are making a significant difference.

Several groups, including our own have reported that morphokinetics and/or dysmorphic patterns may provide an indication of abnormal chromosomal status whilst others dispute the correlation. However, the morphokinetics of preimplantation development may reflect many aspects of embryonic cell development, from genes to other biochemical and metabolic parameters offering clues to viability in addition to or irrespective of chromosome copy number. Patterns of cleavage and visualization of developmental abnormalities are only detectable by using time-lapse imaging; it is imperative that we understand their clinical context.

Time-lapse, which is non-invasive – indeed more protective of embryo culture in some current forms than conventional incubation - and PGS, which is invasive, are different selection tools. However, it is probable that they will become important and mutually inclusive for embryo selection in a new era of IVF; but in all embryo selection tools for clinical outcome their role needs to be balanced against a clear understanding of the variable patient criteria.

The potential benefit derived from the synergy of PGS and time-lapse technology to further improve clinical outcomes still has to be shown – but the possibilities to complement each other will be presented.
Simon Fishel is the Founder and President of the CARE Fertility Group. He has worked in the field of Assisted Reproduction Technology/Assisted Conception for over 40 years and was part of the original pioneering IVF team with Steptoe and Edwards that produced the World first IVF (“Test tube”) baby. Simon has published over 200 academic papers, four books in the IVF field, established numerous clinics worldwide and was the first to introduce IVF to China in the 1980's as part of a WHO initiative.

His research career began at the University of Cambridge, where he worked for several years with Professor Robert Edwards prior to the birth of Louise Brown, in 1978. During this time Dr Fishel was the first to demonstrate that the embryo ‘communicates’ with its environment; and, later, was the first to publish on the synthesis and secretion of HCG by the human embryo. In 1978 he was appointed a Fellow of Churchill College, Cambridge, became a Cambridge University Lecturer and was awarded the prestigious Beit Memorial Fellowship. In 1980 he became Deputy Scientific Director at the world's first “test tube baby clinic”, working with Robert Edwards and Patrick Steptoe until 1985 when he moved to Nottingham. During the mid to late 1980's Simon was responsible for developing techniques for micromanipulation in ART, leading to the first published birth with sperm microinjection, in 1990; a technology that was the forerunner to what is now the well-established ICSI technique.

More recently Simon has been instrumental in driving the first real time array CGH program in IVF that resulted in the first successful use of egg or embryo chromosome evaluation in 2009, which is now used worldwide, and more recently CAREmaps – the pioneering breakthrough involving time-lapse imaging algorithms. In 2009 Simon was awarded the prestigious Liverpool John Moores University Honorary Fellowship for “outstanding contribution to humanity and science.”
How a Physiologically Based Embryo Transfer Medium Facilitates Increased Live Birth Rate

Prof. Bulent Urman, Koc University School of Medicine, Department of Obstetrics and Gynecology, Assisted Reproduction Unit, American Hospital-Istanbul

The quest for a 100% implantation rate has been going on since the early years of IVF. This albeit being very ambitious, success of IVF gradually increased over the years as evidenced by the national registry reports. Potential patients search for clinics providing higher pregnancy rates, therefore even small increases in success rates count. There is also a growing body of frustrated patients who have gone through many cycles of IVF treatment without success. The management of these patients is unfortunately mostly empirical as treatments lacking solid scientific evidence for their efficacy are offered with a hope to do something different and hopefully beneficial. The problem most probably lies within the implantation process of the embryo that we know very little about. Implantation of a morphologically normal and genetically competent blastocyst may fail mostly due to reasons that we do not acknowledge today.

Hyaluronan (HA) has been introduced to create a specialized embryo transfer medium in order to support implantation. Receptors for hyaluronan (CD44) are expressed in oocytes and early stage embryos. Hyaluronan may directly stimulate the growth of the embryo. Cell–cell adhesion and cell–matrix adhesion has been shown to be increased by hyaluronan. This may facilitate the apposition and attachment of the blastocyst. Several studies have demonstrated increased angiogenesis after administration of hyaluronan. EmbryoGlue has the basic composition of an optimised blastocyst culture medium and contains a high concentration of hyaluronan and recombinant human albumin.

In a prospective randomized trial more than 1200 patients we were able to show the beneficial effect of EmbryoGlue on implantation and pregnancy rates. Overall clinical pregnancy and implantation rates were significantly increased with the use of EmbryoGlue. The beneficial effect was more prominent in women who were >35 years of age, in women who had previous failed cycles, and in women who had poor-quality embryos. In a subsequent analysis EmbryoGlue conferred a statistically significant increase of live birth rates, both in cleavage and blastocyst transfers. A Cochrane
After his residency training in Obstetrics and Gynecology in the University of Hacettepe, Dr Urman completed a 3-year fellowship programme in Reproductive Endocrinology and Infertility in Vancouver, Canada. He returned to Hacettepe University in 1991 and participated in the foundation of one of the first IVF clinics in Turkey. He worked as an Associate Professor until 1996 in the same institution. Dr Urman resigned from the university in 1996 and founded the Assisted Reproduction Unit of the American Hospital of Istanbul, one of the biggest IVF centres in the country. His major areas of interest are clinical assisted reproduction, laparoscopic and hysteroscopic surgery, endometriosis and fibroid research. He has published extensively in these fields, having over 150 articles published in renowned international journals. He has written several book chapters and lectured in national and international meetings. He has served and still serving as associate editor and editor for many international journals. He served as the president of the Turkish Society of Reproductive Medicine between 2007 and 2012. In 2011 he was appointed as a clinical faculty of Obstetrics and Gynecology in the Koc University School of Medicine. He is currently the president of the Istanbul Branch of the Turkish Gynecological and Obstetrical Society.

Review² published in 2014 concluded that clinical pregnancy and live birth rates were improved with the use of functional concentrations of HA as an adherence compound in ART cycles. In conclusion despite the urgent need for more randomized studies, today embryo glue appears to be a viable option in poor prognosis patients undergoing IVF.

