Focus on REPRODUCTION

European Society of Human Reproduction and Embryology // MAY 2013 //

Sir Robert Edwards 1925-2013
End of an era in IVF

- Preventable complications in IVF
- ESHRE ready for London
- IVF in Britain since Louise Brown
29th Annual Meeting of the European Society of Human Reproduction & Embryology

For more information, please visit www.eshre.eu

London, United Kingdom
7 to 10 July 2013
Focus on Reproduction

Chairman's introduction

This is my last contribution to Focus on Reproduction as Chairman of ESHRE, and it is a matter of great sadness to me and the Society that it coincides with the death of Sir Robert Edwards. Bob, along with Jean Cohen, was the founder of ESHRE back in 1984, and we pay tribute to this great man on the following two pages.

In my first introduction to Focus on Reproduction in September 2011 I expressed the wish that ESHRE should develop its role as the reference society among European institutions in reproduction. Now, thanks to the work of the European Tissue and Cells Directive (EUTCD) Task Force, an amendment to the directive for the serological screening of patients has been adopted by the European Commission, we are participating in the EC Coding Working Group, and we have been asked by the Commission to tender for an EU-wide economic overview of tissues and cells for transplantation. ESHRE is undoubtedly the society of ART reference to the EC.

Among other highlights of my two-year term is our collaboration with the ASRM begun by Luca Gianaroli. We have now had two successful meetings on the ‘Best of ASRM and ESHRE’ and a third is in preparation. As an embryologist I am also happy to note that the Atlas of Embryology is now in place as an important reference in the field, and that a pilot e-learning programme in embryology is in progress. The working group in culture media has continued its work and is now preparing an ambitious research programme for approval by the Executive Committee. And most recently the SIG Reproductive Surgery has put in place a programme of ESHRE Certification for Reproductive Endoscopic Surgeons (ECRES), which will be launched in London. This programme in reproductive surgery follows ESHRE’s successful embryology certification scheme which, since its inception in 2008, has already certified more than 800 embryologists.

As ever, the end of term brings changes to the Executive Committee and, if approved at the AGM in London, we will welcome five new members to the committee and Kersti Lundin as Chairman Elect. So let me end by saying that it has been an enormous pleasure to serve the Society these past two years and I thank the Executive Committee and especially the Central Office for making my task such a privilege! I will continue for two more years as Past Chairman and will contribute as much as possible for the benefit of the Society. In my home country we say: ‘Hasta pronto! Fins aviat!’ I’ll see you in London!

Anna Veiga
ESHRE Chairman 2011-2013
OBITUARY

Professor Sir Robert Edwards 1925-2013
Joint founder of ESHRE, the ‘father of IVF’

Although not unexpected, news of the death of Professor Sir Robert Edwards was met with great sadness by ESHRE; no-one had done more to give life to the fledgling Society and shape its formative years. Once established, ESHRE grew to become the world’s foremost society in reproductive science and medicine, and, in such growth and influence, a tribute to his foresight and dedication.

It was Edwards, along with the French gynaecologist Jean Cohen, who founded ESHRE in 1984; as developments in assisted reproduction gathered momentum around them, both were determined that European clinicians and scientists should have their own society and journal where their work could be shared and judged. ESHRE would become that society, and *Human Reproduction* that journal.

In a public statement issued shortly after his death, Anna Veiga, Chairman of ESHRE, said: ‘Bob was a tireless and inspirational leader in reproductive medicine, and it’s fair to say that the infertility treatments we have today would not have been so widely and successfully applied without his direction. It was also Bob who laid down the statutes which govern ESHRE’s organisation and define its constitution today. We will remember him for many reasons, but mostly for his sympathetic ear, his constant encouragement and of course his remarkable achievements in human biology. Without Bob’s scientific foresight and care for the infertile couple, the treatments of assisted reproduction would never have gained the universal acceptance they have today.’

The final recognition of Edwards’s remarkable influence in reproductive medicine came in 2010 when he was awarded the Nobel Prize for Physiology or Medicine, the Nobel Assembly noting that his vision had become a reality which ‘brought joy to infertile people all over the world’. Calculations made last year indicated that there are now 5 million IVF babies in the world, and they each reflect the sacrifices Edwards made to establish IVF as a legitimate treatment in world medicine.

The story of Edwards and Steptoe’s pioneering work in *in vitro* fertilisation, which culminated in the birth of Louise Brown in July 1978, has been well told... appeals for funding rejected by the British establishment, long journeys from Cambridge to the small hospital in the north of England where the gynaecologist Steptoe had a source of oocytes retrieved laparoscopically from his gyn patients, and many failed cycles. By 1977 Edwards and Steptoe had endured five years of criticism and clinical failure.

But later that year a blastocyst cultured from the leading follicle of a natural cycle was transferred back to Lesley Brown in a procedure which was to redefine the shape of reproductive medicine. The birth of Louise caused a sensation, not just because of its scientific achievement but because of the ethical challenges it raised (though Edwards never shrank from meeting the ethical difficulties his work created). Even the Nobel Assembly’s announcement of Edwards’s prize in 2010 noted that his research ahead of the birth of Louise ‘became the topic of a lively ethical debate that was initiated by Edwards himself’. These were the battles which Edwards and Steptoe had to fight: accusations that their work was ‘unethical’, grant refusals on the grounds of immorality. Indeed, for many of the other ESHRE pioneers of the early 1980s consensus on the ethics of assisted reproduction was an important reason for their involvement.

Robert Geoffrey Edwards was born into a working-class family in the county of Yorkshire in England in September 1925. He had a straightforward education, with a degree in biology from the University of Wales, followed by a PhD in genetics from Edinburgh, which had already established a strong tradition in reproductive sciences. After short spells at the California Institute of Technology, the Medical Research Council in London, and Glasgow University, he moved to Cambridge in 1963 as a research fellow in the Department of Physiology and a member of Churchill
Robert Edwards was a great man, a prophetic scientist and, for me, a real friend. IVF for him was both a wonderful and frustrating experience - and one which he had to defend against those reluctant to accept fundamental change. We all miss him and, from my side, I will never forget his smile.

Pier Giorgio Crosignani, ESHRE Chairman 1989-1991

I was very close to Bob for 15 years and have too many memories to recall them all. But I can say that he was a great teacher, able to explain complex issues to anyone with even a passing interest. He was persistent in his arguments that his work in human biology had sound ethical values and was of immense benefit to those who could not conceive spontaneously. Yet even with fame he remained humble, and committed to his political conviction that the inequalities of the world should be addressed.

André Van Steirteghem, ESHRE Chairman 1991-1993

He was a man of extraordinary scientific knowledge with the vision to foresee IVF, PGD, IVM and stem cell research - and vision too to be the founder of ESHRE and of four outstanding journals. I feel privileged to have enjoyed his friendship.

Klaus Diedrich, ESHRE Chairman 1993-1995

Bob was both an excellent scientist and self-confessed stubborn Yorkshireman; it was this combination which gave him the tenacity to develop successful human IVF in the face of so many obstacles. His subsequent involvement in ESHRE and its three journals has had an equally lasting impact. He was a great man and will be sorely missed.

Lynn Fraser, ESHRE Chairman 1999-2001

Leaving through Bob’s brilliant 1980 monograph Conception in the human female it suddenly dawned on me that everything was here already - fertilisation and cleavage in vitro, sperm capacitation, fertility in older mothers, donor oocytes, stem cells, reproductive cloning, surrogacy, blastocyst transfer, mild stimulation, IVF in the natural cycle, PGD, GIFT, IVM, the ethical debate. In 1980! Remarkable . . .

Hans Evers, ESHRE Chairman 2001-2003

It often crossed my mind that we would never see his like again. He had a deep understanding of the basic biology of reproduction, but also knew the technical intricacies of the IVF lab. His immense knowledge and status could easily have made him aloof and distant, but not Bob. He was always open and friendly, ready to guide all newcomers in their early careers in reproduction.

Anne Sunde, ESHRE Chairman 2003-2005

I remember attending a lecture Bob gave at Leiden University in 1974 when I was a PhD student. He talked with enthusiasm about IVF, but the vast majority in the audience didn’t accept it and reacted scornfully. Only four years later Louise Brown was born - and today no fewer than 5 million children. For me he has always been the icon of reproductive biology.

Joep Geraedts, ESHRE Chairman 2007-2009

He was above all an outstanding scientist. Having had the chance to collaborate with him since the early days of ART, I can add that he was also a great man. His dedication, intelligence, his way of working and bright personality made him a larger-than-life figure, able to inspire all who met him, especially young scientists. I was completely captivated by his charisma and the way in which he explained extremely difficult and new concepts as if they were the most obvious thing in the world. I still remember receiving his comments on the first papers I sent to Human Reproduction. They filled me with pride and gave me the enthusiasm to move forward with my research. He set an example to all professionals working in our field, stimulating curiosity and innovation as well as persistence and dedication.

Luca Gianaroli, ESHRE Chairman 2009-2011

College. It was from his lab in Cambridge that much of the groundwork for IVF was done, and where many students were trained. His funeral took place in the chapel of Churchill College on 26th April.

The death of Robert Edwards brings to an end the pioneering era of IVF. With 5 million babies born, IVF clinics in most corners of the world, and universal public acceptability, there are few today who need fight the battles which Edwards himself fought three decades ago. Yet the circumstances of today are those which were shaped by his determination and vision, and no one man has done more - or ever will do more - to secure the place of IVF in modern medicine. ESHRE too owes its role in training, data collection and scientific publication to Bob Edwards. For who among those early members of the ‘temporary committee’ of 1984 could possibly have foreseen the impact which ESHRE and its journals would make over the next 30 years? His death will leave a gap which can never be filled, but the progress of the Society (and of reproductive medicine itself) bear rich testimony to the legacy he leaves behind.
From a total of 1589 abstracts submitted before the 1st February deadline for this year’s annual meeting, 223 have now been selected for oral and 600 for poster presentation, an acceptance rate for the oral sessions of just 14%. Abstract acceptance for the ESHRE congress is now tougher than for *Human Reproduction*, such is the scientific quality on offer.

As the list opposite indicates, embryology was yet again the most popular abstract topic, with 351 abstracts submitted. Close behind were reproductive endocrinology, andrology, female infertility and the endometrium. The majority of abstracts were submitted for either oral or poster presentation. As expected, most of the abstracts (969) were submitted from European countries, but there were in addition a healthy number from Asia (372) and the Americas (180). There is little doubt now that this is a truly international meeting.

As host country, the UK submitted most abstracts (157), closely followed by Spain (152), Italy (107), Turkey (89) and Japan (87). Notably, 69 were received from the USA, 68 from Brazil and 64 from South Korea.

All abstracts were reviewed according to our standard procedure of screening and scoring. Screening aims to ensure that abstracts are designated to the correct topic.
Focus on Reproduction  May 2013

Getting around London . . . and to and from the ExCeL congress centre

The main link with ExCeL is via the Docklands Light Railway (DLR), with nearby stops at Custom House and Prince Regent. The DLR is accessible from Central London via the new Jubilee Line, the only line on the London Underground with direct connections to every other line. Jubilee Line trains run every two minutes at peak times, so making connection with the ExCeL and all corners of London quick and efficient. Or if rail links prove too dull, you might also try the Emirates Air Line cable car, with a crossing every 30 seconds between the O2 south of the river Thames (Greenwich Peninsula) and the ExCeL centre, or the river services of Thames Clipper (which runs right to the O2, with cable car connection to the ExCeL).

Best travel tip is to ignore the famous London taxis (great for short trips) but to use public transport for all travel to and from ExCeL. A travel Oyster card can be bought at all Underground stations or online at www.tfl.gov/visitorshop.

As in recent years posters will be presented electronically, but each presenter has also been offered the opportunity of a paper poster. These traditional posters will be presented in the Poster Village, according to special interest subject, as was done last year. Each day, discussion committees will assess the paper posters only, so authors should be prepared for discussion and a brief presentation; the time allocated to each presenting author will be restricted to two minutes only and thereafter three minutes will be available for discussion. Poster discussion schedules will be available in London. However, all authors whose abstracts have been accepted for poster presentation will be asked to submit their work electronically for on-screen availability.

As ever, the meeting will begin with a day of 15 precongress courses on Sunday 7th July, before the three-day scientific programme begins the next day. Sunday’s Opening Ceremony which follows the precongress courses will formally introduce the meeting and this year’s honorary members, Outi Hovatta and Allan Templeton. After the ceremony everyone will have the chance to mingle in the exhibition area. Attendance at the Opening Ceremony and welcome reception are complimentary. The two other official social events are the congress party, to be held this year at the famous Science Museum across town in Kensington (at 8.30 pm on Tuesday 9th July) and the closing and award ceremony on the final afternoon.

Participation in Tuesday’s congress party, which will include a buffet dinner with entertainment, is optional and tickets for this unique event will be €120 per person.

Six presentations will be selected for awards this year, with a prize of €2000 to each winner. One additional presentation will be selected for the annual Fertility Society of Australia Exchange Award, whose winner presents the work at the next FSA annual meeting in Australia. Special award committees make the selection for each award. Awards for oral and poster presentations are available for basic science and clinical science, with additional awards available for the best oral presentation by a nurse and the best oral or poster presentation made by a laboratory technician.

Those without accommodation reserved so far should make hotel reservations through ESHRE’s appointed agent MCI Stockholm via the ESHRE website, where online hotel reservation forms are available (http://www.eshre2013.eu/Plan-Your-trip/Hotel-accommodation.aspx).

2015 annual meeting heads to Lisbon

ESHRE’s 2015 annual meeting will be held in the Portuguese capital city of Lisbon at the Parque das Nações Congress Centre. Dates for your diaries are 14-17th June 2015, a little earlier than recent years, but dates still guaranteed to enjoy the early summer weather. ESHRE’s main local representatives for the meeting will be Executive Committee member Carlos Calhaz-Jorge and chairman of the Embryology Certification Committee Carlos Plancha. As ever, the three-day meeting will be preceded by a day of precongress courses, on Sunday 14th June.
END OF TERM FOR EIGHT MEMBERS OF ESHRE’S EXECUTIVE COMMITTEE

General Assembly to ratify five new nominations

With eight members of ESHRE’s present Executive Committee due to stand down in London having completed their membership terms, replacements have been nominated for ratification at this year’s Annual General Assembly held during the annual meeting. Leaving the ExCo after two terms of office will be Ursula Eichenlaub-Ritter, Antonis Makrigiannakis, Miodrag Stojkovic, Anne-Maria Suikkari and Etienne Van den Abbeel; Milan Macek has decided to step down after one term of office, while Françoise Shenfield has completed her ex officio duties as Co-ordinator of the Special Interest Group & Task Force Sub-committee. She will be replaced by her present deputy Timur Gürgan. Also leaving will be Luca Gianaroli, whose term as Past Chairman will come to an end in London.

Rejoining the ExCo as Chairman Elect of the Society will be the Swedish embryologist Kersti Lundin, who, as a scientist, will take over as ESHRE Chairman in 2015 from the clinician Juha Tapanainen. Tapanainen will become Chairman in London, when Anna Veiga concludes her term of office. Kersti Lundin already has a long record of activity in ESHRE, both in the Executive Committee between 2005 and 2009 and in the SIG Embryology, of which she is presently co-ordinator. She took a major hand in the organisation of ESHRE’s annual meeting in Stockholm in 2011 and has, before and since, organised many training events in Sweden. Kersti was also one of the founders of ESHRE’s certification programme for embryologists, which since its inauguration in 2008 has seen almost 900 embryologists certified at the senior or clinical level. She was co-ordinator of the certification committee from 2007 to 2010.

Kersti is currently laboratory director in reproductive medicine at the Sahlgrenska University Hospital in Gothenburg. She is a popular lecturer and a former associate editor of Human Reproduction.

The five nominations for appointment to the ExCo are Petra De Sutter (BE), Andres Salumets (EE), Grigoris Grimbizis (GR), Tatjana Motrenko (ME) and Georg Griesinger (DE). Their appointments must be ratified by the General Assembly in London before they take up their positions. Renewing their membership of the ExCo for a second two-year term - as allowed under the Society’s rules - are Carlos Calhaz-Jorge (PT), Jacques de Mouzon (FR), Roy Farquharson (GB), Anis Feki (CH), Niels Lambalk (NL) and Cristina Magli (IT).

The process by which the five new nominees were selected for ExCo membership is clearly set out in the Internal Rules of ESHRE, whose first draft was approved by the ExCo in 2008. The rules state that the nominees for new ExCo membership are selected from applications by the ExCo still in office to replace those members whose term will come to an end. The process requires all pre-selected candidates to submit a CV and a statement on how they view their role within the Committee. Candidates are asked to attend an ExCo meeting for presentation of their views and for interview. Each candidacy is discussed by the ExCo in the candidate’s absence before a decision is made. The rules additionally state that, ‘while selecting new candidates, the aim should be to maintain a balance within the final composition . . . between clinicians and basic scientists, male and female’. Selection also aims to ensure that those countries comprising ESHRE’s greatest membership are represented in the ExCo. The rules, however, add that ‘there cannot be more than one member from the same country in the Executive Committee with the right to vote’, unless one of two members from the same country holds the position of Chairman Elect.

‘What we’re aiming for is quality and fair representation,’ says outgoing Chairman Anna Veiga.
The Finnish gynaecologist Juha Tapanainen will become Chairman of ESHRE in London, taking over from Anna Veiga to serve a two-year term until 2015. After more than 30 years at the University of Oulu, Juha has recently become Professor of Obstetrics & Gynecology at the University of Helsinki. He is a former member of ESHRE's Executive Committee and of the SIG Reproductive Endocrinology. He describes his scientific interests as ovarian apoptosis and oocyte physiology, and is well known for his clinical work in single embryo transfer.

Petra De Sutter is Professor of Reproductive Medicine at the University of Ghent, Belgium. She is a well known speaker at international congresses and ESHRE training events, and is currently Co-ordinator of ESHRE's SIG Safety & Quality in ART. Petra is a gynaecologist who is also certified as a senior embryologist in ESHRE’s certification scheme. Her publications and research projects in IVF are considerable.

Andres Salumets is Professor of Reproductive Medicine in the Department of O&G at the University of Tartu, Estonia. With more than 20 years' experience in embryology, he lists his research interests as genomics and the epidemiology, diagnosis and treatment of infertility. He is currently engaged in a research project on endometrial dysfunction funded by the Eureka’s Eurostar programme.

Grigoris Grimbizis is Associate Professor in the Department of Obstetrics and Gynecology of Papageorgiou General Hospital, Aristotle University, in Thessaloniki, Greece. He has a long history with ESHRE, dating back to the 1993 annual meeting in Greece. Grigoris is currently Deputy Co-ordinator of the SIG Reproductive Surgery and an active member of ESHRE’s working group for certification in reproductive surgery.

Tatjana Motrenko Simic is Head of the Human Reproduction Department of Hospital Danilo in Cetinje, Montenegro and is a founder and currently President of the Montenegrin Society for Human Reproduction. She is a member of ESHRE’s EIM Consortium. Her clinical interests are reproductive endocrinology, epigenetics, and implantation failure. Tatjana was one of the authors of Montenegro’s 2009 legislation for ART.

Georg Griesinger is Head of the Department of Gynecological Endocrinology and Reproductive Medicine at the University Hospital, Lübeck, Germany. He is a past associate editor of Human Reproduction (2008-2012), and is presently Co-ordinator of ESHRE's SIG Reproductive Endocrinology. His research and lecturing commitments are considerable, and he is a member of the WHO’s guideline development group on infertility.

Selected candidates for new membership of the Executive Committee 2013-2015

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Agenda of the 2013 Annual General Assembly

To be held on Tuesday 9th July 2013, from 18.00 to 19.00, at the ExCel Centre, London, venue of the 29th annual meeting.

1. Minutes of the last meeting (held in Istanbul and published in Focus on Reproduction, September 2012)
2. Matters arising
3. Membership of the Society
4. Society activities
   - Annual meetings
   - Campus meetings
   - Special Interest Groups and Task Forces
5. Human Reproduction journals
6. Paramedical Group
7. Financial report
8. Ratification of the new Executive Committee
   - Kersti Lundin (SE) to become the new Chairman Elect
   - Ursula Eichenlaub-Ritter (DE), Antonis Makrigiannakis (GR), Miodrag Stojkovic (RS), Anne-Maria Suikkari (FI), Etienne Van den Abbeel (BE), Milan Macek (CZ), Luca Gianaroli (IT) and Françoise Shenfield (GB) to step down
   - Carlos Calhaz-Jorge (PT), Jacques de Mouzon (FR), Roy Farquharson (GB), Anis Feki (CH), Niels Lambalk (NL) and Cristina Magli (IT) to be re-appointed for a second term of two years
   - Petra De Sutter (BE), Andres Salumets (EE), Grigoris Grimbizis (GR), Tatjana Motrenko (ME) and Georg Griesinger (DE) to be appointed as new members
9. Retirement of the Chairman, Anna Veiga (ES), and installation of the new Chairman, Juha Tapanainen (FI)
10. Election of the Honorary Members for 2014
11. Any other business
12. Date of the next Annual General Assembly
ANNUAL MEETING 2013
// OPENING CEREMONY //

Honorary ESHRE membership for
Outi Hovatta and Allan Templeton

This year’s new honorary members, whose awards will be made during the Opening Ceremony in London, are Outi Hovatta, Professor of Obstetrics and Gynaecology at the Karolinska Institute, Stockholm, and Allan Templeton, Emeritus Professor of Obstetrics and Gynaecology at the University of Aberdeen, UK.

Allan Templeton stepped down as Regius Professor of Obstetrics and Gynaecology at the University of Aberdeen in 2007 after more than 20 years in the post. Throughout the three previous years he had been President of the Royal College of Obstetricians and Gynaecologists and was by then, as head of the Aberdeen Fertility Centre, a distinguished figure in reproductive medicine. He became Professor Emeritus at the University in 2012 and continues as Clinical Director of Audit and Research at the RCOG. His long association with the Human Fertilisation and Embryology Authority, the UK’s statutory regulator of ART clinics, began in 1994 and lasted until 2000.

With all UK clinics legally required to give details of every cycle (and its pregnancy outcome), the HFEA database was a fertile ground for investigation, and Templeton’s 1996 report on the predictability of baseline characteristics in IVF would prove a landmark study in outcome modelling. The study was based on more than 52,000 cycles reported to the HFEA, and, even in a 2009 review, this predictive model was still deemed ‘of good performance’. In 1998 a further study of 44,000 cycles from the HFEA database, published again with Joan Morris, showed that older age, tubal infertility, longer duration of infertility, and a higher number of previous IVF attempts were all associated with a significantly decreased chance of live birth - but, importantly, that the chance of live birth was not diminished by the transfer of only two embryos in women with more than four available. Transferring more embryos only increased the risk of multiples.

With the evidence of the HFEA database behind him, Templeton became a forceful critic of multiple pregnancies in IVF and led the recommendation of the RCOG that no more than two embryos should be transferred in women under 40. In 1998 a further study of 44,000 cycles from the HFEA database, published again with Joan Morris, showed that older age, tubal infertility, longer duration of infertility, and a higher number of previous IVF attempts were all associated with a significantly decreased chance of live birth - but, importantly, that the chance of live birth was not diminished by the transfer of only two embryos in women with more than four available. Transferring more embryos only increased the risk of multiples.

With the evidence of the HFEA database behind him, Templeton became a forceful critic of multiple pregnancies in IVF and led the recommendation of the RCOG that no more than two embryos should be transferred in women under 40. Although in a Human Reproduction editorial in 2000 he noted that multiple pregnancy in much of the UK had become a ‘something of a side issue’, he continued to promote the concept of healthy singleton deliveries, a trend which is only now becoming evident in the HFEA’s database.

Outi Hovatta is Professor in O&G, ‘especially Assisted Reproduction’, at the Karolinska Institute in Stockholm and chief physician in the fertility unit of Karolinska University Hospital Huddinge. Her illustrious career in reproductive medicine and science began in her native Finland, where from 1986 to 1997 she was head of the Family Federation of Finland fertility clinic in Helsinki, Finland’s largest centre. It was from a retrospective analysis of one year’s IVF at the clinic (published in 1999) that Hovatta and colleagues showed for the first time that elective single embryo transfer ‘can be highly recommended’, especially in subjects under 35. From there on, the Nordic countries embraced the concept and the data began to accumulate.

In 1998, after a two-year visiting professorship at the Hammersmith Hospital in London, Hovatta moved to the Karolinska in Stockholm to continue her studies in IVF. One strong area of research since then has been the in vitro maturation of oocytes and the cryopreservation of reproductive tissue (from men and women) for fertility preservation ahead of cancer treatment. From 2001, in a further development of interest, she began the creation of human embryonic stem cell line (Sweden’s first) and, more recently, of induced pluripotent stem (iPS) cells derived from somatic sources, all for regenerative medicine. Her group has recently established several animal substance-free feeder-cell-free hESC lines in chemically defined conditions, and is approaching the first clinical trials.

Hovatta was a founder member of the Low-cost IVF Group, working with ESHRE’s Task Force on fertility treatments for developing countries.
Predictability in blastocyst morphology

Appearance of trophectoderm cells found to be ‘most important’

The opening keynote lectures at ESHRE’s annual meeting have quickly established a tradition of breaking the all-comers attendance record at any ESHRE event. Last year in Istanbul around 4000 packed the auditorium for Sonya Desmyterre’s Human Reproduction lecture on the safety of blastomere biopsy in PGD. This year’s lecture, following the presentations of Laura Rienzi in 2011 (on oocyte vitrification) and Gayle Jones in 2010 (on DNA fingerprinting), returns to the IVF lab with a study from Aisling Ahlström and colleagues at Carlanderska Hospital in Gothenburg on the morphological parameters for predicting blastocyst viability. The paper had the highest number of full-text downloads during the first six months of publication of all original articles published in Human Reproduction between January 2011 and June 2012.

The study was a retrospective analysis of 1117 fresh single blastocyst transfers and their live birth outcome related to each of three morphological parameters: degree of blastocoele expansion and appearance of both the trophectoderm and inner cell mass.

‘We began thinking about the study in 2009,’ Ahlström recalls, ‘at a time when we - and many others – were re-evaluating the morphological criteria for blastocyst selection and even ranking their importance. We were looking at all three parameters but were not sure which, if any, was more important in the context of viability. Of course, we were not the first, but because we’d been performing single blastocyst transfer for a number of years we had the advantage of a large study group.’

Against their expectations, and following a complex logistic regression analysis with adjustment for known confounders (such as female age and FSH dose), results showed that all three parameters had a significant effect on live birth, but that the number and cohesiveness of trophectoderm cells were found to be the most important morphological predictor of live birth. Indeed, in the analysis the predictive power of trophectoderm appearance was so strong that it offset the effect of both blastocoele expansion and grade of inner cell mass.

‘The results were unexpected,’ admits Ahlström, ‘because we - like other groups - always assumed that the size and compactness of the inner cell mass would give us the most information about viability. After all, it’s from the inner cell mass that the fetus develops. But now, even though inner cell mass is important, a strong trophectoderm layer seems to provide more predictive information at this stage of development.’

In the statistical analysis grade A trophectoderm cells had a 49.9% chance of delivery and grade B a 33.9% chance, a highly significant difference. ‘Now,’ says Ahlström, ‘we’re not afraid to transfer blastocysts with lower grades of inner cell mass and prioritise higher grades of trophectoderm.’

The same predictive analysis has recently been applied to frozen–thawed blastocysts, with similar results. Blastocele expansion and trophectoderm grade were found to be the most significant predictors of delivery in the pre-freeze assessment, and degree of re-expansion post-thaw. The odds of live birth increased by around 36% for each grade of blastocoele expansion and decreased by 29% for blastocysts with grade B trophectoderm compared with grade A.

Ahlström admits that all these retrospective results should ideally be confirmed in a randomised trial, but so far that study has not been planned, at least in Gothenburg. There, they too have turned attention to time-lapse imaging and have invested resources in a trial of morphokinetics.

Nevertheless, despite the pressure of such hi-tech introductions to the IVF lab, Ahlström still recognises the lasting value of morphology in embryo selection. ‘The new techniques are the future,’ she says, ‘but they are expensive and right now seem more attractive to those clinics willing to invest and compete. But, even if we do eventually adopt microarrays, metabolite profiling and time-lapse technology, I think morphology will always be useful, especially if we can understand the predictive value of each parameter and prioritise those of highest value.’

ESHRE in a ‘sound financial position’ despite the difficulties of recent years

Income from 2012 annual meeting increases, some costs cut

The report of the finance subcommittee to be presented at the annual meeting in London will show a final balance of €1,048,712.19 for 2012, a strong result in what was a difficult year.

The balance was in large part due to the increased income of the annual meeting, which now accounts for 71% of the Society's revenue (see the chart opposite). Although income from ESHRE's journals decreased slightly, it still accounts for 13% of the Society's revenue. By contrast, there were slight increases in income from membership fees, financial investments and Campus meetings, which – all in all – led to an increase in income of €1,364,592.45 over 2011.

Increases in expenditure were kept as low as possible, with only a relatively higher increase in costs for the annual meeting in Istanbul (up by €276,774 compared with 2011) and minor increases in other areas of activity. In a few instances (eg, press and communications, Task Force activities) a decrease in expenditure was noted.

Thus, the Society finds itself in a very sound financial situation, with about €4 million now invested - mainly in bonds - with Van Lanschot Bankers. Although the return on investments has been low, it is salutary to keep in mind that this conservative approach has saved ESHRE from substantial financial losses over recent years, which – needless to say – have been very bad years for many investors. The Executive Committee has agreed that €5 million now accumulating in a short term savings account should also be invested in a longer term portfolio, thus ensuring a greater spread of risk.

The budget for 2013 also plans for an income surplus over expenditure of around €1 million, with the same 55% of expenditure allocated to the annual meeting in London, and almost 20% to the activities of the SIGs.
Run for fun . . . and for charity in London

A 5 kilometre charity run organised by ESHRE has been added to this year’s social programme. This new event has been scheduled for Monday 8th July, when runners (of all shapes and sizes) will gather in front of the East Entrance of the ExCeL congress building at 6.00 pm. The run will follow a course around the old docklands area of London and is a great opportunity to discover the riverside areas.

Registration for the run is €20 and all funds collected will be transferred to our partner patient organisation Fertility Europe to support their promotion of equal access to fertility care throughout Europe. For registrations and more information go to www.eshre2013.eu/run

A mobile app for London

Once again, you can go paperless at ESHRE with the 2013 mobile app congress programme. Whether on the move or in the bar, the full programme and abstracts can be yours at your fingertips, and easily browsed on smartphones and tablets.

New features this year include a photo-sharing platform, and facility to rate the sessions and ask questions to the speakers.

The app will be free and available from the iTunes and Play Stores from 15th June onwards. A web-based version will also be available for users of Blackberries and Windows. You can use the QR code alongside for speedy download.

Poster presenters to have their say at Speakers Corner

Poster presenters at this year’s annual meeting will have their very own ‘Speakers Corner’ where they can defend their work in a lunchtime session of short presentations.

All presenters of posters selected in advance for awards in the clinical or basic science categories will be asked to prepare their work as a paper (as well as electronic) poster and be ready to summarise it in three minutes at the lunchtime session. The 45-minute sessions will take place on each day of the congress, and each will feature ten short presentations.

The poster award winners will be chosen from these presentations. A prize of €2000 is available for each. Each of the three ten-poster sessions will be completed with the addition of presentations from those who simply wish to defend their work in a short oral session. This first-time opportunity is available to all poster presenters, but must be applied for in advance to ESHRE’s Central Office.

‘I’m sure there will be many poster presenters who believe their study was worthy of oral presentation,’ says Programme Committee Chairman Anna Veiga. ‘Well, now they have a chance to tell the committee why and to defend their work. It’s only three minutes, but you can say a lot in a short time.’

Around 600 posters have been selected for London, all of which will be available electronically in the poster area. However, all of those selected will also be given the opportunity of paper presentation in the Poster Village - as well as at Speakers Corner in this short oral session.

Presenters with paper posters are encouraged to be at their poster boards during the coffee breaks to answer browser questions.
NEWS FROM EUROPE

European court confirms legality of PGD in Italy

An appeal by the Italian authorities against a European Court of Human Rights ruling which upheld the rights of an Italian couple to PGD has been turned down by the Strasbourg-based Court. As a result, the Court has effectively confirmed (as ‘definitif’) that couples in Italy at risk of passing on inherited diseases now have the right of access to PGD. The decision, said the Court, which was delivered in February, was in line with the European Union’s charter of fundamental human rights.1

Italy’s appeal followed a Court ruling of August last year which found that Italy’s legal restrictions on the use of PGD to detect genetic abnormalities in embryos was in violation of the rights of an Italian couple. The case before the Court concerned a fertile Italian couple who were healthy carriers of the cystic fibrosis gene mutation and wished, with the help of PGD, to avoid transmitting the disease to their children. Their first child had already been born with cystic fibrosis.

Italy’s Law 40, approved by Parliament in 2004, had outlawed PGD along with embryo freezing and embryo research. However, changes to the law following a Supreme Court ruling in 2009 allowed the reintroduction of PGD, but only in infertile couples. Thus, fertile couples carrying genetic diseases - who comprise the majority of PGD patients - were still denied treatment.

Passing its judgement last year, the Court concluded that Italy’s ‘interference’ with the applicants’ right to respect for their private and family life was ‘disproportionate’. The Court also noted the inconsistency of an Italian law which on the one hand denies a couple access to embryo screening but on the other allows the termination of a pregnancy if the foetus shows symptoms of the same disease.

In its appeal, the Italian government had once again tried to justify its ban on PGD on the grounds that it was necessary to protect the health of the mother and child and avoid any risk of eugenic abuses. But the Court of Human Rights, pursuing a long and complex chain of precedents, was not persuaded.

‘We hope this is now the end of the matter and Italian clinics in Italy can once again provide PGD to couples who need it,’ said former ESHRE chairman Luca Gianaroli. ‘This is yet another successful legal challenge to Law 40 of 2004. We opposed it then, and continue to oppose what’s left of it today.’ In 2009, the requirement to fertilise a maximum of three oocytes in IVF was declared unconstitutional by Italy’s own Supreme Court, and some concessions were made to embryo freezing.


One cycle of funded IVF for Moscow citizens - in public or in private centres

Moscow’s public purse will fund one cycle of IVF for each of the city’s 2500 couples awaiting fertility treatment at the start of 2013. The move, according to the Russian newspaper Izvestia, was proposed as part of Moscow’s basic compulsory health insurance programme, and will allow Muscovites to choose treatment in the city’s private centres.

IVF specialists were quoted as saying that the move will reduce waiting-times in Moscow and give patients greater freedom of choice. Izvestia reports that at the moment there are only two state-run clinics offering free IVF in Moscow, including the Family Planning and Reproductive Centre, the city’s largest public fertility clinic. The funding move is thus likely to bring many of the city’s private clinics into the health insurance scheme.

However, there was criticism reported from experts who said that funding restricted to just one cycle would inevitably force many patients back into the burgeoning private sector.

In October last year, MD Medical Group, a Russian private healthcare company which includes the Mother and Child chain of clinics, was floated on the London stock exchange with an offer value of around $900 million.
Outline programme for nurse certification
Hands-on workshop in trophoderm biopsy for lab technicians

Nurse certification project
The working group assessing the feasibility of nurse certification by ESHRE has started development of an outline programme which reflects the knowledge and skills needed to fulfil the many nursing roles within a fertility clinic. Our aim is to set up a framework for nurses which defines all the competencies and role requirements for ART nurses in Europe. It is our aim that a comprehensive certification scheme will upgrade and preserve the quality of care given by nurses.

We are agreed that the competency of the ART nurse must be evaluated at appropriately specified stages with assurance that each individual nurse has an adequate knowledge and understanding of the scientific, technical and theoretical processes and principles relevant to their designated tasks.

To achieve formal recognition and to increase the quality of care, we have to define levels of knowledge and professional standards at a practical and theoretical level; the latter will be reflected in a curriculum and tested by multiple-choice examination.

Fertility preservation - the next frontier is our precongress course in London this year. This is an advanced course for nurses and lab technicians considering a wide range of hot topics in fertility preservation. The course will consider the ethical issue of social freezing, counselling for social freezing, oocyte banking, and fertility preservation for women affected by malignant diseases. The course will also give the participants the chance to see different devices for oocyte vitrification.

Introducing new techniques to the lab is a Campus symposium scheduled for 4-5th October in Barcelona arranged by the Paramedical Group and SIG Embryology. With new techniques being continuously introduced, often without proper education and validation, our aim is to give participants a framework for setting up such new techniques such as vitrification, DNA and chromosome analysis, and time-lapse imaging, as well as the theoretical background of how to analyse, evaluate and compare results between different methods. The target audience for this symposium is mainly paramedical, and clinical and senior embryologists with working experience in ART laboratories looking to understand the relevance and application of advances in cell biology and genetics and apply good clinical practice.

Our precongress in Munich 2014 is titled Targeting and managing special patient groups, which will include a hands-on session on trophoderm biopsy. This advanced course aims to give a practical update to current theoretical background on treating patients with endometriosis, genetic disorders and recurrent miscarriage. The course will also have an interactive session on counselling which focuses on nurses and midwives working in a fertility clinic. For those working in the lab there will be a practical demonstration of trophoderm biopsy - covering pretreatment of the embryo, timing of the biopsy, co-ordinated use of laser and micromanipulator, and tips for the most convenient biopsy. Techniques will be demonstrated on mouse blastocysts.

Basic training workshop for paramedics working in reproductive health
Following the success of our basic training course in Manchester, Valencia, Berlin and Copenhagen, the PMG board has agreed to update the course regularly and export it to different European countries. This is now a two-day course for paramedics new to reproduction who wish to improve their basic knowledge of the underlying causes, treatments and psychological aspects of infertility. Next year's course will be held in Paris in May.

Helle Bendtsen
Chair Paramedical Board
ESHRE NEWS

// CAMPUS MEETING: PARAMEDICAL GROUP and SIG SQART //</p>

Time-lapse ready for prime time (almost)

Campus meeting reviews the validation necessary for new introductions to the IVF clinic; results from time-lapse imaging trials are due before year’s end

The short history of IVF is littered with abandoned techniques which, when introduced, seemed like a good idea at the time. Some, like GIFT or SUZI, were simply superseded by improved techniques to arrive at the same end point. Others, however, despite the promise of hypothesis and observational data, did not withstand the test of a randomised clinical trial.

Aneuploidy screening by FISH, for example, was introduced into many IVF programmes (especially in the USA) on the back of retrospective uncontrolled studies; yet today, 13 randomised trials have failed to show any benefit, and PGS with FISH and cleavage-stage biopsy is quietly heading for extinction. Similarly, but without such controversy, embryo selection by metabolomic profiling also failed to improve delivery rates when added to morphology and tested in a prospective trial.1 Again, many observational studies had been encouraging, suggesting that the analysis of how a developing embryo modifies its environment during culture might predict its implantation potential. But the first randomised trial would find no difference in pregnancy rate between the active and control groups.

Metabolomics may not yet be consigned to trash-can of IVF history, and labs continue their search for a non-invasive technique of embryo selection. But the disparity between the promise of a retrospective observational study and the reality of an RCT remains a salutary lesson in the evolution of IVF.

A plethora of studies have indeed reflected the huge potential of time-lapse imaging in embryo selection and have already calculated algorithms to predict embryo

Marcos Meseguer told the meeting that confirmation of time-lapse imaging still lacked the evidence of randomised trials

of randomised trials of array CGH are awaited), GM-CSF for blastocyst development, metabolomic profiling and time-lapse imaging.

The greatest excitement among these developments currently lies in the morphokinetic analysis of time-lapse images, but, as Harper insisted, its attraction so far is based only on a valid hypothesis (more information, less physical disturbance), huge enthusiasm, and a wealth of observational data. Indeed, it was remarkable to ESHRE that more than 50% of all abstracts submitted for the embryology sessions of last year’s annual meeting in Istanbul were studies from time-lapse embryology, such was the burgeoning interest.

Even now, according to the IVI group of Marcos Meseguer in Valencia, where much of the initial time-lapse work has been done, ‘the era of morphokinetics’ is already upon us.3 A plethora of studies have indeed reflected the huge potential of time-lapse imaging in embryo selection and have already calculated algorithms to predict embryo
viability. In 2010, for example, a study from Wong and colleagues in the USA analysed the progress of 242 frozen embryos according to morphokinetic development and gene expression, and proposed a combination of three parameters to predict blastocyst formation: duration of the first cleavage, time interval between the first and second mitotic division, and the time interval between the second and third mitosis.\(^4\) The following year, Meseguer’s own group from Valencia used a time-lapse system to analyse more than 2000 embryos (of which 247 implanted) and extended the predictive parameters.\(^5\)

Now, explaining these results in Leuven, Meseguer confirmed that implantation was related to the time interval between the first and second mitotic division (what he called the second cell cycle, ‘cc2’), and the time interval between the second and third mitosis (‘cc3’), but also to the time span between microinjection and five-cell embryo formation (or ‘t5’).

Thus, in a check-list of what morphokinetic embryo analysis might predict on the way to implantation, Meseguer concluded that an algorithm for embryo selection had now been established (with others in development), that kinetics are related to blastocyst formation, and that morphokinetics are related to morphology. However, he too conceded that the ability of time-lapse to improve implantation and delivery rates, while confirmed ‘retrospectively’, would still need the gold-standard confirmation of randomised trials before prime time acceptance.

Several trials are now in progress, ‘and we may expect an improvement in results,’ said Meseguer. Not least of these is a substantial trial programme at his own centre in Valencia, whose completion is expected later this year, with results available before year’s end. Meseguer told Focus on Reproduction that there are three variants to the trial - one in ICSI cycles with day 3 transfer, one in oocyte donation with day 3 transfer, and one in oocyte donation with day 5 transfer. ‘Our intention is to demonstrate that, by culturing embryos in more stable conditions and avoiding observations outside the incubator, our ongoing pregnancy rate can be improved by 9%,’ he said. The study, with 500 cycles in each branch, has been powered to demonstrate such a marked improvement, which, he added, was calculated from the group’s own retrospective data. Already an interim analysis has been performed on 40% of the randomised sample, with no suggestion that the trial should be curtailed.

The history of PGS with FISH and cleavage stage biopsy is a salutary lesson in embryo selection, a warning that ART (as its name implies) is still technology-driven, not evidence-based. It’s easy to be impressed by the kit, but, as Joyce Harper said in Leuven: ‘There’s no point in doing it if it doesn’t work.’ However, the many retrospective studies of time-lapse imaging do indeed seem sufficient grounds for a new wave of enthusiasm. Meseguer’s group has already reported from observational data that time-lapse monitoring can improve pregnancy rates (over standard incubation) by 20% per oocyte retrieval and 15% per transfer. Of course, RCTs need not be the answer to every question in infertility, but, if the clinical trials can now confirm such remarkable progress, then ‘the era of morphokinetics’ may indeed have dawned.

Simon Brown

Focus on Reproduction

References
Accord and a little discord at the second best practice meeting of ESHRE and ASRM

More controversy over Tilly’s neo-oogenesis claims

Yet again, this ESHRE-ASRM joint meeting was an event of many highlights, but none more so than the ‘debate’ between Jonathan Tilly and Kui Liu on neo-oogenesis in the adult ovary. For this was a confrontation of high drama, in which each protagonist mustered his own data not just to defend his own position but also to deconstruct his opponent’s claims.

This dramatic story had begun in 2004 with a report in Nature from Tilly’s Harvard Medical School group controversially suggesting that follicular renewal from germline stem cells was in fact evident in the postnatal ovary. The controversy erupted again in February last year with a further report from Tilly that the ovaries of reproductive-age women, similar to those of adult mice, also possess rare mitotically active germ cells which can be propagated in vitro and can generate oocytes in vitro and in vivo.1

The study was widely reported in the press, with most publications sensationaly suggesting that these ovarian ‘stem cells’ would in effect redefine conventional understanding of female reproductive physiology. At the time, Tilly himself was quoted by the Washington Post as saying: ‘Our current views of ovarian aging are incomplete. There’s much more to the story than simply the trickling away of a fixed pool of eggs.’

While this was a game-changing story for the popular press, in reproductive science the paper reopened an intense debate on the existence of oogonial stem cells, their characteristics in terms of pluripotency, and their reproductive role.

Indeed, six months later a report from the Gothenburg group of Kui Liu, published in the Proceedings of the National Academy of Science, described experiments using the same cell-specific DDX4 antibody as Tilly which failed to find any mitotically active female germline progenitor cells in postnatal mouse ovaries. And it was this study, under the onus of Tilly’s criticism, which the hapless Liu now had to defend in the Bahamas.

Although this was not a classical ‘debate’ with a final vote from the audience, there was little doubt from the applause and comment where the floor’s sympathies lay. Taking a view that reproducibility is a cornerstone of scientific progress, Liu insisted that Tilly’s results could not be considered as ‘evidence’ that neo-oogenesis occurs in the adult ovary. Not only did his own lab’s experiments fail to replicate the results, but, following close examination, Liu also proposed that the germline ‘stem cells’ described by the one group whose work appears to complement Tilly’s (the group of
Ji Wu in Shanghai) were in fact different from Tilly’s in size, proliferation rate and characteristics in culture. And most importantly, no group has as yet obtained live offspring from these cells as Wu’s group reported in 2009.3 ‘No-one else has live pups,’ said Liu; functionality of the cells even in Tilly’s group was only demonstrated by the development of blastocysts.

Despite some aggressive criticism from Tilly, who appropriately or not in the Bahamas delivered his presentation in shorts, Liu’s was a quiet piece-by-piece defence of his work and its failure to reproduce his opponent’s conclusions. Tilly himself, of course, was insistent that his studies were evidence for the existence of functional stem cells in ovarian cortical tissue, which, when expanded over several months, are able to generate structures similar to oocytes as determined by morphology, gene expression and haploid status. ‘Our conclusion is that the dogma [on ovarian physiology] is wrong,’ said Tilly. ‘Oogenesis and folliculogenesis persist in adult female mammals.’

**The safety of ICSI**

There were two separate lectures on ICSI, but each overlapping in concerns about safety. Indeed, Paul Devroey, one of the Brussels investigators reporting the world’s first ICSI birth in 1990, suggested that an assessment of risk for the offspring would determine whether ICSI was the right treatment or not. He found it ‘astonishing’ that so many clinics now use ICSI for every indication, despite the risks which epidemiology now clearly indicates. He said he had ‘no answer’ to the questions raised by last year’s Australian study showing a higher risk of birth defects in all ART births than in those naturally conceived, especially in the ICSI births (an odds ratio of 1.77).4 Not all studies, however, have found such results; indeed, Devroey described a large meta-analysis from Wen et al as ‘reassuring’ inasmuch as the risk of birth defect after ART was small and comparable between IVF and ICSI.

Devroey also questioned whether, with such widespread use of ICSI, adequate genetic and chromosome testing was being done. In an absence of the vas deferens, he said, testing for cystic fibrosis gene mutations is mandatory - as is PGD in cases of high CF risk. Yet despite the overall epidemiological findings, he said, the follow-up data are still missing on the specific health risks associated with ICSI.

There is also a data deficit on the link between ICSI and the inheritance of infertility by any male offspring. Are clinics testing for Y chromosome deletions, Devroey asked. And if so, what’s being done about it? He emphasised that a Y chromosome deletion as a genetic cause of male infertility would be transmitted 100% to any male offspring - and counselling on this risk, said Devroey, is necessary, even though the long-term data on any correlation between male infertility and male children is also missing.

The question of gene defects in male infertility was also the subject of a presentation by Dolores Lamb from Baylor College, Texas, the immediate Past President of the ASRM. She too bemoaned the lack of data specific to gene and chromosomal defects in the offspring of ICSI cases, suggesting that, because of the small numbers, their incidence had been ‘diluted’ in the mass of general epidemiological data. And she also stressed the necessity for genetic diagnostic testing in certain cases. ‘The widespread use of ICSI for minor indications may impair our ability to assess its safety for the couple with a severe male factor,’ she said, noting that chromosomal abnormalities are more common in infertile men (5.8%) than in the general population (0.5%) - and particularly on the sex chromosomes. Deletions on the Y chromosome have been found in up to 12% of azoospermic men, and around 6% of oligospermic men, but are rare in fertile men. ‘These Y chromosome microdeletions will be inherited by the male offspring conceived by ICSI,’ she said, echoing Paul Devroey. So it was her case too that all men with non-obstructive azoospermia and severe oligospermia should be tested for microdeletions.

She also advised that all men with a congenital absence of the vas deferens and their female partners should be tested for cystic fibrosis gene mutations (of which more than 1000 have so far been identified). The tests are available to detect both Y chromosome microdeletions and single gene defects such as cystic fibrosis. And she, like Devroey, emphasised the need to advise patients with severe male factor infertility that, while the studies are largely reassuring, ‘there are still no guarantees of the perfect baby’.

**Aneuploidy screening**

In a debate on what works and does not work in PGS, there was much agreement between the US representative Nathan Treff and Europe’s Joep Geraedts - notably on the recognition that the testing of cleavage-stage biopsied cells can no longer be recommended.

It was Geraedts, of course, who steered ESHRE’s Task Force into the design and launch of a randomised trial of PGS by microarray polar body analysis. That study - ESTEEM - is now under way in seven European centres, with results expected later in 2014. The trial has two aims - to
estimate the likelihood of future euploid cycles in women with no euploid embryos in a first screening cycle, and to improve birth rates following comprehensive polar body analysis by array CGH (in comparison with women having no chromosome analysis). Geraedts reported that around half the women in the pilot study had no normal oocytes - and thus no embryos for transfer.

The accuracy of polar body analysis was also confirmed in the pilot study, which demonstrated high concordance between the chromosomal status predicted by the analysis and the corresponding zygotes in women of advanced maternal age. This accuracy was further underlined during the meeting with publication of a report from Greece and UK in which polar body analysis by array CGH accurately predicted aneuploidies of maternal origin in cleavage-stage embryos. Almost all the aneuploidies detected in the embryos were associated with copy number changes in the polar bodies (93%) and all but one (98.5%) were predicted to be aneuploid.

While the polar body approach, said Geraedts, avoids the distortions of mosaicism and does not ‘touch the future embryo’, it will only detect abnormalities of maternal origin, and none from the post-zygotic stages. However, the technique does not offend embryo protection legislation and is allowed in all European countries.

However, the US approach as reflected in the presentation of Nathan Treff, seems to be heading not towards polar bodies but towards the trophectoderm cell of a biopsied blastocyst. Trophoderm biopsy, said Treff, would allow analysis of both maternal and paternal abnormalities, and is safe. And so far, he added, the only clinical trials to report any benefit from aneuploidy screening have all been from trophectoderm biopsy and blastocyst transfer.

Management of IVF Centres
If light relief came from the kayak challenge, there was much bemusement - especially among the Europeans - in a back-to-back session on the management of fertility clinics. David Adamson, another former President of the ASRM, left no doubt that fertility treatment in the US is a commercial venture. ‘If you don’t make money, you go out of business,’ he said unequivocally, while his advice on recruitment (‘hire slowly, fire quickly’) left many wondering how this might go down with Europe’s employment laws.

Against such commercialism, Luca Gianaroli could do little more than spell out the good-practice principles of running a fertility clinic in Europe - an emphasis on providing an effective healthcare service with a clear patient focus, and then on quality management, technological innovation, and - yes - sales and marketing.

Simon Brown
Focus on Reproduction


Honours even as ASRM wins the kayak challenge

In the absence of snow, the societies’ team spirit was tested not on the ski slopes but on the water in kayaks. Sitting down to the challenge, ASRM emerged as this year’s champions to take the trophy won by ESHRE last year in Cortina. And it’s back to Cortina in 2014 for the third ‘Best Of’ joint meeting of ESHRE and ASRM - and back too to the ski slopes for the entertainment.

With a time lapse measured in milliseconds, Marcos Meseguer leads an ESHRE kayak back to the beach.
For the last several months the PGD Consortium has been in a transition mode whilst new by-laws were developed with ESHRE’s Executive Committee. The by-laws were discussed and implemented at the Steering Committee’s meeting in March. Although the aims of the PGD Consortium remain essentially the same, a major change will be that the number of officers serving on the Steering Committee at any one time will be limited to five, including the Chair and Chair-elect. The revamped Steering Committee now includes Joanne Traeger-Synodinos (GR) as Chair, Edith Coonen (NL) as Chair-elect, Céline Moutou (FR), Martine De Rycke (BE) and Sioban SenGupta (GB). We thank all the departing members, including Francesco Fiorentino (IT), Georgia Kokkali (GR), Katerina Vesela (CZ) and Pam Renwick (GB), and we hope they will continue to contribute their valuable expertise to the Consortium.

In addition, the new Steering Committee will have the (non-voting) support of a Past Chair, the Co-ordinator of the SIG Reproductive Genetics (both posts currently held by Joyce Harper), the ESHRE Science Manager (Veerle Goossens), an ESHRE Executive Committee liaison member (currently Cristina Magli), and, during this transition period, a founding member of the PGD Consortium (Joep Geraedts).

Working groups

One of the major activities of the PGD Consortium remains the collection of data. This is essential to support evaluation of the accuracy, reliability, effectiveness and safety of PGD. The Database Working Group, chaired by Céline Moutou with support of Martine de Rycke, has two major aims: first the analysis of cumulative data collected by the Consortium from 2001-2008; and second, the design and set-up of a new on-line database to facilitate simplified data submission by member centres. Céline has already cleaned-up and merged the data collections for the years 2001-2008 (a massive undertaking of more than 29,000 cycles). We look forward with interest to learning the first results and trends in clinical PGD over the years.

Progress with the creation of the on-line database has unfortunately been held up because the software used to support the database has been discontinued. We will do what we can to rescue the time and effort so far invested (more then two years of work) and hope that a replacement software programme can be found as soon as possible.

With respect to the annual data collection papers for cycles performed in 2009 (data XII) and 2010 (data XIII), there has been a slight delay in data evaluation because of the new by-laws. However, the Steering Committee will make their completion a priority in the next few months.

Because of the sudden reduction in size of the Steering Committee, a decision was made to prioritise working group activities. Some WGs, such as that on Molecular Methods or Accreditation, will be discontinued in the near future at least. However, since the Steering Committee feels that accreditation is important for PGD centres and the Consortium, the accreditation advisory panel, whose names are posted on the ESHRE PGD Consortium web page, can be contacted for advice by any centres working towards accreditation for PGD. Trends in the numbers of accredited PGD centres will be followed by the ESHRE Science Manager through an annual questionnaire to all Consortium members.

The WG on misdiagnosis monitoring and audit, chaired by Jan Traeger-Synodinos, is also winding down. A paper summarising the results of a collaborative study to evaluate PCR-based PGD follow-up has been submitted; the study to follow-up FISH-based PGD, led by Tucge Pehlivan, hopes, with the support of Edith Coonen, to finalise its data analysis and also submit a paper soon.

A new WG will be initiated to collect and evaluate data (prospective and retrospective) on the use of PGD to support the birth of HLA-compatible donors for bone-marrow transplantation in siblings affected by serious haematological and immunological disorders.

Finally, we also intend to play an active role in e-learning in collaboration with the SIG Reproductive Genetics and will have regular interactive webinars to share experience, case discussion and problem solving among members.

Joanne Traeger-Synodinos
Chair PGD Consortium
E-learning proposals begin to take firmer shape

E-learning has taken centre stage for the SIG. After discussions with the ESHRE PGD Consortium, we now aim to begin by recording four introductory webinars, hopefully with on-line tutorials and online questions to help with continued professional development. The four are:

- An introduction to genetics, with Joep Geraedts and Edith Coonen
- An introduction to PGD, with Joyce Harper and Jan Traeger-Synodinos
- Embryo biopsy, with Georgia Kokkali and Cristina Magli
- An introduction to accreditation; Mike Morris and Sioban SenGupta

Future workshops
Milan Macek and Katerina Vesela (in collaboration with the SIG and PGD Consortium) have developed a dynamic programme for the workshop to be held in Prague on 12-13th September this year on Application and challenges of emerging technologies in preimplantation and prenatal diagnosis. As well as speakers from the PGD and PND community, companies will be given a chance to tell us about their new technologies and developments. The full programme can be viewed on the ‘Calendar’ pages of the ESHRE website.

It has also been proposed to develop a workshop on stem cells, epigenetic and genetic stability and prospects of fertility preservation. The workshop is being developed by Ursula Eichenlaub-Ritter, Stéphane Viville, Claudia Spits and Karen Sermon and will hopefully be a joint meeting in Brussels with the SIG Stem Cells and Task Forces Basic Science and Fertility Preservation.

Francesco Florentino is developing a workshop on An update on PGS to be held towards the end of 2014, which will allow time for some of the randomised controlled trials to be published.

Publications
The paper from our joint Campus meeting with the SIG Ethics & Law on the ethics of comprehensive pre-implantation genetic testing has has now been published.1

The joint ESHRE/European Society of Human Genetics and Eurogentest collaborative paper ‘Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy’ has also been submitted to the Executive Committees of ESHRE and ESHG for approval before submission to Human Reproduction and the European Journal of Human Genetics for simultaneous publication.

Joyce Harper
Co-ordinator SIG Reproductive Genetics


New ESHRE guidelines on endometriosis ready for London

New guidelines on The management of women with endometriosis will be officially presented at the annual meeting in London. The guidelines offer best practice advice on the care of women with suspected endometriosis and with endometriosis diagnosed by laparoscopy and/or histology.

This is the first of many guidelines to be developed by ESHRE according to the 12-step process described in the ESHRE manual for guideline development. This includes key questions, literature search, evaluation of the evidence, recommendations based on the evidence and clinical expertise, and a broad open review.

The new guideline provides recommendations on diagnosis, which include the symptoms predictive of endometriosis, the utility of medical technologies, and clinical examination. Treatments for endometriosis, including surgery, are discussed for both pain relief and infertility. The effectiveness of ART for endometriosis-associated infertility is discussed, as are adjunctive therapies (medical and surgery) for ART. Information is also provided for the management of women in whom endometriosis is found incidentally (without pain or infertility), to prevent recurrence of disease and/or pain, to treat menopausal symptoms in women with a history of endometriosis and for patients questioning the possible association of endometriosis and malignancy.

The guideline was open for review between February and April and the development group thanks the 61 reviewers who provided comments; these are now being processed for the final text, which will be published in Human Reproduction and on the ESHRE website.

Nathalie Vermeulen, ESHRE Research Specialist
Stage now set for ESHRE certification in reproductive endoscopic surgery

ESHRE ‘core’ project to polish skills and formalise status

Initial proposals made by the SIG Reproductive Surgery for ESHRE certification for reproductive endoscopic surgeons have been approved by ESHRE’s Executive Committee and adopted as a core project of the Society. In making the proposals, the SIG said the objectives of the programme were to improve patient safety, reduce unnecessary costs, and enhance the knowledge and skills of reproductive surgeons.

The Executive Committee has now appointed a working group to develop and run the project consisting of Luca Gianaroli, Carlos Calhaz-Jorge, Anis Feki and Antonis Makrygianakis for the Executive Committee, and Stephan Gordts, Grigoris Grimbizis and Vasiliis Tanos for the SIG Reproductive Surgery.

The programme, known as the ESHRE Certification for Reproductive Endoscopic Surgeons (ECRES), will be based on both laparoscopic and hysteroscopic skills and will allow gynaecologists to prove their surgical ability and experience in reproductive medicine and to establish their status as reproductive surgeons. Prerequisites for those wishing to apply are membership of ESHRE and participation in the educational activities of the SIG RS.

With high-level training in laparoscopic surgery already successfully in place in Europe, ECRES will join forces in training with the Winners Project of the European Academy of Gynecological Surgery (EAGS), a new online learning programme with validated standards.

To achieve ESHRE certification, applicants must:

- Pass the Winners programme examinations in reproductive surgery - with silver or gold degree of the EAGS.
- Submit a log book detailing at least 50 surgical procedures performed by the applicant within a period of one to three years and signed by the director of department and/or hospital.
- Provide evaluative proof of surgical skills in 15 operation reports performed by the applicant accompanied by unedited videos held in the ECRES electronic database. Those cases will be blindly assessed by independent reviewers.
- Pass a written examination.

Continuing update of the log book, results of reviewers’ reports on the log book and written examination results will all be essential parameters for renewing the certification every five years.

According to Vasiliis Tanos, Co-ordinator of ESHRE’s SIG Reproductive Surgery, ESHRE’s quality criteria for gaining ECRES certification will be strict, guaranteeing the highest standards in reproductive surgery. ‘We would expect certified surgeons to have the ability to solve most fertility problems in a safe and accurate way,’ says Tanos, ‘and provide patients with the best chance of pregnancy.

‘New technological advances as well as evidence based data show that endoscopic surgery is now the first option for the diagnosis and treatment of female infertility. Such a dynamic yet minimally invasive approach will spare patients unnecessary hospitalisations and offer them reliable diagnostic results and surgical treatments when needed. This is why the certification programme concentrates on reproductive endoscopic surgery.’

Tanos adds that the ECRES scheme will help improve ART results while supporting the importance of natural conception in the restoration of reproductive anatomy and functionality. ‘So the aim of the programme is to encourage gynaecologists with an interest in reproductive surgery to dedicate time and effort to reproductive medicine and their surgical skills,’ says Tanos. ‘ECRES will allow them to prove their competence and capabilities.

Certification issued by the leading society in reproductive medicine will increase their professional value and confirm their expertise. As far as we are aware, ECRES will be the first international certification scheme in the field of reproductive surgery.’

ECRES will be launched during the annual meeting in London. The psychomotor and hand skills will be examined by using LASTT (Laparoscopic Assessment of Skills in Training and Testing), HYSTT (Hysteroscopic Assessment of Skills in Training and Testing) and SUTT (assessment in laparoscopic suturing). The theoretical exam will test knowledge of reproductive medicine, imaging in infertility and reproductive surgery.

Steering committee
Vasiliis Tanos (CY), Co-ordinator
TC Li (GB), Deputy
Gregoris Grimbizis (GR), Deputy
Natasa Kenda Suster (SI), Junior Deputy
Marco Gergolet (IT), Past Co-ordinator

Vasiliis Tanos: ‘We would expect certified surgeons to have the ability to solve most fertility problems.’
Electronic interaction for London course debut

Precongress course London
After our very well attended precongress course in Istanbul we are keen to learn how the new format of e-voting will be received in London. The programme, on the efficacy and safety of ovarian stimulation for ART, will encourage interaction with the audience by means of an electronic response system, with voting and opinion polls on controversial topics. The speakers are expected to interact with the moderator and audience, and will need to defend their points of view based on scientific data and sound reasoning. We will, from the workshop evaluation, have an idea if this format provides an additional incentive for participants to enrol for a precongress course and if we should endorse the system further in other ESHRE meetings.

The business meeting of the SIG RE will take place during the lunch break (13.00-14.00) on Sunday 9th July.

Other activities in 2013
On 25-26th October our Campus workshop on Polycystic ovary syndrome: A new look at an old subject will be held in Rome with local host Daniela Romualdi. A truly comprehensive programme will cover the aetiology of PCOS, phenotypical classifications around the individual aspects of the syndrome, metabolic disorders associated with PCOS, cancer risk and long-term health implications, infertility and infertility treatment, course of pregnancy and child health. A fantastic array of international experts will speak and share their latest data. The venue for the workshop is quite centrally located, with the Vatican and many major attractions only a short walk away from the workshop site.

The date for the premature ovarian insufficiency workshop to be held in Utrecht (with local host: Frank Broekmans) has now been decided as 6-7th December 2013. The programme has been finalised and will be online soon.

Future plans for 2014
Our Deputy Co-ordinator Efstratios Kolibianakis from Thessaloniki has proposed a Campus workshop for early 2014 on When IVF fails: Managing recurrent implantation failure. We believe that this difficult topic has been educationally underexposed recently. Beyond a critical appraisal of management strategies for implantation failure, important ramifications will be discussed, from psychosocial wellbeing to treatment alternatives such as oocyte or embryo donation.

Georg Griesinger
Co-ordinator SIG Reproductive Endocrinology

Guidelines on psychosocial care at heart of this year’s agenda

These are very productive times for the SIG Psychology & Counselling. We are working on the implementation of the new guidelines and organising several relevant workshops, some in collaboration with other ESHRE SIGs.

Guidelines in development
The Guidelines Developing Committee has collected and reviewed all relevant empirical evidence and will now concentrate on writing the final recommendations which will constitute the core of the guidelines. These aim to provide best practice advice on how psychosocial care can be incorporated into daily practice to the benefit of patients and health care providers in the field of infertility and medically assisted reproduction.

Our precongress workshop in London will also be dedicated to the guidelines. Entitled High standard psychosocial care in your clinic: how to implement new guidelines, the workshop brings together physicians, nurses and mental health professionals to discuss how we can facilitate the implementation of the guidelines in daily practice. We will discuss, for instance, how clinical staff can tackle the burden of ART treatment, how physicians can introduce psychosocial care, how mental health professionals can work with other clinic staff to provide psychosocial...
Precongress course considers new introductions

Our precongress course in London is organised jointly with the SIG Ethics & Law on Responsible innovation in medically assisted reproduction. The course reflects the growing awareness in reproductive medicine that safety is a crucial aspect of innovation and deserves more systematic attention than it has sometimes received in the past. Thus, lessons will be learned from the past, but we will mainly focus on challenges for the future: how can we develop and introduce innovations in medically assisted reproduction in a responsible way?

The balanced course programme will give participants an overview of the issues, challenges and responsibilities relevant to the safety and quality of innovations in ART. For example, we will pay attention to health outcomes, the usefulness of research in animal models and embryos, and the importance of registries and follow-up studies. Furthermore, we will discuss the level of risk that should be deemed acceptable and how in this respect the sector can be more accountable. The programme comprises state-of-the-art lectures but leaves enough space to discuss these issues and consider the adoption of findings to the individual situation.

The course will be of value to everyone with an interest in the safety and quality of new reproductive technologies, the ethics of assisted reproduction or is involved as researcher, embryologist, clinician or policy maker in reproductive medicine.

Steering committee
Peta De Sutter (BE), Co-ordinator
Willianne Nelen (NL), Deputy
Arianna D’Angelo (UK), Deputy
Jan Kremer (NL), Past Co-ordinator
Kelly Tilleman (BE), Junior Deputy

The course will of value to everyone working in the field of reproductive medicine.

Further activities
Another upcoming event is the workshop on Fertility preservation: from technique to implementation, which will be held in Amsterdam in March 2014. We are working in collaboration with members of the SIGs Ethics & Law, Quality & Safety in ART, the Paramedical Board and Task Force for Fertility Preservation to cover a wide range of relevant clinical topics. This workshop will be of interest for professionals from several different backgrounds, including gynaecologists, oncologists, paediatricians, psychologists, ethicists, biologists and nurses. Examples of topics to be covered include options for fertility preservation in post-pubertal women, pre-pubertal girls, post-pubertal men and pre-pubertal boys, the barriers in communicating fertility preservation issues with children and their parents, and the role of fertility in the quality of life of cancer survivors.

Finally, our 2014 annual meeting precongress course will result from a collaboration with the SIG Safety & Quality in ART and will focus on The value of empirical evidence. Do patients and health professionals attribute the same value to empirical evidence? How do patients perceive evidence? Why do they choose treatments without any evidence? What is the role of placebo? What is the role of communication in translating evidence to patient behaviour? These fundamental questions will be discussed from the perspective of patients, doctors, basic scientists, psychologists and yogi masters.

These events offer several opportunities for multi-disciplinary discussion on a wide range of state-of-the-art issues within the field of reproductive medicine. We hope they meet your needs and interests!

Sofia Gameiro
Junior Deputy Co-ordinator
SIG Psychology & Counselling

Guidelines Development Group, from left to right, Petra Thorn, Cora de Klerk, Christanne Verhaak, Christos Venetis, Eline Dancet, Sofia Gameiro, Tewes Wishmann, Clare Lewis-Jones, Marysa ‘Emery and Nathalie Vermuelen.

Support, and strategies to assure the implementation of guidelines. This will be an informative and useful workshop for everyone working in the field of reproductive medicine.

Sofia Gameiro
Junior Deputy Co-ordinator
SIG Psychology & Counselling
SPECIAL INTEREST GROUPS

// ANDROLOGY //

Joint organisation gives added value to meetings

A second Basic Semen Analysis Course has just ended in Birmingham, UK, designed for laboratories outside the Nordic countries. The course, organised jointly with the British Andrology Society and Nordic Association for Andrology, complied with the latest ESHRE syllabus for basic semen assessment courses related to the 5th edition of the WHO manual.

Precongress London

Our precongress course in London is now finalised with a very exciting programme (full details at www.eshre2013.eu/Programme/Pre-Congress-Courses/Course-2-Andrology.aspx). The course will present the latest research on male reproductive health and feature two controversial issues: first, whether semen quality and male fertility are declining, and second, if ART is a realistic solution to Europe’s demographic demise. Speakers - of differing opinions - include Stefan Schlatt (DE), Joelle Le Moal (FR) and Harry Fisch (US). We can promise an energetic and interactive day of debate and lectures.

Future activities

With so many budgets cut and little to spend on meetings, we are now involved in the planning of several joint Campus workshops, to offer maximum information and interaction to as many as possible. Building on the success of the best attended ESHRE Campus meeting of 2012 (The best sperm for the best egg organised with the SIG Embryology), we are now planning a workshop on stem cells, epigenetic and genetic stability and the prospects of fertility preservation; this is organised with the SIG Stem Cells, SIG Embryology, TF Basic Science and TF Fertility Preservation for Spring next year.

Another date for diaries in Spring 2014 will be a workshop organised by Willem Ombelet (BE) for the SIGA and TF Developing Countries and Infertility on Donor sperm banking: medical, socio-cultural, ethical and juridical considerations. Again, this is a very topical issue, and the course will provide an overview of DI regulation and socio-cultural factors in Europe, and a review of organisational problems, including donor recruitment.

Finally, SIGA has secured the bid to provide ESHRE’s exchange postgraduate course at the 2014 annual meeting of the ASRM. Our theme is From spermatogenesis to the take-home baby - how important is sperm quality? Our speakers will include Mona Bungum (SE), Nicolas Garrido Puchalt (ES) and Sheena Lewis (GB). Keep checking the SIGA website for updates.

Sheena Lewis
Co-ordinator SIG Andrology

// EARLY PREGNANCY //

London session on gathering evidence for clinical trials

Our precongress course in London is titled Risk factors for recurrent pregnancy loss – more pieces of the puzzle, and will focus on pregnancies of unknown location, thyroid abnormalities in early pregnancy, social and lifestyle factors and their impact on early pregnancy - and a review of the UK’s 2012 NICE guidelines.

During the main meeting there will be an invited session on Monday 8th July on Gathering evidence in early pregnancy research - making trials happen with presentations on Pregnancy of unknown location and The secret of successful trials.

Future events

The concept of developmental origins of health and disease attracts much attention. Major impact of environmental and other influences for pregnancy outcome already exist in the pre-pregnancy and early pregnancy period. On 28-29th November we will host a joint Campus meeting in Brussels with the Basic Science Task Force whose central theme is the concept of developmental origins of health and disease. Topics to be covered are early implantation, the prediction of pregnancy outcome by biomarkers, clinical evidence in early pregnancy, effects from preconception and early pregnancy to later in life.
Hot topics on the congress learning agenda

The SIG Embryology aims to promote both the scientific discipline of embryology as well as the profession of embryologists, and to these ends we hope to inspire our members with continuous education and updates in the field.

Our activities are in:
- Workshops and precongress courses
- Guidelines and quality control
- Certification of embryologists and continuous embryology education merits
- The Atlas of Embryology
- E-learning within embryology

We also believe it important that the work of our members is based on solid science, and in our precongress courses and workshops we try to provide a basic background of biology and methodology mixed with clinical applications, as well as the latest findings and theories.

Looking at what is happening in embryology right now, we can see two main tracks. One is cryopreservation, whose hot topics include the pros and cons of open versus closed vitrification devices, the possible contamination risk in cryo tanks, and the relative importance of cooling speed versus warming speed. In addition, the relative efficacy of vitrification and slow freezing, particularly with cleavage-stage embryos, remains a matter of discussion. You will hear much more about these topics in our precongress course in London this year, *Cryopreservation - What is hot and what is cold?*. The other main track, of course, is time-lapse imaging and the timing of events in early embryo development. Lots of new data are emerging, algorithms calculated and new predictors for implantation sought. By next year we should have more reliable data, including larger randomised studies, that can tell us how to proceed with this system optimally. So, our precongress course in Munich in 2014 will be a state-of-the-art update on time-lapse techniques, including their use in clinical embryology and in other clinical and research areas.

In October this year we will be running a joint workshop in Barcelona with the Paramedical Group as a crash course on the introduction of new techniques, both from a scientific and clinical point of view.

So, we hope to see you in at least at one of our meetings, and please take a look at our webpage to see more of what is going on.

And since I will be stepping down from the position of SIGE Co-ordinator this year, I would like to end by giving a huge thanks to everybody in the SIGE group, and to the ESHRE central office who work so hard to help achieve all our goals.

*Kersti Lundin*
Co-ordinator SIG Embryology

Debate is sure to be lively, particularly on the predictive value of endometrial and embryonic biomarkers. Young scientists are encouraged to submit an abstract for the meeting (which is titled *From early pregnancy to later in life*).

For availability of places and more details please check the calendar section on the ESHRE website.

*Mariëtte Goddijn*
Co-ordinator, SIG Early Pregnancy
European Patients’ Forum
To improve our future planning we applied to take part in a capacity building project launched by the European Patients’ Forum (EPF), whose overall objective is to strengthen the capacity of European level patient organisations such that they are more effective in feeding their experiences and expertise into the work of EPF and utilising the outcomes of our collective work in a national, and/or disease specific context. The programme responds to needs and concerns identified by EPF members during previous activities and will focus on improving organisational and advocacy skills.

We were delighted when we were picked as one of six European organisations to benefit and undertake a pilot exercise which will run until 2014. Elín Einarsdóttir (Tilvera – Iceland), Renate Kurszus (Ønskebarn – Norway), Ofra Balaban (Chen – Israel) and Kalina Nedelcheva (Iskam Bebe – Bulgaria) are our representatives on this project. Following a meeting with the EPF in February we decided to develop a strategic plan ready for Council meeting approval in 2014. We expect that this process will encourage a review of our mission and agreement on a clear set of organisational values. The plan will also include a set of strategic goals for the years to come and a list of key action fields on which we will need to focus to achieve those aims. This will involve a great deal of work and dedication by our members – but it will be worth it and we look forward to moving this important work forwards.

Special families project
Our Vice-Chair, Denisa Priadkova, is the lead in our Special Families Campaign which is now a global initiative and run very professionally. The campaign is our way of raising awareness of infertility in a visual image of both its impact and the success of treatment for many. Thousands of postcards have been sent across Europe and shown that members of Fertility Europe working together have not just a strong voice but thousands of faces and stories of hope for families to show their creativity, dedication, emotions and love. The Special Families postcards on our website are very powerful and show the enormous courage and determination of parents to become a family. Help us spread the news and share the banner, link or postcard on your website too. You could provide a link to the campaign on your website. Just go to www.fertilityeurope.eu/specialfamiliescards/ for more information.

Policy progress
Our policy work has continued unabated. We are currently finalising a document titled Fertility Matters which includes information on key facts on fertility and its consequences, ART, ethics, equality of access to treatments, criteria to ensure equality of access, prevention and a set of recommendations from Fertility Europe. We are also seeking meetings with a further six MEPs.

Spring meeting
Our annual members spring meeting took place on 21-22nd March in Warsaw, Poland, a country which still has no ART-specific legislation. The EU Tissue and Cells Directive has not been implemented, there is no official competent authority, no national ART registry (all data for ESHRE’s IVF Monitoring are given on a voluntary basis and without validation, no national registry for donors, and no licensing/inspection procedures. However, good clinical and patient guidelines are in place, but on a voluntary basis and without official sanction.

As Focus on Reproduction reported in January, a national reimbursement scheme is planned to start in July and it is important that the views of patients are heard - which is why Anna Krawczak, Chair of the patient...
organisation for Poland Nasz Bocian and colleagues organised a meeting prior to our Fertility Europe meeting to which were invited myself as Chair of FE, members of Nasz Bocian, Polish clinic representatives reporting to ESHRE, and politicians including Agnieszka Kozlowska Rajewicz, the government representative for equal status, and the Polish Ministry of Health were invited. The objectives of the meeting were:

- To promote the FE view that European governments should provide safe and equal access to ART.
- To encourage the link between patients and doctors for reliable information and better treatment quality.
- To represent patient needs without a legal framework. What can be achieved if the law does not exist?
- To consider other European examples: how does ART legislation work elsewhere in Europe? What is the Polish position and what does it mean for patient's safety?
- To support the position of Nasz Bocian in terms of the national reimbursement scheme.

In my presentation I discussed the provision of equality of access to ART for patients and the protection of safety. Co-operation with patient organisations such as Nasz Bocian will forge a link between patients and doctors and improve information and quality of treatment.

The members meeting which followed as always raised a great deal to discuss. Members were updated on the activities and plans from the Executive Committee and were delighted to welcome three new candidate members - Deti Budo from the Ukraine, Crostvo za večjo rodnost from Slovenia, and RODA from Serbia, who all gave presentations looking at how their organisations work, reimbursement policies in their respective countries and key achievements. Erikjan Bor (Freya – Netherlands) presented the latest draft of the Fertility Matters document produced by the Policy Working Group and later chaired a workshop on fundraising. Finally, we were privileged to welcome Professor Rafal Kurzawa, President of the Polish Society of Gynaecologists, who gave an excellent and thought provoking presentation on the current situation in Poland with respect to fertility treatment. We are grateful to Professor Kurzawa for kindly agreeing to speak.

I also wish to thank my colleagues on the FE Executive Committee, our wonderful volunteers on our working groups, and especially our host organisation Nasz Bocian and in particular Anna, Agata and Agnieszka for their kindness and generosity – fantastic!

We are now working towards ESHRE’s annual meeting in London, in my home country! We have planned an excellent session in the main scientific programme of the congress which will take place on Tuesday 9th July at 14.00. The title for the session is ‘Managing relationships through infertility’ and we have some excellent speakers lined up for this interesting subject. I urge you to attend. And visit us at our stand in the exhibition area where you can learn more about Fertility Europe and how we can hopefully help you.

Finally, on behalf of Fertility Europe can I thank ESHRE for the continued support of our work.

Clare Lewis-Jones MBE
Chair, Fertility Europe
IN PROFILE

The next few years will be a busy time for the German gynaecologist Markus Kupka. Markus will take over the chairmanship of ESHRE’s European IVF Monitoring Consortium in July, and is already working with local colleagues on the organisation of ESHRE’s 2014 annual meeting in Munich. He talked to Focus on Reproduction about data collection in IVF and about Munich.

Strength in numbers
What the future holds for IVF monitoring in Europe

FoR: In June you will become chairman of ESHRE’s European IVF Monitoring Consortium in its 14th year. How would you summarise the EIM’s achievements?

Most developments in our field have been analysed and much research has been done, but only numbers will tell you the real truth. Everyone asks for numbers, and that’s the big thing for this Consortium. We know what’s going on not just in one country, but in more than 30 countries. However, for us in the Consortium it’s very difficult to motivate some countries to provide their data, in particular where there are no registries. It’s been our big aim to encourage these countries, so I’m very happy that we have 34 countries now giving us data. There are only two or three which are not able or willing to do so. Right now I am hoping that Russia can resolve its political and financial problems to provide complete information collected by doctors.

The EIM has received and published a huge amount of data. Its annual reports are some of the most downloaded from Human Reproduction. What are the data telling you about clinical trends?

From my point of view the most important is the reduction in multiple pregnancies. There has also been a marked decrease in IVF and increase in the use of ICSI, but it’s not clear if this is just for medical reasons. It’s certainly a trend seen in many countries. The implementation of new techniques is apparent too - such as blastocyst culture and PGD. It’s also interesting to see how people are moving about in Europe to get treatments which are not allowed or reimbursed at home. This is a big issue here in Germany for egg donation.

You are about to start a two-year term as EIM chairman. What are your greatest challenges?

There are no new countries coming into the Consortium. And even some of the countries which have participated in the past are today less able to provide data. So our biggest challenge is getting these countries to continue with the Consortium - and of course to optimise data quality. We have some countries where just one representative is responsible and he or she will phone around the clinics and ask for the numbers. This is a hard job. They don’t have a computer-based system but are collecting the data by hand. It’s centre-based, not cycle-based, and it’s my view that good quality data can only be derived from a cycle-based system. It would be preferable if we could offer a simple internet-based system to these countries - perhaps in the form of a starter-kit.

So do you think the EIM can keep going as it is? Can it sustain the level of information there has been in the past?

Well, the early years are over and everyone now knows what’s going on. We are talking about a mature programme and mature data collection systems, but we are still seeing several countries where the collection of the data is shifting from the medical to the governmental sector. This can be an advantage, or a problem. In France we had a registry run by doctors, but it’s now a bureaucratic process, mainly to provide numbers for the politicians. These new figures won’t necessarily answer clinical questions or identify emerging trends. So I think there will be changes, but no-one can dispute the value of the Consortium’s work, and I think it will certainly continue.

Focus on Reproduction  May 2013
And pregnancy rate as an endpoint?
We have to find a balance. It’s very hard for most clinics to find out what happened to each of their pregnancies - especially when so many patients come from abroad. On the other hand, delivery rate is certainly the most relevant endpoint, but I think it’s only possible to focus on delivery rates when the data are coming from well established registries - as in Scandinavia or Germany or UK. But for the less established countries it will only be discouraging if we ask for birth rates as well. Maybe we need to run sub-groups where delivery rate is the endpoint.

You have spent time working with CDC and SART in the USA. How do their data compare with Europe’s?
It’s not always fair to compare them - for example, when you look at availability relative to inhabitants, or when you compare costs. I think there is also a problem in the US figures because they report data on a named centre-by-centre basis. So the data reports have something of an element of advertising about them, and the named centre system may encourage biased information. CDC and SART have an excellent internet-based process for data collection, but that simplicity is not possible in Europe. We have more than 30 countries, each with its own language, political system, its own rules for IVF. SART and CDC can also put a lot of pressure on centres to provide data, which is not the case in most European countries.

Do the US and European datasets reflect differences in the approach to treatment?
When I was at SART it was astonishing to me how similar each clinic’s data were - the same protocols, many multiple pregnancies. I was also surprised that there was nothing more than the complicated ASRM guidelines to deal with this. In Germany, transfer policy is strictly controlled by law. But of course there was none of that in the USA.

Are you saying that the datasets reflect a difference in regulation and in attitude?
Yes. Overall, US pregnancy rates have always been a little bit higher than in Europe - and everyone is asking why. The answer from my point of view is clear in the data - that clinics are freer to do what they think is appropriate. I’m sure that if CDC and SART did not publish hard data from each centre then maybe the pressure to transfer multiple embryos would be removed - or at least reduced. The question of how a patient chooses a clinic would not be so dependent on its success rates.

And Germany?
We have had a very good system running for 20 years. But now a lot of things will change. It’s very expensive to run a good system which is paid for by the IVF centres themselves and not by the government or insurance. Every centre pays around €1.60 for each cycle for the registry. In the UK each clinic also pays a fee to the HFEA.

But there are big clinical differences between Germany and the rest of Europe?
Yes. It’s a problem that we can’t offer egg donation. And there are still big problems with the legality of PGD. A court judgement in 2011 appeared to accept PGD, but we still have to work on a couple-by-couple basis and put the evidence before a local committee of eight
people. Germany seems afraid to develop a list of diseases appropriate for PGD.

And this goes back to Germany’s embryo protection laws?
Yes. It makes a big difference to how we practise our medicine. We have many patients over 40 - it’s our daily work - but we are not allowed to offer oocyte donation. We have a huge sperm bank here at my clinic, and sperm donation is OK, but not egg donation. We are not even allowed to discuss ‘egg donation’. And there are always checks to see if clinics are working with overseas centres. So the end result is that there’s little we can do with these older patients. There is some discussion about using pronuclear stage oocytes, which are not yet embryos under German law. Maybe this will provide a solution.

You’re involved in the organisation of ESHRE’s annual meeting next year in Munich. How is it going?
As ever, the scientific programme will be fixed by ESHRE’s programme committee, and I understand that that is already well advanced. The ambition of the local committee is to develop a meeting which is as good as - or even better than - the previous year’s. I think that London will be of a very high standard - as was Istanbul last year. So I expect Munich to be fantastic. It’s a wonderful congress centre, with excellent connections to the city - and Munich has become a very important venue for medical congresses over the past few years. So the expertise is there.

And the city?
Munich is in a very interesting area of Germany and the city has many fine historic buildings. Fortunately, the meeting is not happening in February or November, so we can also expect very pleasant weather. The city is renowned for its museums and restaurants . . . and for its beer. I am sure everyone will have a wonderful time.

And you? How did you end up in this position running an ESHRE congress and the EIM Consortium . . . both at the same time?
My father was also a gynaecologist who did a lot of donor insemination before ICSI was established. I followed in his footsteps somewhat and began to study in Bonn, where Klaus Diedrich and Dieter Krebs were based. This was in the mid-1980s and I started my doctoral thesis there on GnRH analogues in ovarian stimulation. So I was in Bonn and thinking about IVF when the first ESHRE congress was organised, and my interest escalated from there. I’ve been to almost every annual meeting since. I guess the EIM Consortium and the annual meeting are a natural progression.

The Proust questionnaire*

Your greatest virtue?
I can organise many things at the same time.

Your favourite pastime?
Spending time with my family, which includes three very active children.

If not yourself, who else would you be?
I would be most proud to be the man who invented the washing machine. It is extremely useful and saves enormous energy for so many people.

Your favourite novelist?
Gabriel Garcia Marquez.

Which book are you reading now?
Streß und Freiheit by Peter Sloterdijk. He’s professor of philosophy and media theory at the University of Art and Design in Karlsruhe.

Your most recent holiday destination?
Italy - Tuscany.

Your favourite food and drink?
Pasta cooked in Italy, and a robust red Italian wine like Brunello di Montalcino.

Your favourite composer?
Albinoni.

Your favourite artist?
Giacometti

Your favourite film?
Kiss of the Spider Woman with William Hurt.

Your main fault?
Impatience.

Your motto?
Et kütt wie et kütt - or what will be will be.*

*A personal questionnaire celebrated and originally made popular by the French writer Marcel Proust
Forty years on, and counting for the British Fertility Society

While London prepares to welcome ESHRE’s 29th annual meeting, members of the British Fertility Society are celebrating their own birthday. BFS Chairman Allan Pacey reviews the first 40 years and the Society’s current activities.

It was Patrick Steptoe and a small number of colleagues who came up with the idea of a British Fertility Society in 1972. However, it was not until July 1973 that the first ‘provisional’ committee met and the society was officially born and breathed life for the first time. This, of course, was a few years before Patrick and Robert Edwards achieved the world’s first successful IVF pregnancy, but even then Patrick had written to some 50 British gynaecologists known to have a special interest in infertility.

The first clinical meeting of the BFS was held in March 1974 at the Royal Northern Hospital in London, at the invitation of the local consultant gynaecologists. Originally it was intended to keep membership small enough to form a travelling club where members or invited guests could demonstrate surgical procedures in their own hospitals. This was deemed appropriate at a time when, in the pre-ART era, gynaecologists had a one-to-one relationship with their fertility patients and when surgery was the only treatment available for women with damaged tubes, however severe the damage.

So it was the original intention to keep BFS membership at no more than 75. Thankfully, this decision to keep membership small was overturned in 1983 - and today the Society has about 1000 members.

Forty years on, the membership profile has changed too. At the start it was largely a society for gynaecologists, but now doctors number just over half the total, with nurses, scientists, managers and counsellors comprising the rest.

The objectives of the BFS are to:

- Promote high quality practice in the provision of fertility treatment
- Provide a common forum for members of various disciplines with an interest in the science and treatment of infertility
- Promote high quality scientific and clinical research in the causes and treatment of infertility
- Provide professional leadership in the provision and regulation of infertility services
- Promote the increase of National Health Service (NHS) funding for and equity of access to fertility treatment.

To achieve these aims, the BFS has an Executive Committee which meets four times a year and comprises 15 elected members and six co-opted/ex-officio members. Much of the day-to-day work in between meetings is performed by the three Executive Officers; so, alongside Allan Pacey as the current Chairman, Jane Stewart works as Honorary Secretary and Sue Avery as Honorary Treasurer. The BFS also has an Honorary President (Richard Kennedy) who is there to advise and provide support.
Some UK landmarks in assisted reproduction

● In the beginning...
The world's first successful IVF pregnancy, delivered in Oldham, UK, in July 1978. Despite two further births, there was little support for IVF in Britain and, after a hiatus of two years, Edwards and Steptoe would set up privately at Bourn Hall near Cambridge.

● Down-regulation
The use of GnRH agonists to prevent the LH surge in ovarian stimulation was first proposed by Richard Fleming and colleagues in Glasgow in 1985.

● PGD
Alan Handyside and colleagues at the Hammersmith Hospital, London, reported the world's first successful birth following PGD for a sex-linked disease in 1990.

● Fertility preservation
The 1996 report from Roger Gosden's group in Leeds would set the parameters for ovarian tissue cryopreservation and transplantation for the next ten years.

● Controlled ovarian hyper-stimulation regimens: a review of the available evidence for clinical practice
Documents are ultimately published in the BFS journal Human Fertility and are highly cited. The Practice and Policy sub-committee also coordinates the BFS response to specific consultations being held in the UK. These are then published on the website.

Finally, the Training Sub-committee manages the busy schedule of training meetings and workshops. These take place twice a year, the first, in April, a joint course with the RCOG on subfertility and assisted conception. Integrated into the RCOG specialist training programme, this is typically attended by over 100 trainees from around the world and continues to be successful. Then, in June each year the BFS holds a week of training courses which cover running an effective fertility service, embryo transfer and IUI training, pelvic ultrasound and, new for 2013, male fertility. These are linked to six recognised training modules that lead to BFS certification.

A major part of BFS work now involves raising the profile of our profession within the UK. Over the past 10 years the BFS has responded to more than 3300 enquiries from the press. We now have a growing archive of press comments and statements and provide members with a daily e-mail digest of each
morning’s news. This is in addition to
a biennial newsletter and, from
January this year, our first BFS
experiments with Twitter (@britfertsoc).

Since 1998 the BFS has had its own
journal *Human Fertility* which in
2012 was awarded a first impact
factor of 1.377. From this year, the
journal is no longer published in
document format and becomes entirely
electronic, but it is freely available to
all BFS members through their
membership portal on the website.

Since the annual membership fee
for the BFS is only £135 (around
€160) for associates and clinicians
and £65 (€75) for everyone else apart
from students, this represents
excellent value.

Since the days of those first 75
members 40 years ago, the BFS has
developed enormously into a complex
organisation working on behalf of
reproductive medicine in the UK.
There are now approximately 60,000
cycles of IVF or ICSI provided each
year to 47,000 women, well over half
of which takes place in the private
sector. State funding for IVF remains
patchy in the UK and although in
early 2013 the National Institute for
Clinical Excellence published new
funding recommendations, it remains
to be seen how comprehensively these
will be implemented. Over the next
year the BFS will be working closely
with patient organisations to help
lobby for more state funding.

However, given the current economic
climate and major reforms now
planned for the NHS, this will be a
major challenge.

So the members of the BFS will give
a hearty welcome to ESHRE members
as they arrive in London for this
year’s annual meeting, and we hope
that it is a great success. BFS members
will be attending in numbers - both to
present their work and as delegates in
what we anticipate will be an
informative and exciting congress. In
return, please remember our 40th
anniversary too, as we look forward
to the next 40 years of the BFS and
hope that they will be as successful
and rewarding as the first.

Assisted reproduction in the UK today

All ART clinics in the UK are inspected and licensed by the HFEA and must
observe the terms of the Human Fertilisation & Embryology Act. An update
to the Act in 2008 shifted emphasis from ‘welfare of the child’ to ‘supportive
parenting’, thereby making it easier for lesbian and single women to access
treatment. Details of all cycles must be reported to the HFEA, whose latest
report (for 2011) made the following points:

- The number of IVF cycles (including ICSI) has increased almost every year
  since 1991 to a 2011 total of 61,726 IVF/ICSI and 4091 donor insemination
  cycles. Almost two-thirds of the women treated were aged 37 or younger
  (average 35 years). Most of the treatments (59.7%) were privately funded.
  The proportion of IVF and ICSI treatments was roughly equal.

- The overall pregnancy rate (per
  ET from fresh
  embryos) was
  steady at around
  34%, with
  substantial
  differences
  according to age,
  number of embryos
  transferred and
  embryo stage.

- Overall live birth rate per started cycle in 2012 was 25.6%.

- Overall multiple pregnancy rate declined from 22.3% in 2010 to 20.6% in
  2011; 16.8% of transfers were elective SET. By December 2011, 40.5% of all
  transfers were at the blastocyst stage; however, nearly two-thirds of the SETs
  (65.1%) were with blastocysts. Since
  2009 the HFEA and
  BFS have promoted
elective SET to
reduce the multiple
pregnancy rate (and
all clinics must have
their own ‘multiple
births minimisation
strategy’). The
HFEA has set a
multiple birth rate
target each year,
which currently
stands at 10%.

- The number of transfers with frozen/thawed embryos increased by 7%
  from 2010. Overall pregnancy rate after FET was 24.7%, a rate which the
  HFEA acknowledges as ‘generally lower’ than with fresh transfers. The
  overall multiple pregnancy rate is also somewhat lower (17.5%).

- The HFEA also notes that the proportion of all babies conceived by IVF in
  the UK has steadily increased. In 1992, 0.3% of all babies were born as a
  result of IVF treatment; in 2002 this had reached 1.4% and by 2010 had
  reached 2%.
Safety first in IVF

While multiple pregnancy poses by far the greatest risk of ART, there is an additional catalogue of other avoidable problems for the patient. Petra De Sutter reviews the risks and complications of ART, and how they can be avoided.

Ovarian hyperstimulation syndrome
The most important risk of the hormonal stimulation for ART is ovarian hyperstimulation syndrome, or OHSS. This syndrome arises in women with a high number of oocytes and occurs in its mild form (not clinically important) in 20–33% of cycles, in a moderate form in 3–6%, and in severe form in 0.5–5% of cycles. OHSS can be associated with severe complications as a
Focus on Reproduction  May 2013

result of electrolytic imbalance, neurohormonal and haemodynamic changes, pulmonary manifestations, liver dysfunction, hypoglobulinaemia, febrile morbidity, thromboembolic phenomena, neurological manifestations, adnexal torsion and psychological distress (see pathophysiology and clinical cascade of OHSS in the figures below).

The thromboembolic risks are especially important and may be fatal. Prevention is therefore important, not just because of the potential complications (mostly underreported) and the fact this is a iatrogenic complication of a non-vital treatment, but also because there is still no specific treatment for OHSS.

Nevertheless, prevention of OHSS is difficult; there is still a shortage of large, prospective randomised trials reporting on the prediction of OHSS and on strategies for its prevention. The aetiopathology of OHSS remains only partly understood, and there are still only indirect signs to identify patients at risk.

Primary prevention rests on identifying the patient at risk, adapting the choice of ovarian stimulation in both IVF and non-IVF treatments, and adequate monitoring.

Risk factors are a young patient age, low body weight, polycystic ovarian syndrome (or PCO-like patients), the use of GnRH agonists and hCG for luteal support, a high number of resting follicles, the size and number of mature follicles, a history of OHSS, and high estradiol levels.

There is no consensus on secondary prevention because there are no evidence-based measures. The administration of albumin or hydroxyethyl starch may be helpful, as may treatment with cabergolin. In antagonist cycles agonist triggering and extra luteal support seem to be effective. Good results have also been reported from a freeze-all policy, which avoids the transfer of fresh embryos.

Thromboembolism following OHSS is the most dangerous manifestation of the syndrome. Most thromboses will be venous (80%), but they can often occur at uncommon locations (such as the internal jugular or subclavian vein, or the inferior vena cava). Arterial thromboembolisms have also been described. Although most thromboembolic events following ART are associated with OHSS, some may be related to ovarian stimulation without OHSS, especially in patients at risk of thrombophilia. If patients present with a family or personal history of thrombosis, heparin prophylaxis may be indicated throughout the whole treatment.

**Cancer risk**

An important question remains whether ART stimulation or treatment increases cancer risks. Despite a flurry of newspaper headlines, the use of fertility drugs per se has not been associated with any increase in cancer risk, but there has been a consistent observation that women with infertility resulting from hormonal disorders have an increased risk of endometrial cancer.

A possible association between ovulation induction and ovarian cancer does not necessarily indicate a causal effect, since infertility alone is an independent risk factor for ovarian cancer. Indeed, nulliparous women with refractory infertility may harbor a particularly high risk of ovarian cancer, irrespective of their use of fertility drugs.
Blood loss and infection
Egg retrieval may be complicated by bleeding, and vaginal haemorrhage has been shown to occur following 8.6% of oocyte pick-up procedures. Indeed, in 0.8% of all egg retrievals significant (>100 ml) blood loss has been demonstrated and very serious bleeding in 0.1%. Bleeding typically occurs in the retroperitoneal ovarian space or from sacral or iliacal vessels. In some cases laparoscopy or laparotomy is necessary. Studies have shown that patients have lost on average 230 ml blood after egg retrieval and that a drop in haemocrit of 5% or of hemoglobin of 1.6 g% is normal.

To avoid excessive blood loss, it is advised to limit vaginal punctures to two, visualise peripheral follicles with ultrasound in a cross-section before puncture, and use colour Doppler if available.

If blood loss after oocyte retrieval is estimated as normal, any postoperative acute abdomen must be infectious in origin. Infections after egg retrieval occur in 0.6% of cases, half of them with abscess formation. Abscesses are often asymptomatic, and diagnosis may be delayed. Cultures often reveal E. coli, B. fragilis or Enterococcus, but are also often negative. Special risk of infection is caused by puncture of endometriotic cysts, pseudocysts or hydrosalpinges. It is not advised to administer routine antibiotica prophylactically nor to disinfect the vagina.

Multiple pregnancy
Although multiple pregnancies specifically affect the health of the children, which is outside the scope of this article, they also increase the risk of maternal morbidity and mortality. Pre-eclampsia, gestational diabetes, myocardial infarction, heart failure, venous thromboembolism, pulmonary oedema, postpartum haemorrhage, Caesarean delivery and hysterectomy all are significantly more frequent in multiple than in singleton pregnancies.

Multiple pregnancies as a rule occur following transfer of more than one embryo and occur in 20-25% of ART pregnancies worldwide. It is, however, possible to reduce twinning rates by applying a single embryo transfer (SET) policy, and many countries have started to implement such policies for this reason. It is to be hoped that the multiple pregnancy rate in Europe continues to reduce to acceptable rates in the decade to come.

Ectopic pregnancy
Ectopic pregnancies occur in about 4% of all ART pregnancies. Risk factors are damaged tubes, previous myomectomy and difficult transfer. Heterotopic pregnancies (the combination of an intrauterine and an ectopic pregnancy) have the same risk factors as ectopic but their incidence also depends on the number of transferred embryos. The diagnosis is often delayed and symptoms are sudden abdominal pain, bleeding and shock at rupture. Immediate surgery is indicated and 72.5% of the intrauterine pregnancies will remain intact and lead to live birth.

Interstitial or cornual pregnancies consist of 2-6% of all ectopic localisations, and may also be combined with an intrauterine pregnancy. Again, the diagnosis is difficult, often delayed and interstitial pregnancies may end in rupture, haemorrhage and shock (even leading to hysterectomy). They occur typically after salpingectomy. An important adage therefore is ‘Look beyond the most obvious diagnosis and always expect the unexpected’. Think ectopic, think heterotopic! During diagnostic laparoscopy for suspected ectopic pregnancy, the whole abdomen and pelvis, and especially the contralateral tube, should be inspected.

Adnexal torsion
Adnexal torsion occurs in one in 5000 pregnancies, but is much more frequent following ovarian stimulation. It is thought to occur in 0.1% of all ART cycles, if pregnant in 0.6%, and, if OHSS also occurs, in 7.5%. Treatment consists of laparoscopic untwisting (even after ischaemia, the ovary should not be removed), optionally after puncturing. Transvaginal puncture may also relieve pain symptoms in case of partial torsion of heavily stimulated ovaries.

In conclusion, ART treatments are not free of risks and complications for the patient, many of which can be avoided. The most important complications are OHSS and multiple pregnancies, and only adapted and careful ovarian stimulation and transfer of fewer embryos can reduce these iatrogenic risks. Avoiding such complications in high risk patients, and especially in egg donors and recipients or in cross-border patients, is an ethical issue and should be the priority of every clinician dealing with these patients.

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