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SCIENCE MOVING
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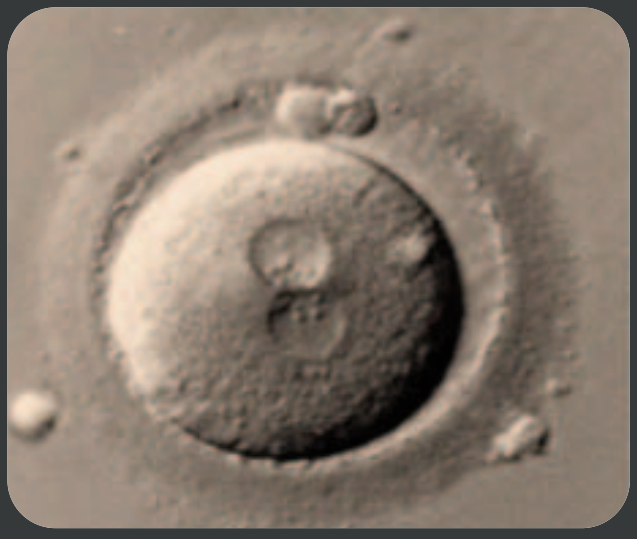
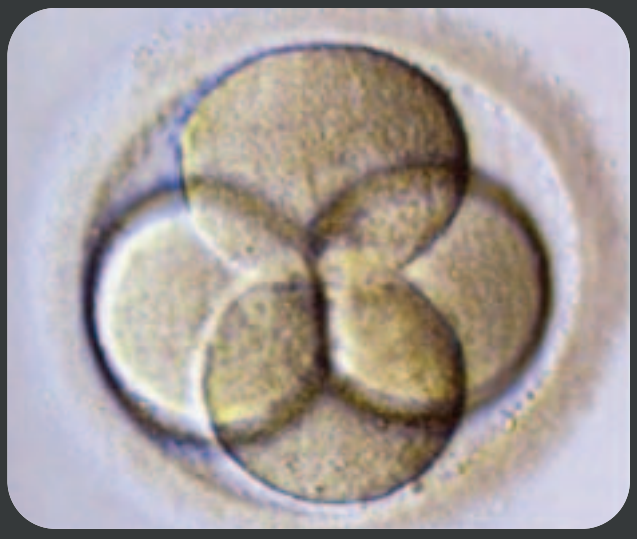
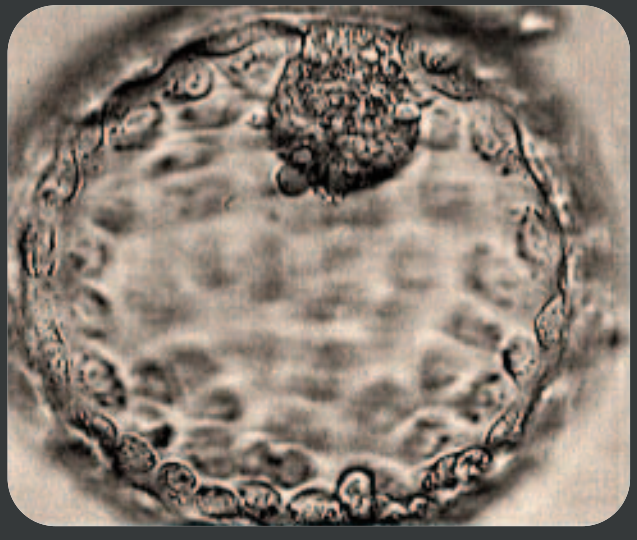
focus on REPRODUCTION



New generation embryos

How the IVF lab can improve implantation

// JANUARY 2014

- 30 years of ESHRE
- 20 years of PGS
- A new look at PCOS
- Munich preview

JANUARY 2014

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CONTENTS

CHAIRMAN'S INTRODUCTION

The results of the delegate satisfaction survey from the annual meeting in London support our preliminary opinion of a very successful event. With an almost 90% satisfaction score, participants' perception of the overall organisation of the congress was excellent, with 80% of respondents believing that what they had learned would help them improve their daily professional work. The same percentage said that they were satisfied with the level of scientific quality. And so moving ahead, the scientific programme committee has finalised the invited programme for Munich 2014, while the programme for Lisbon 2015 is almost complete. In February the Executive Committee will review applications to organise the annual meeting in 2016, and the country and venue will be announced in the Spring.

ESHRE's certification programmes are expanding. In 2008 the first ESHRE certifications for clinical embryologists were introduced, and today there are more than 1000 ESHRE-certified Senior and Clinical Embryologists. Starting last year, non-Europeans have also been able to apply for certification. The new ESHRE Certification for Reproductive Endoscopic Surgeons (ECRES) is the first international certification in the field of reproductive surgery. The goals of this innovative programme are to increase patient safety, enhance good clinical practice, and establish surgical endoscopic treatment based on the best available evidence. The first theoretical exams will start in Munich. Furthermore, as we note on page 16 of this issue of *Focus on Reproduction*, an accreditation programme for nurses and midwives specialising in ART is now under way, with the first candidates sitting their exams in Lisbon in 2015.

The ESHRE accreditation programme of specialist training centres, which is co-ordinated by EBCOG, is increasingly attractive. Recent requests have triggered an update of our application process (from paper to electronic) and accelerated decision-making for approval.

E-Learning is an important part of the overall education offered by ESHRE. The contents are planned by the Special Interest Groups (SIGs) and several initiatives are now under way. They include the recording of lectures in precongress courses with relevant questions, linking them, for instance, to the continuous embryology education credit (CEEC) activities or to the CME European credits system.

In 2013 the first ESHRE guideline based on our manual for guideline development - on the management of women with endometriosis - was completed. The text is on the ESHRE website and a summary has been published in *Human Reproduction*, with an app due for release soon. Currently, ESHRE has three other guidelines in development, and the Executive Committee has now decided to make all ESHRE guidelines freely available.

This year marks the 30th anniversary of ESHRE, an anniversary which will be recognised in ESHRE workshops, Campuses and the annual meeting. So I wish you all a successful jubilee.

Juha Tapanainen
ESHRE Chairman 2013-2015

// JANUARY 2014

The momentum moves on to Munich

Deadline for abstract submissions is 1st February

It is almost 29 years since ESHRE staged its first annual meeting in Bonn, Germany, with just 650 visitors. The whole scientific programme was printed on a small piece of paper which could be folded conveniently into the name badge. How things change . . . and we can now look forward to a multi-session programme with many thousands of participants, lively discussion, and the chance to meet colleagues from all around the world - and of course to hear the very latest developments in reproductive medicine and embryology. And it is against this background of change and growth that the local organising committee invites invite you to the 30th Annual Meeting of ESHRE in Munich, Germany, from 29th June to 2nd July 2014.

The city and surrounding areas are especially attractive and certain to echo our own welcome with hospitality, culture and entertainment alongside the science of the congress. Following Hamburg in 1995 and Berlin in 2004, Munich will be the fourth city in Germany to host an ESHRE annual meeting.

Munich is known throughout the world as a dynamic and economically successful city which combines the traditional with the modern. And the Bavarian capital offers all the advantages you would expect of a leading international congress and exhibition venue in the heart of Europe. Although the Octoberfest is in the autumn, the city still offers numerous beer gardens and breweries with traditional food and waiters, as well as fine international restaurants and a lively quarter for student pubs, restaurants serving national and international cuisine, and of course shopping.

For those who like outdoor life and a break in the sun, time in the English Garden, the Botanical Garden or in one of the many parks or open air Vitualienmarket may be more attractive. There are many historical and modern buildings to explore - at the lively atmosphere of the Marienmarket, the Nymphenburg or at the Stachus.

Munich is also a centre of art and culture, with exquisite collections of old, 19th and 20th century and

modern pieces of art. The German museum or the BMW Forum will be especially attractive to those with an interest in science, technology and cars, while the Olympiapark and the Olympia tower offer attractions for those interested in sports.

Munich is surrounded by beautiful countryside and a tour with a boat ride on one of the picturesque lakes - such as the Chiemsee, Starnbergersee, Ammersee or Tegernssee with views of the mountains - or a hike through the Bavarian meadows, a visit to the brewery in Andex Monastery, or a tour to the spectacular royal castles Neuschwanstein and Linderhof are all within reach. The Alps and Germany's highest mountain, the Zugspitze, are also not too far away.

Although the towers of the Frauenkirche are currently under reconstruction and not open to the public, the beautiful baroque church of St Peter in the city centre is open, from where the Alps can be seen on a clear day. Schwabingen is the quarter for night life, with lively bars and pubs, while those interested in classical music can plan an evening at the Bayerische Staatsoper, German theatre or a concert with the Munich Philharmonic or Bavarian Radio Orchestra.

Munich has an excellent public transportation system and most places are within easy reach - and we of course will do all we can to make your stay an enjoyable and happy one. We can assure you that Munich in the summer is a charming and exhilarating venue.

Places to explore - the Nymphenburg Palace, above, and English Garden.

But Munich is also a place of science and medicine, with its famous Ludwig Maximilian University and centres for gynaecology and obstetrics, ART and reproductive medicine, genetics and biology, so a place to encourage critical discourse in a friendly setting.

The venue chosen for this year's annual meeting is the ICM, the International Congress Centre Munich, one of the most modern and successful congress centres in the world. The ICM is about 20 minutes from the city centre by subway and within reach of numerous hotels.

The city itself is easily reached by air or train and there is good public transportation to and from the

ALL ABSTRACTS MUST BE SUBMITTED ONLINE

All abstracts intended for selection for this year's meeting must be submitted online to arrive at ESHRE no later than 1st February.

All submissions must be categorised as Basic Science or Clinical Science and identified according to a list of topics set out on the ESHRE website.[1] The substance of the abstract should be original material which has not been published or presented at any other meeting. For London last year almost 1600 abstracts were submitted, of which only 223 could be accommodated in the oral programme - so competition for selection is tough.

To ensure that abstracts are robust and able to answer the reviewers' questions, all submissions must follow a strict format (as also applied to abstracts for *Human Reproduction*). There are full details on the ESHRE website,[2] but in brief the text of the abstract should be arranged according to the following subheadings:

- Title (maximum 25 words)
- Study question (maximum 50 words)
- Summary answer (maximum 50 words)
- What is known already (maximum 75 words)
- Study design, size, duration (maximum 50 words)
- Participants/materials, setting, methods (maximum 50 words)
- Main results and the role of chance (maximum 125 words)
- Limitations, reasons for caution (maximum 50 words)

- Wider implications of the findings (maximum 75 words)
- Study funding/competing interest(s) (maximum 30 words)
- Trial registration number (maximum 20 words)

And the full abstract text must not exceed a maximum of 600 words.

1. http://www.eshre2014.eu/Programme/Abstract-submission/Abstract-topics.aspx.
2. http://www.eshre.eu/Programme/Abstract-submission/Abstract-content-and-format.aspx.

ALL YOU NEED TO KNOW IS ON MUNICH'S DEDICATED WEBSITE

Information on the programme, registration, exhibition, transportation and accommodation is presented in detail on the dedicated website for this year's annual meeting. The site enables online registration (which is obligatory for individual participants) and online submission of abstracts. Individuals registering early (before 30th April) can benefit from substantial fee reductions, which are greatest for ESHRE members.

Hotel accommodation is organised through ESHRE's congress partner MCI. A hotel reservation form is available on the congress website. Last year more than 10,000 took part in the annual meeting in London, so, with similar numbers expected in Munich, early booking is recommended this year too.

● Visit the website at www.eshre2014.eu.

airport and main station, as well as to the conference centre and places of interest.

Once again, ESHRE's SIGs and International Scientific Committee have assembled a fantastic programme of precongress courses and invited lectures. There will be 14 precongress courses on topics ranging from patient management to improved treatments to novel developments and techniques, from basic and applied research to ethical and social aspects of ART and embryology. In the main programme there will be invited sessions on fertility preservation and fallopian tube failure, ovarian stimulation, and Turner syndrome. These sessions will also include presentations on the generation of gametes and stem cells, oocyte activation, and a critical appraisal of delayed embryo transfer. And there will be several session on paramedical and laboratory topics.

Overall, 69 sessions have been reserved for selected oral communications, so all ESHRE members (and non-members) working in the field are urged to submit their abstracts in time for review and invitation.

We are looking forward to seeing you in Munich!

Local Organising Committee, Munich 2014

Tina Buchholz, Klaus Diedrich, Ursula Eichenlaub-Ritter, Klaus Friese, Markus Kupka, Christian Thaler

More than 1000 embryologists have achieved ESHRE certification - with many more expected in Munich

ESHRE's Clinical Embryology Certification programme continues to grow with now more than 1000 certified.

Not surprisingly, there has been a strong increase in exam applications for Munich - this is the first year that clinical embryologists from outside Europe are able to apply, following the introduction of seniors from outside Europe in 2012.

ESHRE's Steering Committee for Embryologist Certification and SIG Embryology are currently collecting data from all European countries on education, requirements for employment, and professional public and private positions in which embryologists are employed, as well as their legal status within national health service systems. We hope to obtain an updated picture of those institutions which license embryologists and of the regulatory authorities which ensure adherence to professional guidelines for IVF laboratories throughout Europe. The answers are expected to vary widely, but will help to obtain an overview on the education of IVF laboratory staff and their professional status in Europe. We hope the information will help increase the impact of the programme on careers in clinical embryology.

Cumulative total of certifiedf embryologists reached 1000 in 2013. The numbers are expected to rise even further with non-Europe admissions.

The ESHRE Embryology Certification Committee

Next 'Best Of' meeting heads back to the Italian Dolomites

Scientific programme for third ESHRE/ASRM event conceived on both sides of the Atlantic

The first 'best practice' meeting of ESHRE and the ASRM, held in 2012 in the Italian ski resort of Cortina d'Ampezzo, was, according to former ASRM chairman Roger Lobo, 'an experiment' but one which proved popular, stimulating and enjoyable. Last year's event hosted by the ASRM was held in the Bahamas and now, with ESHRE once again the host, the meeting returns to Cortina. The programme, again devised to encourage both scientific exchange and social interaction, will take place over three days from 27th February to 1st March. Full details are available on the ESHRE website (www.eshre.eu/cortina).

'The meeting aims to assess the evidence for both established and emerging approaches to the science and art of reproductive healthcare,' says ESHRE Chairman Juha Tapanainen. Subjects have been chosen for their topicality and for their relative difference in approach between Europe and the USA.

The 'best of' meetings are seen by both societies as annual events alternating between venues in Europe and the USA held during the Spring season. With mornings free, leisure time this year can be spent on the ski slopes or enjoying the spectacular scenery.

Lectures

Back-to-back sessions, during which different topics and practices will be analysed from the American and European points of view

Debates, in which two experts will discuss controversial issues, illustrating different point of views and supporting different theories and approaches

Cutting-edge lectures, aiming to illustrate innovations and new findings in reproductive medicine and embryology

Thursday 27th February

14.30-15.00	Preconception genetic screening and genetic counselling. What do we want to know? *José Horcajadas Almansa (ES)*
15.00-15.30	Male fertility preservation *Christine Wyns (BE)*
15.30-16.20	Repeated miscarriages - male and female contributions *Ruth Lathi and Dolores Lamb (USA)*
16.20-16.50	Update in office reproductive surgery *Vasilios Tanos (CY)*
17.10-1800	Cell free fetal DNA in maternal blood - the US perspective *Joe Leigh Simpson (USA)* - the European perspective *Gian Carlo Di Renzo (IT)*
18.00-19.00	Uterine transplantation or surrogacy? *Mats Brännström (SE) and Richard J. Paulson (USA)*
19.00-19.30	Are we ready to freeze all? *Miguel Angel Checa Vizcaino (ES)*

Friday 28th February

14.30-15.30	The treatment of fibroids and preservation of fertility *Elizabeth Stewart (USA) and Vasilios Tanos (CY)*
15.30-16.20	Implantation failure - embryocentric or uterocentric? *Mina Alikani (USA) and Carlos Simon Valles (ES)*
16.20-16.50	Health risks for infertile men M. Eisenberg (USA)
17.10-1800	Vitrification of oocytes and embryos *Ana Cobo (ES)* The ethics of male and female social freezing *Françoise Shenfield (GB)*
18.00-19.00	Thyroid replacement therapy in fertility patients with 'normal' TSH *Ulla Feldt Rasmussen (DK) and Christos Coutifaris (USA)*
19.00-19.30	Mitochondrial DNA: Source of information or source of confusion? *Giovanni Romeo (IT)*

Saturday 1st March

14.30-15.30	Infertility and the ageing male *M. Eisenberg (USA)*
15.00-15.30	Update on medical treatment of endometriosis *Linda C. Giudice (USA)*
15.30-16.20	Ectopic pregnancy - the US perspective *Ruth Lathi (USA)* - the European perspective: Can we wait? *Emma Kirk (GB)*
16.20-16.50	Paternal ageing and health of the offspring *Rebecca Z. Sokol (USA)*
17.10-1800	How old is too old for ART? *Richard J Paulson (USA) and Adam Balen (GB)*
18.00-19.00	Patients with Turner syndrome should not be denied the chance for pregnancy by donor oocytes *Viveca Söderström (FI) and Richard Reindollar (USA)*
19.00-19.30	Special considerations dealing with obese infertile patients *Richard Legro (USA)*

Pro-life campaign threatens EU funding for embryo-derived stem cell research

One million signatures gathered for citizens' initiative

ESHRE has described as 'misguided' a pro-life campaign whose declared aim is 'a concrete ban of life-destroying policies in the EU budget'. In meeting the requirements of the European Citizens Initiative, the 'One of Us' campaign has apparently gathered the one million signatures necessary to invite the European Commission to propose legislation on matters in which it has legislative power.[1]

The One of Us organisers have set out their arguments in a 'statement of support' and base their case on the right to life 'of every human being from conception'.[2]

Thus, according to a report from the Catholic News Agency in September last year, 'since One of Us has met the requirements, the European Commission will ask the EU "to end the financing of activities which presuppose the destruction of human embryos, in particular in the areas of research, development aid and public health".'

ESHRE posted a statement of concern on its website, noting that the opinions expressed in such campaigns as One of Us will jeopardise EU funding for research in reproductive science and regenerative medicine.

ESHRE remains especially critical of the campaign's description of embryo research as solely 'embryo-destructive', a description which, said ESHRE, 'misrepresents the advances already achieved in stem cell research, or indeed in the world's five million babies conceived by reproductive technologies'.

Detailed negotiations continue over Horizon 2020, the EU's research funding programme for the period 2014-2020, whose (slightly reduced) budget of €70 billion was approved in September. Previous negotiations in 2006 cut the scope of stem cell research eligible for EU funding by excluding research on embryos or the creation of new embryonic (hESC) cell lines - and it now seems likely that the same restrictive rules will apply in Horizon 2020. ESHRE has already described as 'worrying' proposals from several religious organisations to extend even further these restrictions on stem cell funding.

1. See http://ec.europa.eu/citizens-initiative/public/basic-facts.
2. http://www.oneofus.org.uk/downloads/OneOfUsSignatureForm.pdf.

ESHRE's e-Learning programme moves forward, with first lectures now recorded for presentation

From the first webinars recorded by the SIG Reproductive Genetics.

ESHRE has begun the development of an e-Learning platform whereby audio-visual and interactive educational content will be made available to members. The provision of continuing education to its members is one of ESHRE's missions and e-Learning represents an opportunity to expand and share the knowledge of its experts via a simple Internet connection. The ESHRE e-Learning platform will be accessible via the 'Education' section of the ESHRE website (www.eshre.eu/education).

ESHRE is currently selecting relevant lectures and developing quality material to meet a range of educational needs. The role of the Special Interest Groups is crucial at this stage to propose appropriate subjects, create content and find the best speakers. Once the course is developed, all lectures will be professionally recorded in a studio or during an ESHRE Campus workshop.

The SIG Reproductive Genetics has already shown much enthusiasm to the project and initiated a first series of lectures on the basics of reproductive genetics, which were recorded in a studio in Brussels in November last year. The SIG Embryology will also include their lectures as a way of obtaining credits for upgrading the embryology certificate. And a series of lectures was filmed during the workshop 'From early implantation to later in life' organised by the SIG Early Pregnancy in October.

ESHRE is keen to receive suggestions from members to choose the most suitable lectures for its e-Learning platform. Ideas of topics or speakers considered relevant and interesting should be sent via email to Christine Bauquis, ESHRE's communications co-ordinator (christine@eshre.eu).

Accreditation for specialist training centres in reproductive medicine: simpler procedure

- Could your clinic be accredited by ESHRE for specialist training?
- Could your clinic be recognised as an ESHRE-approved centre and part of the educational network for sub-specialists in reproductive medicine?

For the past ten years ESHRE has had the authority to recognise, subject to satisfactory assessment, all IVF units as accredited for subspecialist training. Indeed, several centres, with or without national regulatory support for training in reproductive medicine, have successfully applied to ESHRE for accreditation. As a result, these units attract specialist trainees keen to become specialists in their own right following a two-to-three year specialist training programme.

In recent years, the demand for a structured, recognised training which provides such specialist recognition (and consistent standards) has increased. This demand is evident both here at ESHRE and with our sister regulatory body, the European Board and College of Obstetrics and Gynaecology (EBCOG).

The approval of both EBCOG and ESHRE are required for the formal recognition of a clinic for subspecialist training in reproductive medicine. The historical ties between ESHRE and EBCOG are bound by a shared vision to promote optimal subspecialist educational provision.

Making the process simpler

The application process has now been upgraded and redesigned to be online, accessible and simple (eshre.eu/Accreditation and Certification). The first step for centres considering accreditation is completion of a straightforward application form that accurately reflects the activity of the training unit and the availability for educational support; this should be submitted to ESHRE (Catherine@eshre.eu).

After successful application, the unit is visited by at least two ESHRE/EBCOG approved assessors, who will spend at least one day in the unit examining the structure and content of the proposed training programme and meeting all relevant personnel. Notification of the visit to the national society of O&G within that country should be made by the head of the training centre out of courtesy wherever possible. The reasonable costs for the assessors' travel and accommodation are borne by the application centre. At the end of the visit, it is customary for both assessors to provide an on-the-spot debriefing and a summary of the recommendations and conclusions to the head(s) of centre.

An assessors' report will be written and signed shortly after the visit and submitted to ESHRE and EBCOG. When approved, both ESHRE and EBCOG Executive Committees will propose recognition of the training centre for specialist training in reproductive medicine for up to a maximum period of five years. A Certificate of Accreditation signed by the Chairs of both ESHRE and EBCOG is then issued to the centre in recognition of its new educational status.

ESHRE-funded research projects, such as ESTEEM, would in future prefer centres that demonstrate full subspecialist training accreditation as part of the centre profile. The acquisition of educational approval is seen as a desirable standard that promotes excellence in research as well as care provision.

Roy Farquharson
ESHRE Executive Committee,

THE REWARDS OF ACCREDITATION

VU Brussels, already accredited for specialist training.

To date, there are six recognised ESHRE-approved clinics, with the numbers expected to grow as demand for specialist training increases. This activity can now be met by dedicated support at ESHRE Central Office aiming to streamline the whole process of application, inspection visit and award of certification. An updated list of accredited centres appears on the ESHRE website. The achievement of obtaining the ESHRE 'badge' of approval for specialist training in reproductive medicine has been enthusiastically taken up by many clinicians and IVF professionals, and the increasing need for status recognition by individual clinics is undoubted. The opportunity to apply may represent a challenge, but the reward is greater.

All ESHRE committee members to declare potential conflicts of interest

A move to ensure good governance and transparency

Everyone holding office or membership in any of ESHRE's committees (including the Executive Committee and SIG and Task Force steering committees) must now complete a declaration of interest form disclosing any potential conflicts of interest. It was also agreed at a meeting of the Executive Committee in September that committee members should disclose any potential conflicts of interest before their meeting began and, if a conflict of interest was apparent, that member should leave the room when discussion covered the conflicting subject.

The intention of the move is not to prevent someone with a potential conflict of interest from occupying a position of responsibility in ESHRE, said Juha Tapanainen, ESHRE's Chairman, but to ensure good governance and transparency.

ESHRE defines a conflict of interest as 'a conflict between the private interests and the official responsibilities to ESHRE of a person in a position of trust and responsibility'. A 'conflict of commitment' describes a difficulty in balancing responsibility to ESHRE with external activities, which can result in conflict with regard to allocation of time and energy.

In addition, all those making presentations at any ESHRE event - from the Annual Meeting to Campus workshops - must similarly include a slide at the beginning of their presentation which makes a brief declaration of such interests.

Speakers will also be asked to complete a declaration of interest form as required by the European Accreditation Council for Continuing Medical Education (EACCME), which, in paragraph 24 of its requirements for CME accreditation, states: 'The Provider must ensure that all members of the Scientific and/or Organising Committee provide written declarations of potential or actual conflicts of interest.' Without such declarations, CME accreditation would not be possible at ESHRE events.

ESHRE has also put in place a review committee to consider personal interests thought to be problematic. This committee will have an advisory role, and any final decision will be made by the Executive Committee.

POTENTIAL CAUSES OF CONFLICT OF INTEREST

- (Un)paid consultancy (in fields relevant to ESHRE)
- Editorship in field-related international journals
- Employment by a company in fields relevant to the Society
- Financial (personal) reimbursement (travel expenses)
- Grants/grants pending from commercial companies
- National or international political mandates
- Officer or board member of other societies in related fields
- Participation in sponsored trials (personal or institutional)
- Patents (planned, pending or issued)
- Payment for lectures
- Payment for manuscript preparation
- Royalties (in the fields relevant to activities of ESHRE)
- Stock/stock options or other ownership interests (in the fields relevant to activities of ESHRE)
- Other (in fields relevant to the activities of the Society)

ESHRE Chairman Juha Tapanainen said this was not a move to prevent people from holding office in ESHRE.

Top prize-winning presentation from 2013 annual meeting published in NEJM

Prize winner and study first author Carrie Williams receiving her prize in London.

The top oral presentation in clinical science from last year's annual meeting in London has been published in the *New England Journal of Medicine*.[1] The prize was unanimously awarded to a huge linkage study performed at the Institute of Child Health in London whose results showed emphatically that the children born after ART have no greater risk of cancer than children conceived spontaneously.

The HFEA records of all 106,381 children born after ART in the UK from 1992 to 2008 were linked to records of the UK's National Registry of Childhood Tumours to calculate the number who subsequently developed cancer.

Once the databases were linked, cancer rates in the ART cohort were compared with population rates, whilst stratifying for potential mediating factors. The average duration of follow up was 6.6 years. Results showed that there was no overall increased risk of cancer in ART children born throughout the 17-year study period. Overall, 108 cancers were identified in the ART children, which was comparable with the 109.7 cases which would have been expected from general population figures.

1. Williams CL, Bunch KJ, Stiller CA, et al. Cancer risk among children born after assisted conception. N Engl J Med 2013; 369: 1819-1827.

A new SIG for ESHRE on the 'socio-cultural aspects of (in)fertility'

The formation of a new SIG on the 'Socio-cultural aspects of (in)fertility' was approved at last year's AGM and its viability will now be assessed over the next two years.

The new SIG stems from the achievements of two Task Forces - Fertility & Society and Cross-border Reproductive Care. The former's focus was essentially the impact of fertility treatments on demographic markers in Europe, while the latter has studied European egg donors and patient movements across European borders.

How will the new SIG be useful among the already active other SIGS?

First, aware that our subject comprises societal, economic, demographic and policy matters, we already have in place a precongress course for Lisbon on a little discussed but recurrent problem in our specialty, when to stop treatment. For the following year we hope to collaborate with the SIG Ethics & Law with a further precongress course on the sociocultural issues of commercialisation in ART.

Second by proposing collaborations with all SIGS in joint workshops, remembering that socio-cultural aspects apply to many of specific SIGs interests.

Last but certainly not least, we are making research plans to continue the work already achieved by the Task Forces. I have already discussed with the SIG's Deputies (Paul Devroey and Anna Pia Ferraretti) two projects - one on the motivations of surrogates in the few countries where surrogacy is allowed in Europe, the other on oocyte banking for self use.

Finally, I am certain that all members of this new SIG will wish to thank Guido Pennings for his input, although his many commitments prevent his active participation in the Steering Committee. There will be many opportunities to continue working with him and with ESHRE members interested in the larger societal picture which we represent.

Françoise Shenfield
On behalf of the SIG Steering Committee

Britain abandons multiple birth target requirement following judicial review

Britain's IVF regulator has withdrawn its requirement for UK clinics to keep multiple births below a fixed target limit. The HFEA's move follows a judicial review in which Mohamed Taranissi on behalf of two London IVF clinics claimed that the number of embryos transferred should not be determined by the HFEA but on an individual clinical basis. The High Court found in favour of Taranissi, leaving the HFEA with little option but to withdraw its target. Lisa Jardine, chair of the HFEA, said it was 'simply not appropriate' for two out of 83 clinics to be outside the scope of the restrictions.

Since 2009 the HFEA has enforced a multiple births policy for UK fertility clinics, and since 2011 has set targets for multiple rates as a condition of the licence to practise. The target is currently 15%, and that policy still stands, said the HFEA chair. 'We will still expect clinics to bring the multiple birth rate down to 10% – in the interests of IVF mothers and their babies,.' The UK's overall multiple birth rate has fallen from 24% in 2009 to close to 15% today.

A statement issued on behalf of the British Fertility Society, Association of Clinical Embryologists and RCOG said that 'elective single embryo transfer (eSET) can be achieved without adversely impacting on pregnancy rates . . . and that responsible professionals will continue to do all they can to minimize multiple births through good clinical practice'.

Taranissi too expressed his own support for the 'need to reduce multiple births', but 'in a way which allows the clinicians to make these decisions in the best interests of individual patients on a case by case basis.' Taranissi added that a 10% target was 'unworkable' and unlikely to be met by many clinics.

. . . while twin deliveries found to be five times more costly than singletons in US cohort study

An American study has found that the cost of twin deliveries is five times higher than that of singletons, while triplets are nearly 20 times higher.[1] The adjusted total healthcare cost was around $21,000 per delivery for singletons, $105,000 for twins, and over $400,000 for triplets or more.

The study, which evaluated medical costs incurred by mothers during the 27 weeks leading up to and 30 days after delivery, also considered medical costs for infants up to their first birthday. The cohort included women between the ages of 19 and 45 who delivered at least one live infant between 2005 and 2010 – nearly 440,000 deliveries. Of these, around 97% were singletons, 2.8% twins and 0.13% triplets or more.

Not only were multiple births associated with significantly higher morbidity and mortality rates for both mothers and infants, said the investigators, but with 'significant health care expenses impact for payers'.

1. Lemos EV, Zhang D, Van Voorhis BJ, Hu H. Healthcare expenses associated with multiple vs singleton pregnancies in the United States. Am J Obstet Gynecol 2013; 209:586.e1-586.e11

Controversy persists in the diagnosis of PCOS

AMH emerges as a marker of the severity of symptoms

Full house. More than 190 took part in the PCOS Campus workshop of the SIG Reproductive Endocrinology in Rome.

It is now ten years since the first ESHRE/ASRM consensus on the diagnosis of polycystic ovarian syndrome was published, and in that short time it has become a citation classic - indeed, the most frequently cited article ever in *Human Reproduction*.[1]

These 'Rotterdam criteria' proposed a diagnosis based on at least two of three features: irregular or absent cycles; clinical and/or biochemical signs of hyperandrogenism; and polycystic ovarian morphology. Multiple ovarian follicles were thus not even essential for diagnosis.

Since then, according to Rome gynaecologist Daniela Romualdi, PCOS has been in a state of 'constant evolution', in terms of both treatment and indeed diagnosis. Which was why she and her colleagues in ESHRE's SIG Reproductive Endocrinology thought the time right to take a new look at this old subject. 'PCOS is a continuing challenge,' said Daniela. 'We have to consider the most appropriate short term treatments as well as the prevention and management of its long-term consequences, and there are still many questions about diagnosis and pathogenesis.' Recent genome-wide association studies, for example, have identified possible candidate gene variants associated with PCOS, while epigenetic and environmental factors (particularly obesity) appear to exacerbate any underlying genetic predisposition. Such emerging considerations remain subject to investigation.

The meeting was organised by the SIG's Deputy Daniela Romualdi, who said that evolution in the diagnosis and treatment of PCOS justified this 'new look at an old subject'.

With more than 190 registered for this Campus meeting in Rome, there is clearly considerable clinical interest in what is still described as the most common cause of anovulatory infertility - and much debate too over its diagnosis. Consensus, like Rome, was clearly not built in a day.

Indeed, Georg Griesinger, Past Co-ordinator of the SIG Reproductive Endocrinology, argued that it was time to end these seemingly interminable diagnostic debates. The Rotterdam criteria had added two new phenotypes to PCOS (normal cycles + androgen excess + polycystic ovaries; and irregular cycles + polycystic ovaries + normal androgen levels), but a statement from the US Androgen Excess Society in 2006 had - not surprisingly - made hyperandrogenism a diagnostic requirement (along with ovarian dysfunction) - which had once again shaken the frail transatlantic consensus of Rotterdam. Indeed, speaking by video from the USA, Rick Legro insisted that hyperandrogenism, either biochemical or clinical, is 'necessary to make a diagnosis of PCOS', and that hyperandrogenism 'identifies all the phenotypes of PCOS'. In particular, Legro proposed that hyperandrogenism is the one feature of PCOS which allows a differential diagnosis and the exclusion of other disorders.

However, an 'evidence-based methodology workshop' hosted by the NIH in late 2012 did support the diagnostic criteria of Rotterdam, with four phenotypes specifically identified: androgen excess + ovulatory dysfunction; androgen excess + polycystic ovarian morphology; ovulatory dysfunction + polycystic ovarian morphology; and androgen excess + ovulatory dysfunction + polycystic ovarian morphology.

While this diagnostic conclusion of the NIH was largely welcomed in Rome (four of the Rome speakers

FERTILITY IN PCOS: OVULATION INDUCTION

According to Andrea Borini speaking in Rome, fertility treatment in PCOS cases remains largely as recommended in the second ESHRE/ASRM consensus:[3]

- Lifestyle modification before ovulation induction in obese PCOS cases
- Clomiphene citrate is still the medical treatment of first choice
- Aromatase inhibitors are as effective, but more safety data are needed
- Metformin alone is less effective than clomiphene for inducing ovulation
- The addition of metformin to clomiphene may be indicated in certain groups
- Gonadotrophins in low-dose protocols aiming for monofollicular development represent an effective treatment option
- Laparoscopic ovarian drilling is as effective as gonadotrophins for ovulation induction and pregnancy, with lower risk of multiples
- IVF is a 'reasonable option', especially because of its potential to keep the number of embryos transferred to a minimum

Roy Homburg: made a strong case for AMH as a marker of symptom severity.

presented evidence to the NIH workshop), there was exasperation that the NIH had described the very term 'PCOS' as a 'distraction and impediment to progress'. 'The name focuses on a criterion —polycystic ovarian morphology — which is neither necessary nor sufficient to diagnose the syndrome,' the NIH panel concluded. 'It is time to expeditiously assign a name that reflects the complex metabolic, hypothalamic, pituitary, ovarian, and adrenal interactions that characterize the syndrome — and their reproductive implications.' The desire to rename PCOS, said Legro, reflects a wish to divide its reproductive dysfunction from its metabolic. But few at this meeting seemed sympathetic, and one suspects that territorial ideologies persist.

However, while diagnosis proved the hot topic of debate at this meeting, the star of the show may well turn out to be AMH, an endocrine revolution of the past decade which does indeed merit a new look. Roy Homburg, who presented data from his own London group's study of AMH in the ovarian physiology of PCOS, did not claim any definitive diagnostic role for AMH but did conclude that the severity of symptoms in PCOS is directly related to the number of small follicles present in the ovary, which in turn is reflected in AMH levels.[2] Serum AMH concentrations are thus able to distinguish between normal ovaries, polycystic ovaries ('polycystic ovarian morphology') and PCOS.

A further study not yet published which Homburg and colleagues are running in India also shows from a preliminary analysis of more than 1000 subjects that AMH levels are directly associated with BMI (unlike data described by Legro showing AMH levels declining with increasing obesity) and with dietary type. AMH, Homburg suggested, may well play an important role in the pathophysiology of PCOS in reflecting the density of preantral follicles (and thereby ovulatory function in PCOS).

Homburg's was a practical approach to PCOS, with ovarian physiology at its core. And others too seemed more inclined to the practicality of fertility in PCOS cases and the prevention of long-term disease than to agonising over diagnostic ideologies. Adam Balen, adopting the concept of Didier Dewally, described PCOS as a 'long-term' disease, characterised in the earlier reproductive years by menstrual irregularity and infertility, and in the later years by glucose intolerance, CVD and type 2 diabetes. Balen reported that the prevalence of risk factors for CVD is roughly three-times higher for women with PCOS than for controls - and two-times higher when BMI-matched. Much of this risk, he added, is mediated through total and abdominal adopisity.

Weight control, therefore, was a constant theme of this meeting - a 'lifelong challenge', according to Annemieke Hoek from the Netherlands. BMI, she said, not only has adverse effects on ovulation and fertility but is directly associated with PCOS. A study last year found that BMI was the strongest correlate of PCOS status, with every BMI increment increasing PCOS risk by 9.2%. A 2011 study from her own group showed that consistent loss of intra-abdominal fat is associated with resumption of ovulation. But drop-out, she conceded, is a recurring theme of lifestyle programmes - hence the lifelong challenge.

Nevertheless, 'preconceptional care', which comprised improved diet and regular exercise, was the first-line strategy of the second ESHRE/ASRM consensus report on PCOS treatment - and from this meeting there seems no controversy about that.[3]

Simon Brown
Focus on Reproduction

1. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19: 41-47.
2. Homburg R, Ray A, Bhide P, et al. The relationship of serum anti-Mullerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study. Hum Reprod 2013; 28:1077-1083.
3. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod 2008; 23: 462-477.

After 20 years, preimplantation genetic screening is in a new technology phase

But still a lack of strong evidence from clinical trials

It is a sign of the times that a meeting held to look back on 20 years of preimplantation genetic screening was part live theatre and part virtual reality (via Skype). Many of those instrumental in shaping the short history (and no doubt future) of PGS in Europe were there live in Bologna to describe the roles they played, but those in the USA hovered online over the stage, flickering down on an audience sometimes mesmerised at how far the US can advance its technology into the IVF clinic.

The meeting was organised in September last year by former ESHRE Chairman Luca Gianaroli, who with the young Spanish embryologist Santiago Munné had reported the first major claims for PGS back in 1997.[1] Three years previously Munné himself and colleagues in New York had found higher than expected rates of chromosomal abnormality in embryos derived from stimulated cycles, and these, they suggested, may well be the cause of failed implantation in IVF.[2] Hence the persuasive rationale for PGS - that if 50% of embryos are chromosomally abnormal, the transfer of normal ones should double implantation rate.

The introduction of fluorescence in situ hybridisation (FISH) analysis encouraged the uptake of PGS, which, according to Anver Kuliev speaking from New York, had by 1994 still only recorded 25 cycles for aneuploidy detection. Munné described the subsequent explosion of FISH analysis with day 3 biopsy (and up to 12 chromosome probes) as the first 'wave' of PGS activity, an upwardly mobile trend driven by optimistic study results and the growing availability of reference laboratories. By 2007, he reported, there were more than 6000 PGD procedures in the US, the majority for aneuploidy screening.

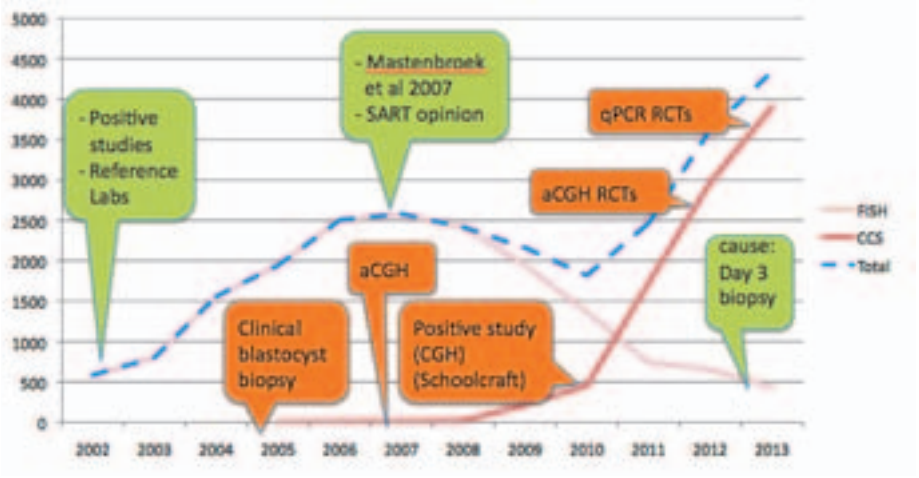
Although studies throughout the first decade of this century (notably from the VUB in Brussels) had cast a doubt on the validity of PGS with FISH, it took the large randomised trial of Mastenbroek et al to hammer the first nail into its coffin.[3] For, while the Brussels trials had found a neutral effect of PGS on delivery rates, the Amsterdam study actually found harm. The contradictory results prompted a storm of protest from the USA, and even Munné speaking via Skype in Bologna attributed the Dutch results to biology (self-correction, mosaicism) and technique (insufficient chromosomes tested, 'substandard' methods).

Nevertheless, the Amsterdam study reversed the PGS trend and for Munné initiated the second wave of PGS technology - in 24-chromosome analysis and blastocyst biopsy. The techniques used - array CGH, quantitative (real time) PCR and SNPs - were helped on their way by the wide-scale introduction of vitrification in 2007 and the application of blastocyst biopsy a couple of years before. It was this new wave of technologies, said Munné, 'which led dramatically to an increase in the number of PGS cases'.

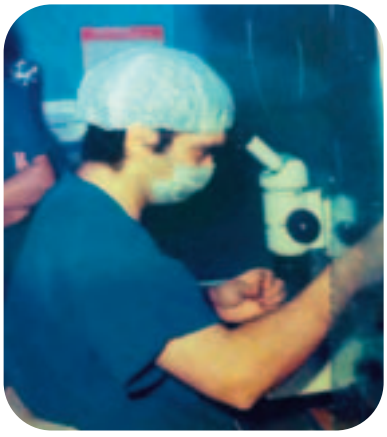
Blastocyst biopsy, he added, gives more DNA to analyse (fewer nil results), shows less mosaicism (lower error rate), has less invasive impact, means fewer embryos to process, and encourages single embryo transfer. And array CGH - as the most widely used PGS platform today - allows detection of all 24 chromosome aneuploidies and translocations, can give results within 16 hours, and is so far associated with a low error rate comparable with SNPs and qPCR.

Four randomised trials of these techniques have been published in the past three years, each with encouraging results. One, of array CGH and fresh transfer in women over 35, reported a remarkable ongoing pregnancy rate of 69% in the active group (n =

Virtual reality: via Skype from New York, Jamie Grifo explains results of aneuploidy screening in patients over 40.



The 'waves' of PGS uptake as described by Santiago Munné.



Sceptical clinician 1993.

55) and 42% in the controls (n = 48).[4] The most recent trial found comparative ongoing pregnancy rates between single euploid transfers and double untested transfers.[5] Such results, Munné emphasised, 'eliminate the effect of maternal age on implantation' - but not everyone was so impressed with the results.

Sjoerd Repping, one of the Amsterdam investigators in the Mastenbroek group, was not so bullish, comparing the similarity of papers now trickling into print with those of two decades ago. The title of Gianaroli's paper of 1997 - that PGD 'increases the implantation rate' of IVF - was exactly what Scott and colleagues announced last year for their technique of 'comprehensive chromosome screening'.[6] And for Reppping the evidence is just as thin now as it was 20 years ago - with big questions hanging over the Scott study (only good prognosis patients, skewed randomisation, low aneuploidy rates). 'All recent trials are of low quality,' said Repping.

Even more depressing, he added, is the paucity of ongoing RCTs. Numerous studies initially listed on www.ClinicalTrials.gov are now identified as 'terminated', many because of poor recruitment. With only one trial of sufficient power ongoing (ESHRE's ESTEEM study of polar body analysis by array CGH), there is still little evidence for scientific conclusion, said Repping, even if enough for marketing.

So where will PGS go? Will day 5 transfers set the standard? Do we even need to select embryos?

There were few doubts from across the Atlantic, most notably from Jamie Grifo from NYU Fertility Center in New York, where the application of a 'single thawed euploid embryo transfer' (STEET) programme appeared - from his data at least - to overcome most of the problems inherent in IVF (multiple gestations, preterm delivery, miscarriage, OHSS, high cost, medical risk, and the adverse effect of age). Neither morphology nor morphokinetics can reliably predict aneuploidy, insisted Grifo, but a treatment of SET following PGS (trophectoderm biopsy) and freezing in women over 40 produced ongoing pregnancy rates far higher than those following fresh transfers (58% vs 19% per transfer). And the explanation, said Grifo, 'is because we're putting back euploid embryos'. Cost per delivery was $55,000 with fresh transfers, and $45,000 with STEET, 'with results most dramatic in patients over 40'. 'The age impact disappears if you only transfer euploid embryos,' said Grifo.

Santiago Munné reported that over the past three years the number of cases of PGD in the USA had increased by more than 30% a year, while ART procedures had risen by only 5%. Thus, he calculated, 'if nothing changes by 2020, 50% of all ART procedures will be PGD'. Of course, as Munné readily acknowledged, everything *will* change in this fast moving field, not least in technology (next generation sequencing, said Dagan Wells), but whatever the approach PGS seems here to stay, with or without the hard clinical trials to validate it. For some the evidence is already strong enough, and the technology so progressive that the second wave of progress in comprehensive screening is now well under way.

Looking back on 1993 Gianaroli described himself then as a 'sceptical clinician', little aware of where it would all end. 'The journey is not finished,' he said in Bologna, 'but I feel more relaxed about PGS than I did then.' But the story of PGS with FISH has proved a salutary lesson, and reason enough that a technique with such huge clinical implications for the future still demands the evidence of strong clinical trials.

Simon Brown
Focus on Reproduction

1. Gianaroli L, Magli MC, Ferraretti AP, et al. PGD increases the implantation rate in human in vitro fertilization by avoiding the transfer of chromosomally abnormal embryos. Fertil Steril 1997; 68: 1128–1131.
2. Munne S, Lee A, Rosenwaks Z, et al. Diagnosis of major chromosome aneuploidies in human pre-implantation embryos. Hum Reprod 1993; 8: 2185-2191.
3. Mastenbroek S, Twisk M, van Echten-Arends J, et al. In vitro fertilization with preimplantation genetic screening. N Engl J Med 2007; 357: 9-17.
4. Yang Z, Liu J, Collins GS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet 2012; 5: 1755-8166.
5. Forman EJ, Hong KH, Ferry KM, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril 2013; 100: 100-107.
6. Scott RT Jr, Upham KM, Forman EJ, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril 2013; 100: 624-630.

Go-ahead for ESHRE certification of ART specialist nurses and midwives

Following logbook completion, first exams in Lisbon 2015

With continuing changes in technology, law and ethics, the role of the nurse or midwife specialising in ART is continually evolving. That role generally involves multiple responsibilities, including nursing care and counselling, patient education, treatment plan management, accurate record management, participation in quality assurance, and research activities. Currently, no framework for the role definition and education of ART nurses and midwives in Europe exists.

Following regular basic training events staged by the Paramedical Group over the past five years, we have now come to believe that a more professional structure is needed to acknowledge the competencies and roles of specialist ART nurses and midwives in Europe. Thus, in consultation with the instigators of ESHRE's certification programme for embryologists, the first steps towards an ESHRE certification for nurses and midwifes were made at the 2011 annual meeting in Stockholm. A working group was formed, with its first official meeting in January 2013. The members are Jolieneke Schoonenberg-Pomper (Co-ordinator), Helle Bendtsen (Chair Paramedical Board), Eline Dancet, Inge Rose Jorgensen, Helen Kendrew, Anja Pinborg (Clinical adviser) and Catherine Plas (ESHRE Central Office).

In September last year an expert meeting took place in which nurses and midwives from ten different European countries were present to comment on initial drafts of a logbook and reading-list. We wished in particular to ensure that the educational level we were aiming for was appropriate for European nurses and midwives. We were happily surprised at the enthusiastic response. And now, after further checking with the Special Interest Groups, the logbook and preliminary reading-list for the ESHRE certificate for nurse and midwives are ready.

Requirements

The ESHRE certificate for nurses and midwives has practical (logbook) and theoretical (examination) components. Thus, the requirements for certification are to:

September's expert meeting identified curriculum topics and competencies for ESHRE specialist nurse certification.

- be an ESHRE member
- have a nurse or midwifery degree
- have three years of clinical experience as an ART nurse or midwife
- submit a completed logbook (completed over a maximum of two years)
- complete 66% of the 100 multiple choice questions

The curriculum covers 17 different topics

CERTIFICATION CURRICULUM

- The epidemiology of infertility
- Female reproduction
- Male reproduction
- Ultrasound scanning
- Clinical fertility treatments
- Laboratory procedures in ART
- Embryology
- Genetics
- Early pregnancy
- Fertility treatment prognosis
- Fertility treatment safety
- Quality assurance
- Legislation and ethics
- Psychosocial support
- Patient-centered care
- Lifestyle, age and infertility
- Research.

according to the different roles and skills needed by a nurse or midwife in a fertility clinic. We are aware that there are big differences here between different European countries. Moreover, our expert meeting in September made it clear that there are also discrepancies in skills, roles and responsibilities in the different countries.

However, despite this diversity the nurses and midwives present at the meeting all agreed on the importance for all ART specialist nurses to have a sound knowledge of all ART techniques, even though these techniques might not be performed in their own clinic or country. We consider that this knowledge will encourage a higher standard of patient care offered by nurses and midwives.

The logbook

The practical part of the certification is completion of a logbook, which must be done within two years of downloading. Candidates must perform (P) all the techniques themselves, although it is also possible to observe (O) or assist (A). For instance, a medical history in most countries is taken by the doctor, so for most nurses and midwives their most likely role is observing. Once the number of cases required for a given task is completed, the supervisor of the nurse or midwife must sign the logbook for that task. The supervisor may be a more experienced

nurse or a doctor. On completion, the logbook must be signed off by the head of the clinic before its return to ESHRE's Central Office for checking.

Once the candidate has met these requirements, (s)he becomes eligible for the exam. The deadline for handing in logbooks will be 15th December in the year preceding the exam, which will always be held at the annual meeting.

The logbook is now available on the ESHRE website, so nurses or midwives wishing to take the first exam at the annual meeting in Lisbon in 2015 can already begin.

The reading-list

The working group established a reading list which nurses and midwives can use to prepare for the exam. A preliminary reading list is also now ready and available on the ESHRE website.

The exam

The exam is taken at the annual meeting. The first exam will be held in Lisbon 2015 and will comprise 100 multiple choice questions. The exam will be in English and 66% must be answered correctly to receive ESHRE certification.

What next?

Currently the working group is busy finalising the reading-list and collecting/developing multiple choice questions for the exam. When all this is completed the working group will become a steering committee of ESHRE, responsible for maintaining the quality of certification and updates of the curriculum, logbook, reading-list and exam.

We hope that all nurses and midwives will benefit from this certification.

Jolieneke Schoonenberg
Chair of the Working Group on ESHRE Certification for Nurses and Midwives

Call for paramedical abstracts for this year's annual meeting

Introducing new techniques in the lab

Our Campus course in Barcelona organised in collaboration with the SIG Embryology was fully booked and offered a timely warning to exercise care in implementing new techniques into our clinics. Among the speakers, embryologist Kersti Lundin covered a wide range of new techniques from different methods of sperm selection to genetic analysis and metabolomics. We were also given a nice introduction to microarrays with the encouragement - if the timing is right - to offer this sensitive technique in our own clinics or outsource it. Since the introduction of vitrification, survival rates of cryopreserved oocytes have improved drastically, with vitrification now playing a huge role in fertility preservation. But one thing became very clear during this symposium: each fertility clinic must perform its own proper validation of each new technique before implementation.

A full house for a follow-up symposium on the introduction of new technologies into the IVF clinic, organised in October by the Paramedical Board and SIG Embryology in Barcelona.

Paramedical Board

One of the Paramedical Board members will complete her term of office at this year's annual meeting in Munich. We thus invite paramedic members of ESHRE to apply for this vacant position. We are looking for a nurse/midwife who can make a four-year commitment, with possible re-election for a further four years. Board meetings are held three times a year, in the spring, one during the annual meeting and in the Autumn.

Events to come

Fertility preservation: from techniques to implementation in clinical practice workshop, Amsterdam, 14-15th March, organised with the SIGs Ethics & Law, Psychology & Counselling, Safety & Quality in ART, and the TF Fertility Preservation in Severe Diseases.

Basic training course for paramedics working in reproductive health workshop, Paris, 15-17th May. The competency of all paramedics working in ART must be evaluated at appropriate intervals specified in the quality system; this course aims to help ART paramedics achieve these requirements up to a recognised level.

Paramedic programme Munich 2014

The paramedical board is looking for lab technicians and nurses who are considering a report of their research. We are offering you a platform to present your work at the ESHRE annual meeting in Munich from 29 June to 2nd July 2014. If your report has not yet been published, an abstract of your study should be submitted before 1st February. Your abstract will be screened along with others sent in by lab technicians and nurses. The five best articles in both groups will be presented at the annual meeting. Instructions for submission are on the ESHRE website, and prizes are available for the best poster and oral presentations

Helle Bendtsen
Chair Paramedical Board

It was 30 years ago today . . .

ESHRE looks back from the latest milestone in its history

ESHRE was founded by the late Robert Edwards in the Spring of 1984, when he and the French gynaecologist Jean Cohen set out their plans to a few like-minded colleagues during the third World Congress of IVF in Helsinki. What followed was a temporary committee to draw up by-laws, and ambitious plans for an annual meeting and a journal. ESHRE was formally founded in September, when the temporary committee agreed that 'the Society should be formed'. Its aims were 'to facilitate the study and the analysis of all aspects of human reproduction and embryology'. The Society's first Chairman was Robert Edwards, who also edited the journal.

MEMBERS

6000

5000

4000

3000

2000

1000

1984: Robert Edwards and Jean Cohen propose a society and journal for Europeans working in reproduction. ESHRE is 'formed' with Edwards as Chairman.

1985: The first annual meeting - in Bonn, where 650 attended. First Executive Committee comprised Edwards, Cohen, Diedrich, Van Steirteghem, Crosignani, Egozcue and Sunde. Cohen presented the first ESHRE logo.

ESHRE

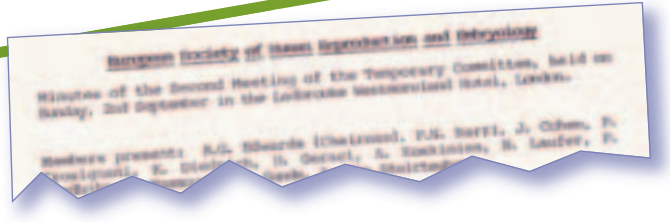
1986: First issue of *Human Reproduction* published, with Edwards as editor.

1987: Second Executive Committee formed, with Cohen as Chairman. Subscriptions to *Human Reproduction* now total 500. Edwards organises third Annual Meeting in Cambridge, with 850 in attendance. Patrick Steptoe is local chairman.

1988: ESHRE membership reaches 1000. Paramedical Group hosts first event at Barcelona congress.

1989: Pier Giorgio Crosignani becomes third ESHRE Chairman. Safety committee is formed and ethics committee sets about guidelines for ART and PGD. 700 attend Annual Meeting in Malmo.

1990: *Human Reproduction* records its first profitable year. First report from Safety Committee advised that the number of embryos transferred in IVF 'should be limited to three'. A Society reorganisation sees the first Campus events begin and sub-committees formed (to include the Special Interest Groups, whose consideration is requested in the newsletter *Focus on Reproduction*).


European Society of Human Reproduction and Embryology

Minutes of the Second Meeting of the Temporary Committee, held on Sunday, 2nd September in the Lehrenke Westmorland Hotel, Leuka.

Members present: R.G. Edwards (Chairman), P.R. Barri, J. Cohen, P. Crosignani, E. Diedrich, H. Geriel, A. Hamilton, H. Lauber, P.

1984 1985 1986 1987 1988 1989 1990

By the 1990s ESHRE had grown beyond any expectations - such that growing pains were a common symptom: workshops oversubscribed, congress venues unable to cope with attendance. Much of this growth was fired by the development of ICSI by the Brussels group of Devroey and Van Steirteghem. All publications after the first announcement (in *The Lancet*) were in *Human Reproduction*, many workshops were hosted by ESHRE, and data were collected by an ESHRE Task Force. At the same time, following the widespread introduction of down-regulation, IVF itself was on a roll - simpler, more efficient anf friendlier. ESHRE was well placed to represent this growth in Europe.

1991: Andre Van Steirteghem becomes ESHRE's fourth Chairman. Annual Meeting organised in Paris in conjunction with World Congress of IVF, the last joint event in ESHRE's history; Jean Cohen defends charges from WHO that IVF is inefficient and expensive. ESHRE's first multicentre clinical trial (on unexplained infertility) published

1992: First Annual Meeting (in Maastricht) for which abstracts were scored blind and selected on merit. Advisory Committee (later Committee of National Representatives) elected by full membership ballot to ensure geographical representation..

1993: A big year for ESHRE. At the Annual Meeting (in Thessaloniki), the first to be organised independently to ESHRE's own rules, Van Steirteghem makes landmark presentation on ICSI (and will publish all subsequent reports in *Human Reproduction*). Brussels hosts a first Campus workshop on ICSI, the first of many. Thessaloniki also sees first exchange session with the AFS (later ASRM), and hears safety session refute claims that ovarian stimulation increases risk of ovarian cancer. *HR* steps up frequency to 12 per year, and subscribers reach almost 2000. Klaus Diedrich becomes fifth Chairman of ESHRE, while Robert Edwards is made an Honorary Member.

1994: ICSI Task Force and SIG Reproductive Genetics formed. First course held in semen assessment.

1995: Updated guidelines on ethics of ART and on good laboratory practice published. *Human Reproduction* subscriptions reach 2500. First report from ICSI Task Force (in *Focus on Reproduction*). Annual Meeting (in Brussels) advertised on the Internet. Jose Egozcue ESHRE's sixth Chairman.

1996: Central Office moves to first dedicated offices outside Brussels. *Human Reproduction Update* and *Molecular Human Reproduction* launched by Edwards. ESHRE website goes live.

1997: ESHRE membership reaches 3000; almost 2500 attend Annual Meeting in Edinburgh. PGD Consortium established. ESHRE agrees to five-year moratorium on reproductive cloning. Basil Tarlatzis becomes seventh Chairman.

20 position papers have been published by the SIG/Task Force on Ethics & Law, originally ESHRE's first sub-committee, including the latest on sex selection.

NUMBERS

650 participants at ESHRE's first Annual Meeting in Bonn; more than 10,000 attended last year's event in London.

6223 are now registered as members of ESHRE, up from just 349 in 1985.

8.847 the impact factor of *Human Reproduction Update*, the world's leading journal in O&G and reproductive biology.

5,312,318 ART cycles monitored by ESHRE's EIM Consortium since 1997.

1991 1992 1993 1994 1995 1996 1997

ESHRE'S 30th ANNIVERSARY

Although the new millennium began with the resignation of Robert Edwards from the editorship of the three ESHRE journals, the decade saw huge consolidation in ESHRE's reach and representation. Almost two-thirds of the world's ART was now being performed in Europe, and the annual data monitoring reports from the IVF and PGD Consortiums would provide ESHRE with a database of activity unmatched throughout the world. In addition, Europe itself had opened up to many 'new' countries and their representation in the Advisory and Executive Committees - in accordance with article 15 of the by-laws - had instigated events impossible a few years before. ESHRE's consolidation also owed much to a long-term strategic plan devised by Evers and Sunde which put an emphasis on training, transparency and financial planning.

MEMBERS

6000

5000

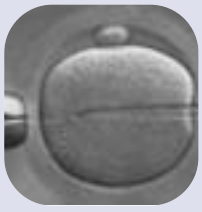
4000

3000

2000

1000

1998: Second and third reports from ICSI Task Force published. First web publication for some *Human Reproduction* papers. *HR* and *Update* reach numbers 1 and 2 in impact factor index for Reproductive Biology



2000: David Barlow takes over from Robert Edwards as editor of *Human Reproduction*. New editors for *Update* and *MHR* appointed. EIM Consortium publishes first report on ART data for 1997. Third guidelines on good laboratory practice from SIG Embryology. Campus workshop on prevention of multiple pregnancies prompts formation of new Task Force on risks of ART. More than 3300 attend 16th Annual Meeting in Bologna.

2002: Responsibility for training handed to SIGs.Stem cells high on ESHRE agenda - SIG Stem Cells formed, Ethics & Law Task Force publishes statement on stem cells, and Alan Trounson delivers keynote lecture on embryonic stem cells at Annual Meeting in Lausanne (where 3808 attended).

2004: For the first time attendance at the Annual Meeting (in Berlin) is more than 5000; in just ten years that total will have doubled. ESHRE renews its moratorium on reproductive cloning. European Commission publishes its directive on 'human tissues and cells'; ESHRE forms special Consortium to ensure that the ART sector is not ignored in developments.

2001: Ethics & Law Task Force publishes first statement - on the moral status of the embryo; seven more position papers will follow over next three years. Hans Evers and Arne Sunde present their strategy report for ESHRE, with training at its centre. Evers confirmed as ESHRE Chairman at Annual Meeting in Lausanne. ESHRE membership reaches 4243.

2003: Oversight of the day-to-day running of the Society is put in the hands of a 'chairman's group' working alongside Central Office. Joint ESHRE/ASRM Rotterdam consensus on the diagnosis of PCOS - the report would become the most frequently cited paper ever in *Human Reproduction*. Embryologist Arne Sunde, after having joined the temporary committee in 1984 and having steered much of ESHRE's growth in training, becomes the tenth Chairman at the Annual Meeting in Madrid (where more than 4500 attended). ESHRE formally opposes plans in Italy (Law 40, enacted in 2004) to restrict IVF and PGD (with bans on embryo freezing and egg donation).)

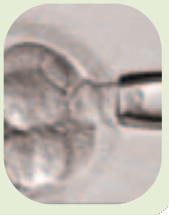
1999: ESHRE's second data Consortium founded, for monitoring ART in Europe. First press office introduced at 15th Annual Meeting in Tours. Lynn Fraser becomes first female Chairman of ESHRE.


DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004

1998 1999 2000 2001 2002 2003 2004

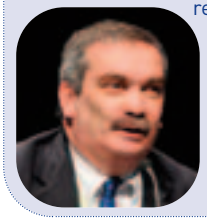
Despite the global financial crisis, ESHRE has remained cautiously sound and built its reputation on a tradition of science and clinical medicine. Day-to-day activities have concentrated on the SIGs - in training events, position papers, guidelines, certification programmes and clinical trials. The Society has also remained faithful to the aim of reducing rates of multiple pregnancy and ensuring safety in IVF. The ESHRE journals now occupy the first three impact factor places in reproductive biology.

2005: Paul Devroey, another of the ESHRE pioneers, becomes Chairman at the Annual Meeting in Copenhagen. Major SIG publications include: revised terminology from Early Pregnancy; management guidelines from Endometriosis; statements on surrogacy and HLA tissue typing from Ethics & Law. PGD Consortium issues best-practice guidelines on PGD and PGS.



2007: After 23 years, new logo is approved. Dutch geneticist Joep Geraedts takes over as Chairman at Annual Meeting in Lyon. Second ESHRE/ASRM consensus conference on treatment of PCOS (ovulation induction with clomiphene 'first-line' therapy). Administration of SIGs and training put in hands of dedicated sub-committee; Campus and precongress courses reach record level, with almost 25 events staged.

. 2009: Wide-ranging 'internal rules' approved to provide greater clarity in day-to-day activities. First basic training course for paramedics. Cross-border Task Force announces study in overseas fertility treatment trends. Annual meeting in Amsterdam attracts more than 8000 participants. EIM data show European twin delivery rate below 20% for the first time; ICSI now represents two-thirds of all ART procedures. Luca Gianaroli confirmed as ESHRE's 12th Chairman.



2011: ESHRE guidance on cross-border reproductive care. ESHRE joins European alliance for medical research. Working group on culture media is formed. Anna Veiga confirmed as 13th ESHRE Chairman. Satisfaction ratings in Stockholm were the highest ever.

2006: SIG Embryology announces certification programme for clinical and senior embryologists; by 2012 almost 900 had achieved certification. Almost 6500 attend Annual Meeting in Prague; electronic posters introduced for first time. André Van Steirteghem takes over as Editor-in-Chief of *Human Reproduction*, with new editors also appointed to *Update* (John Collins) and *MHR* (Steve Hillier). Joint recommendations of ESHRE and European Society of Human Genetics published. Executive Committee agrees to new Task Force for developing countries. Mission statement agreed.

2008: SIG Embryology updates laboratory guidelines to comply with EU tissue directives. Task Force on PGS formed to set up ESHRE multicentre trial (of polar body analysis by array CGH, which in 2012 will become ESTEEM). ESHRE publishes first position paper on EU Tissue and Cells directives. First revision to ESHRE's by-laws since foundation in 1984. Proposals from SIG Safety & Quality to standardise ESHRE guidelines. New style introduced to ESHRE and its publications at Annual Meeting in Barcelona (where almost 8000 attend and first embryology certification exams were held). Position paper on Good Clinical Treatment published. Membership of ESHRE reaches 5000.

2010: Abstract submissions for Annual Meeting jump by 33%; another attendance record will be broken. First budget defecit recorded as emphasis swings to training. Twenty years of PGD celebrated in Rome, and ten years of EIM data collection. Consensus on embryo scoring with ALPHA, and on definition of poor ovarian response. Results of ESHRE's polar body PGS study demonstrate feasibility. Robert Edwards awarded Nobel Prize.

2012: Embryo certification welcomes candidates from outside Europe. First 'Best Of' joint meeting with ASRM takes place in Italy. Updated *Atlas of Embryology* published online. ICMART reports 5 million IVF babies at Istanbul Annual Meeting.

2013: London Annual Meeting breaks all-time attendance record with 10,007 participants. Juha Tapanainen confirmed as 15th ESHRE Chairman. ESHRE report on oocyte donation in Europe. Updated guidelines on endometriosis completed. Proposals for nurse certification programme accepted. Certification for Reproductive Endoscopic Surgeons launched in London. EIM Consortium reports European multiple delivery rate below 20% for first time.

52,000 cycles monitored by PGD Consortium since first data collection.

40 training courses staged in peak year of 2010

2005 2006 2007 2008 2009 2010 2011 2012 2013

The Swedish embryologist Kersti Lundin became Chairman Elect of ESHRE at last year's annual meeting in London and will take over as Chairman next year. She talks to Focus on Reproduction about her new responsibilities and the changing shape of ESHRE.

A focus on the bigger picture

'We have to embrace our broader responsibilities. We are the collective force of our profession and certainly have to represent our membership.'

FoR: You were asked to become Chairman of ESHRE last year. What was your first reaction?
KL: I knew very well how big a responsibility the job was, so when I was first asked I actually said no, I didn't think I had the time to do it. But I asked around - at home, at work - and everyone said, of course, you have to say yes. I also felt that this would be my last chance and I'd regret it if I didn't.

Did you have an idea of what would be involved?
I had been in the Executive Committee for four years, so I know more or less what goes on, but I didn't really have an insight of what the chairmanship involves. Our protocol of having a two-year term as Chairman Elect first is also a very good way to get into the ESHRE system.

You've now been Chairman Elect for six months, so how is the reality shaping up?
So far, it's not more than I expected, but there are very many different things to deal with . . . educational, political, other societies, questions from Central Office which all need an answer.

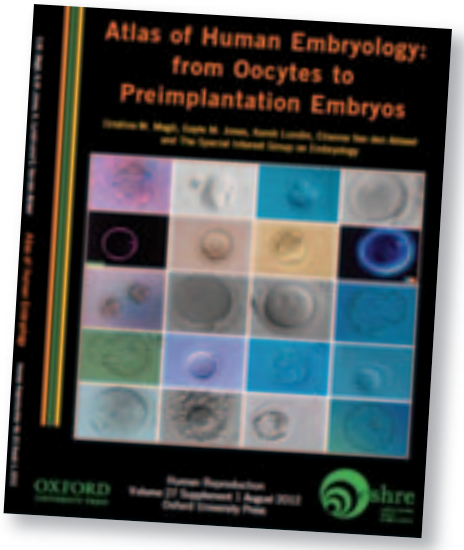
So has your day-to-day life changed much?
No that much so far. I was involved with the ExCo, then with the SIG Embryology, which was quite a lot of work, and then of course with the certification programme for embryologists. So I've got a long track record with ESHRE, which has always been rather time consuming.

And which of those ESHRE activities have been the most rewarding so far?
I would say there were many great highlights working in the ExCo and in the SIG Embryology. But certainly, the certification programmee for embryologists exceeded all our expectations.

That has been one of ESHRE's great successes?
Yes, I'm still amazed. Embryologists really feel that ESHRE certification is something they have to go for. In my own lab in Gothenburg they ask . . . Kersti, when can we do it? It's becoming really important for embryologists, especially the young ones.

Did your perception of ESHRE also change over this time?
Yes. There are many more issues now. When I started in the ExCo we had fewer meetings per year and shorter agendas. But now there are so many committees and reports, so much communication. I like it that all the committee members are very much involved. They're a group who want to participate and give their views. But it's also important how we do things. We have to be confident in how we reach our decisions and act upon them. For example, in the early days of the embryologists certification programme we did make some mistakes, which led to one or two difficult situations. So we have to be strict, and above all consistent, in what we do.

You seem to have a calm Scandinavian spirit. Do you need a certain personality to take on this responsibility?
Well, let me tell you there are many nights that I can't sleep because I'm so stressed. But yes, I think it helps if you get on with people and are able to keep detached and see



ESHRE's Atlas of Human Embryology, published in 2012 and a 'highlight' of the SIG Embryology.

problems from different angles. But you only have to look at our previous chairmen to see that they are all quite different types of personalities.

Sweden itself has been a model for restraint and discipline in IVF. How have you as a country achieved this when other countries have not been able to?
It's a difficult question, but I think it's fair to say that we Swedes have a way of scrutinising ourselves. We're also quite accommodating in how we behave - we stand in line, we follow the rules - and we are also quite open in what we do. We had an English embryologist working in our lab and he thought it strange to see that the results from Swedish clinics were all so similar. In England, he said, results were quite varied. But in Sweden we're not naturally competitive, we're usually happy to share information, and I do think that is an important key to success. I believe we often have this open way of doing things in Sweden - which is apparent in many areas, not just IVF.

You're IVF laboratory director at Sahlgrenska University hospital. How long have you been there?
Since 1991. Before that I was a PhD student in biology at Gothenburg University.

And is this the job you always thought you'd be doing?
No, not at all. I started studying languages and wanted to be a translator. But I switched to natural sciences during high school, and that was my first degree. Then I began studying chemistry and pharmacy, but realised that a pharmacist today is not about making pills and mixing medicine, but more like being a shopkeeper. So I switched to biology, and then began to think about medical research. And that's really how I moved into reproduction. I was head-hunted into Sahlgrenska after my PhD exam. So basically I'm still in my first job.

So you're not restless, and not ambitious?
No, I am ambitious, and my job is developing all the time. Not just in the lab, but also working here in ESHRE and with the Swedish government on the EU Tissue and Cell Directives, for example. I am now very involved in national and international decisions, and I enjoy it.

It's a busy life. Does it affect family life?
Of course it affects family life, but my youngest daughter is now 18 so she doesn't need that much supervision, nor does my husband! And I'm usually not away for too long. So it's not a big problem.

And ESHRE? It's early days for priorities, but what's beginning to emerge in your mind as worthy of attention?
I am becoming quite aware of the bigger issues and ESHRE's place within them. We are now facing new issues, such as the campaign by One of Us to restrict EU funding. I think we have to embrace these responsibilities rather than just ignore them. But we have to be careful too. These are complicated problems which are outside our comfort zone, where we haven't really been before – global political issues, legal issues. We aren't experts in these areas. But I think this is part of what we should be doing - we are the collective force of our profession and certainly have to represent our membership. So I think we should accept that responsibility and act upon it, knowing that we're not in isolation and have fantastic advice and expertise around us. I believe that's where ESHRE will be going in the future. Of course, the core activities of ESHRE - training, publishing, data collection and monitoring, certification, the annual meeting - they will all remain, but I think the range of our responsibilities will continue to widen over time. But I still think the most rewarding thing about working with ESHRE will always be the fantastic people you meet, and that we all continue to work towards the same goal.

PROUST QUESTIONNAIRE*

● **Which person do you admire the most?**
My husband, who puts up with me.

● **What is your greatest virtue?**
To see things from many perspectives.

● **And greatest weakness?**
Laziness.

● **Who is your favourite writer?**
There are many, but I enjoy Paul Auster and Haruki Murakami. And love crime stories!

● **Which living person do you most admire?**
I admire those who devote their time to the care of other people.

● **What was the last book your read?**
Every Man Dies Alone, by Hans Fallada. Fantastic book about civil courage during the Nazi regime in Berlin.

● **And the last film you saw?**
The Great Gatsby

● **What is your greatest regret?**
I'm fortunate not to have any.

● **Where did you spend last year's vacation?**
At our house by the sea in Sweden.

● **Your favourite dinner?**
Something I don't have to cook myself.

● **What is your greatest extravagance?**
Buying Christmas presents.

* A personal questionnaire celebrated and originally made popular by the French writer Marcel Proust

GETTY IMAGES

After the scientific and clinical stages of its history, IVF is now in the full swing of a commercial boom. Simon Brown considers the life cycle of the fertility sector, currently a hot target for corporate investors.

Business i$ booming

When the definitive history of IVF comes to be written, historians will surely look back on three distinct eras in its progress. The first was scientific, characterised most graphically by Robert Edwards in his Cambridge laboratory working all hours to unravel the physiology of reproduction. Indeed, long after the birth of Louise Brown, Edwards would insist that even the triumph of IVF was no more than a milestone on the way to greater scientific discovery. 'As a scientist,' he later wrote, 'my main interest has always been to arrive at a thorough understanding of human conception. It was my interest in this type of research . . . that really drove me to develop IVF.'

The second era of IVF history was clinical, with fertility centres opening up in all corners of the developed world and the indications for treatment expanding to cover every possible pathology, even of male cause. To this extent, ICSI would prove as great a milestone in the clinical era as IVF was in the scientific.

And now, it seems, IVF has entered the third phase

of its history, loosely defined by commercialisation and characterised by conglomerates of clinics, private equity funding, the consolidation of services, and the encroachment of business into the IVF lab.

Indeed, says Norwegian embryologist Arne Sunde, a former Chairman of ESHRE, 'it is not unlikely that we will see the emergence of large commercial entities which are essentially one-stop shops for providing ART clinics with everything they need - hardware, computer software, consumables and culture media, as well as pharmaceuticals and standard operating procedures.'

It's tempting to believe that the commercialisation of fertility is nothing new and has always been the working model for IVF in the USA. There, the treatment of infertility is now said to be worth $2 billion a year, with more than 400 clinics listed by SART in competition for the business. The ASRM last October put the average price of one standard IVF cycle at $12,400, which, according to the patient advocacy group Resolve, is mainly paid for from private out-of-pocket funds. Only 15 states have passed laws requiring insurance policies to cover (or even offer to cover) some level of infertility treatment - and most insurance plans simply have no provision for IVF or advanced fertility treatments.

As a result US clinics have led the world in promoting their services to a captive population desperate for success - direct-to-consumer advertising, fertility shows, outcomes reported as pregnancy and not live birth rates, money-back deals (coyly termed 'shared risk' or 'outcome-based reimbursement'), financing plans, tried but no-so-tested new technologies, brokers touting for egg donors and surrogate mothers . . . and press releases announcing yet another world first (complete with pictures of mom and baby).

Yet, while such blatant competition has been hailed as the unacceptable face of fertility capitalism here in Europe, the USA is not where the greatest commercialisation of IVF is to be found right now. For that, following the world's first stock exchange listing of a private equity-owned conglomerate of fertility clinics, is now to be found in Australia. Indeed, when shares in Virtus Health hit the Australian stock market in June last year, it was Australia's largest IPO of the year thus far - and investors couldn't get enough. Within hours, the shares had jumped from an opening price of Au$5.68 to close at Au$6.20, valuing the company at more than Au$480 million in a frantic day's trading. At the time Virtus ran 33 clinics in Australia and was the country's largest provider of fertility services (covering around 35% of all treatments). Virtus posted a profit of Au$27 million for 2012-13 and is reportedly now valued at more than Au$700 million.

What was attractive to investors, said the company's CEO at the time, were demographic trends (advancing maternal age), greater public acceptability of IVF, and the introduction of genetic testing. This, she explained, would drive an expected annual growth of around 4%, with potential for even further growth to be found overseas, particularly in the tiger economies of Asia. Indeed, even before the Virtus IPO, several Australian clinics were already running joint ventures in Asia, fostering long-term working relationships and raising at least the 'potential' for added growth.

Onwards and upwards. Share price for Virtus Health (VRT) on the Australian stock exchange since flotation in June 2013.

The private equity invasion of IVF in Australia had begun in 2007 when the venture capital arm of Dutch banking giant ABN Amro bought an 80% stake in Monash IVF, at the time Australia's largest provider and slowly moving into profit as a commercial operation of Monash University. In 2010 the Monash business was merged with that of Repromed, a management buy-out from the University of Adelaide, to form Healthbridge IVF. And it was over this same period that similar private equity deals brought together the IVF Australia, Melbourne IVF and Queensland Fertility groups to form Virtus.

What difference has such huge change in the management of IVF made in Australia? There have been claims in the Australian press in recent months that the costs of IVF services in Australia have soared as clinics look to profit from the booming business of fertility. In October the *Sydney Morning Herald* reported that a 'single fresh IVF cycle at Melbourne IVF . . . has increased from about $3833 in 2007 to $8640 last year', an average increase of 18%, and way above the rate of health service inflation of 5%. A similarly alarmist feature in the *Melbourne Age* claimed 'there are fears that greed has already begun to eclipse good and that the new business models, driven largely by profit targets, undermine the integrity of fertility medicine, which traditionally saw doctors thoroughly investigating people's problems to ensure that the least invasive and most cost-effective treatments were pursued'.

Gab Kovacs: 'As far as I can see, the new business managements have not got involved in practice.'

Gab Kovacs, one of the Monash IVF founders and still professor of O&G at Monash, lived through the buy-outs and the acquisitions but still sees no compromise in quality or an inappropriate rise in price. 'The acquisitions have brought capital into the business,' he told *Focus on Reproduction*, 'but that's the only difference I've seen. As far as I can see, the new business managements have not got involved in practice, which is still the responsibility of the doctors.' Kovacs added that these centralised business models in IVF also make good sense for IT systems, budgets, compliance and quality management - and even lab technology. 'These are all better in large businesses,' he said. 'Small single clinics just can't operate at this level of efficiency.'

Up the road at IVF Australia Professor Mike Chapman was similarly upbeat, telling the *Sydney Morning Herald* that 'corporatisation' had been a good thing for patients because more secure finances meant more research for better outcomes. 'I don't think there is any doctor that runs a practice that is not focused on their financial position over time,' said Chapman, 'but patients will always still come first.'

Even though Europe (and even the USA) is still to see its first public listing of IVF services, fertility is no stranger to private equity funding. At least seven fertility clinic groups in Britain are now said to have private equity funding, either as development capital or to finance mergers and acquisitions. The most publicised came in June 2012 when the CARE group of clinics was reportedly sold to Bowmark Capital for 'around £60 million'. Until then there had been little activity in the 'fertility sector' (as this medical discipline had now become known on the financial pages). However, interest by mainstream mid-market private equity firms has changed the environment, and self-managed UK clinics seem now a target for commercial investors. Similar movements have been proposed in Sweden and Germany, where both private and state schemes are in operation.

Another fear cited by those contemplating the conglomeration of clinics is that research will suffer. This, however, has not been the case with all private groups; indeed, many have built their public profile on a base of research and new technology. The IVI group, for example, which currently boasts 15 clinics in Spain and others in Latin and South America (with alliance deals recently concluded in India), has built its reputation not just on effective treatment but on a strong tradition of research and new technology development. With a huge throughput of patient numbers (more than 33,000 cycles of IVF, egg donation and donor insemination were recorded in 2012) IVI has the capacity for large randomised trials which few other clinic groups can match. Thus, IVI is behind some of the world's most important trials of oocyte vitrification and time-lapse imaging - and many other studies in implantation, PCOS, ovarian stimulation, and array CGH for PGS. Indeed, ClinicalTrials.gov lists 67 IVI studies as either completed or recruiting.

Arne Sunde: 'An opportunity for increased standardisation and increased efficiency and quality.'

Similarly, several of the large conglomerates in the USA continue substantial research programmes. Embryo testing for single gene defects and aneuploidy screening, although largely pioneered and evaluated in Europe, has also been seriously pursued in US centres, even if many of those studies are not as robust in numbers as they ideally might be. Reproductive Medicine Associates of New Jersey, for example, have led the way in trials of blastocyst trophectoderm biopsy and 24-chromosome analysis for PGS (with various technologies), but are equally keen to promote these advances to patients - '. . . extended embryo culture, trophectoderm biopsy, select CCS and single embryo transfer are just some of the ways that we're helping to redefine the IVF experience and expectations of success', the RMANJ website promises.

Despite these studies, there have nevertheless been increasingly vocal concerns that this encroachment of commerce into IVF will ultimately stifle research. Indeed, the Belgian bioethicist Sigrid Sterckx, speaking in an ESHRE debate in London last year on the introduction of new technologies into fertility clinics, emphatically claimed that business interest in these technologies was now the main reason for so few randomised trials in fertility. Time-lapse imaging, vitrification, the new aneuploidy screening technologies have all been introduced without substantial clinical trials - and all, without exception, have behind them the interest of business. ClinicalTtrials.gov is littered with studies in fertility abandoned because of poor recruitment. Yet why should patients accept randomisation to a control group when what they want is a baby and the best technologies to achieve that? Thus, even when randomised trials are reported, their numbers are small and their methodology open to criticism. The New York iconoclast Norbert Gleicher, for example, recently complained that some recent PGS studies were 'fundamentally flawed because their outcome analyses are not based on intent to treat and involve only patients who do reach embryo transfer'.[1]

The other fear of commercialisation in the IVF clinic is that the freedom of clinicians and scientists to do what's best for their patients will be compromised. For example, in their recent commentary on time-lapse patents Sterckx and colleagues proposed that a patent challenge might safeguard competition and protect the clinical freedom of doctors.[2] 'There is a serious risk,' they wrote, 'for the market in [time-lapse microscopy] to be dominated by a single player able to charge monopoly prices.'

Nevertheless, with ever more technology developments in sight, it seems likely that the profile of the IVF lab will indeed change from one equipped with off-the-shelf technology and consumables for the subjective evaluation of gamete and embryo quality to one with expensive custom-designed hardware and diagnostics. Such labs will favour the larger clinics or chains

GROWTH TOO FOR IVF'S BIOTECHNOLOGY SERVICE PROVIDERS

Growth is not confined to the clinics themselves. New biotechnology start-ups, particularly in the USA, are also enjoying a purple period in fertility. Many owe their origins to discoveries made in academic institutions and commercialised by researchers themselves or by university departments whose sole purpose is to translate the discoveries of science into revenue.

Of these many biotechnological developments, 'genetic testing' was one of three reasons identified by Virtus's CEO to explain the attraction of investors to the fertility sector, and these young companies are roaring ahead to develop and improve the technologies for PGD and aneuploidy screening. The result is likely to be more efficient (and cheaper) gene technologies moving rapidly as translational projects from the research bench to the IVF lab - particularly for even more accurate analysis of genomes of single cells biopsied from blastocysts.

And here too alliances and acquisitions are beginning to define a strong growth phase of the business life cycle. In September 2012 Illumina in the USA acquired the UK-based BlueGnome Ltd for a reported $88 million, thereby creating the combined 'microarray and sequencing platforms for our next generation products' (according to the BlueGnome press release).

The majority of US clinics now offer some form of PGS, and that, added to a growing public demand for single embryo transfer, seems likely to guarantee a strong market for the technology. Waiting in the wings are other PGD technologies in development - whole-genome amplification combined with DNA microarrays can detect not only chromosome aneuploidy but even changes in the base pair of a gene (single nucleotide polymorphisms, SNPs), while 'next generation sequencing' (whose costs are rapidly coming down) provides an opportunity to detect single-gene disorders and chromosome aneuploidy in concurrent sequencing from millions of DNA reads.

of collaborating clinics able to share these specialised techniques. 'This may,' says Arne Sunde, 'give less freedom to the individual clinics, but may on the other hand be an opportunity for increased standardisation and increased efficiency and quality.'

Similarly, there are those who see the development of IVF conglomerates as intrinsically good for patients - because of intensified competition and an emphasis on choice, performance and price. Only those able to perform most efficiently will survive.

Of course, fertility is not the only medical discipline to witness the business effect. In cardiology, for example, most of the huge late-breaking clinical trials presented at the congresses of the European Society of Cardiology or American Heart Association are commercially sponsored. The numbers and budgets are vast, the stakes high. And many of the other developments now being introduced to improve the fate of cardiac patients - tiny lead-free pacemakers, biodegradable stents, replacement valves - are the developments of commercial organisations. In PGS the platforms now being explored for large-scale genomic sequencing, or the microarray systems for comprehensive chromosome analysis are similarly commercial properties, just as laboratory hardware has always been. Only in the very earliest days of ICSI did those pioneering embryologists have to grind their own pipettes.

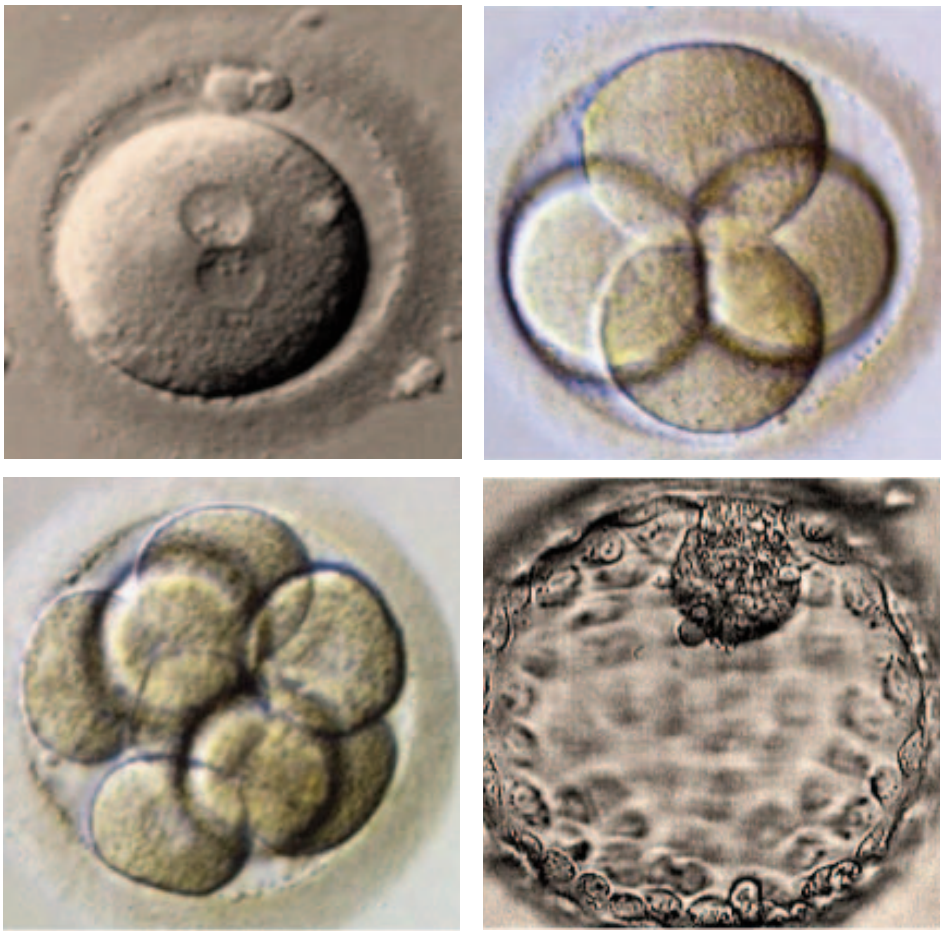
Today, however, few would disagree that the inventors of pharmaceuticals or surgical equipment or specialised diagnostic kit merit a reward for their invention - and a patent can both enable and protect that reward. Where the objections have arisen is in the 'technique' itelf, not in the technology. And this as a principle is not too far away from the claims made by Jacques Cohen which set this whole commercialisation debate rolling - that 'naturally occurring phenomena' are beyond the scope of commercial protection.[3]

However, from the classical business-school perspective, the consolidations now being seen in IVF reflect the natural evolutionary progress of any commercial life cycle: from start-up to growth to maturity and decline. Within the IVF sector the pharmaceutical industry is surely in the maturity phase, while some of the traditional equipment providers may even be in decline - and certainly under threat from the new start-ups and spin-offs now in their early growth phase. As for the clinics themselves, consolidations, mergers and acquisitions are the cornerstones of classical industrial growth, as services gain acceptance, profits rise, and capital investment allows expansion. This surely describes IVF right now - a clearly identified commercial sector in the growth phase of its life cycle. If the textbook life cycle continues, maturity and decline are yet to come.

Simon Brown is a freelance journalist and in that capacity is editor of *Focus on Reproduction* for ESHRE.

1. Gleicher N, Kushnir VA, Barad DH. Preimplantation genetic screening is alive and very well: really? Fertil Steril 2013; 100: e36.
2. Sterckx S, Cockbain J, Pennings G. Patenting time-lapse microscopy: the European story. Reprod Biomed Online 2013; doi:10.1016/j.rbmo.2013.09.018
3. Cohen J. On patenting time and other natural phenomena. Reprod Biomed Online 2013; 27, 109-110.

Is there still room for improvement in IVF delivery rates? Can we make embryos more viable? And if so, how? Cristina Magli looks into the IVF lab of tomorrow and makes five realistic proposals which, she says, can maximise the chance of implantation and delivery.



New generation embryos

How the IVF lab can improve implantation

When I think of Bob Edwards in the early days of IVF, I am aware not just of the greatness of the pioneer but of something common to all embryologists: the desire to see our in vitro grown embryos implant and develop into beautiful, healthy babies. In practice, this wish implies culture conditions able to maximise embryo viability and treatment opportunities for more and more couples.

Throughout the 35 years of IVF history, the evolution in assisted reproductive technologies has been extraordinary. ICSI was certainly the most remarkable breakthrough, while PGD gave ART an important role in the field of preventive medicine. This was at the end of the 1980s, when it was discovered that the biopsy of polar bodies and blastomeres could be performed without affecting the embryo's further development. The concomitant refinement of molecular biology and cytogenetic techniques made it possible to analyse the oocytes and embryos for monogenic and chromosome abnormalities. And so in this way did couples at high reproductive risk find a new treatment to prevent the implantation of affected embryos.

At the same time, the improvement in culture conditions contributed substantially to the increased success of many ART procedures as assessed by key performance indicators. These indicators have also evolved with time, starting with the evaluation of laboratory techniques and moving to the measurement of pregnancy and implantation rates. Today, the true measurement of treatment success is the birth of a healthy singleton, with attention also paid to the

KEY PERFORMANCE INDICATORS IN IVF

Laboratory
* Fertilisation rate
* Cleavage rate
* Top quality embryos
* Blastocyst rate
* Survival rate after thawing/warming

Clinical
* Pregnancy rate
* Implantation rate
* Ongoing implantation rate
* Delivery rate
* Single live birth rate
* Follow-up: obstetric, neonatal, long-term

follow-up of pregnancies and babies born.

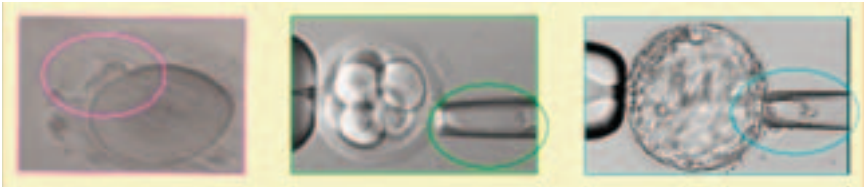
Yet given the constant introduction of new technical advances in ART, as well as the significantly improved success rates we have seen over the years, is it still reasonable to ask if there's still room for improvement. Can we still set up the conditions for a new generation of embryos yielding an even higher delivery rate?

Clearly, implantation is a play with two actors: embryo viability and endometrial receptivity. However, clinical data in which a single implantation often results from the transfer of two or more embryos suggest that a large proportion of failed implantations must be ascribed to the embryo. It is my view, therefore, that further improvement in culture systems and in the design of innovative approaches can improve embryo viability as well as selection at the time of transfer, thereby maximising the chances of implantation and the delivery of a healthy baby. How might it be done? Where are the new generation embryos?

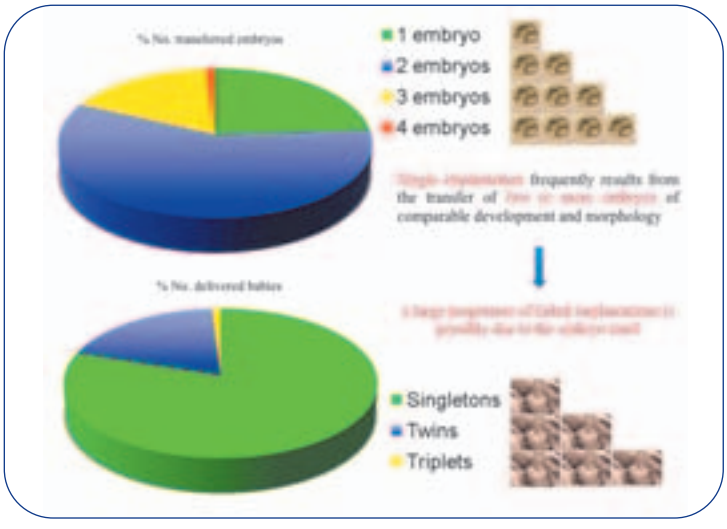
The intrinsic constituents: genome, transcriptome, proteome, secretome, metabolome

Dosage imbalance of a whole chromosome, known as aneuploidy, has long been recognised as one of the most prominent explanations of embryo demise. PGS was introduced with the aim of increasing delivery rate by deselecting embryos with such abnormalities. The vast majority of published data on PGS derive from the analysis of 9-12 chromosomes by FISH (fluorescence in situ hybridisation) on blastomeres from cleavage stage embryos. The prevalence of abnormality was shown to be between 50 and 70%, with variations dependent on maternal age. This figure is significantly higher than the incidence seen in spontaneous abortions or samples from prenatal diagnosis, suggesting that a sizeable percentage of chromosomally abnormal embryos is eliminated around the time of implantation.

Although large studies implied the clinical advantages of this approach, the benefit of PGS has been severely questioned by randomised trials. However, even some of these well designed studies had some evident technical weaknesses implying that their reported conclusions might be different if the technique were properly implemented. Now, novel strategies have been introduced in PGS with the biopsy of trophectoderm cells and analysis of 24 chromosomes by array CGH (comparative genomic hybridisation) or CCS (comprehensive chromosome screening). New trials have been reported and finally a sharp clinical advantage is evident following the application of PGS in different patient groups - women advanced maternal age and younger women with repeated IVF failure.[1,2]



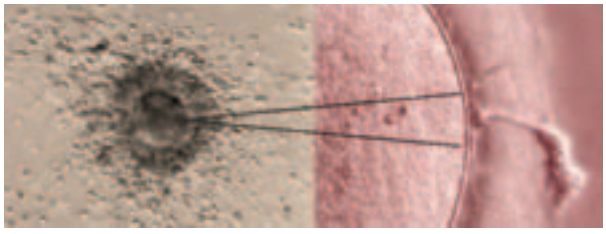
Strategies in PGS: left, polar body biopsy; centre, blastomere biopsy; right, trophectoderm biopsy. In all cases, the biopsied cells, tested for many years by FISH, are now analysed by array CGH or CCS. The ESHRE ESTEEM trial is evaluating polar body analysis.



The shortfalls between embryo transfer, implantation and delivery, based on ESHRE's 2008 IVF data monitoring report. 'A large proportion of failed implantations must be ascribed to the embryo.'

Approximately 25,000 genes have been identified in the human genome. The profile of gene activation or silencing at a particular time controls cell differentiation, proliferation or death. Recent studies, investigating the pattern of gene activation in blastocysts, have reported a close correlation between competence to develop to term and gene expression profiling. This is not surprising given the key role of gene expression in the regulation of all cell processes.

The developmental competence of an embryo is already established in the oocyte which provides the raw material necessary for further growth. The oocyte becomes competent during its maturation and this composite process is regulated by a bi-directional communication between the oocyte itself and the surrounding cumulus cells. Therefore, a specific gene expression pattern in cumulus cells could reflect the status of the corresponding oocyte. Indeed, it has already been shown that some transcripts are peculiar to aneuploid oocytes, while others show a tendency to



A bi-directional communication between the oocyte and the surrounding cumulus cells regulates the exchange of factors and nutrients that regulate the acquisition of oocyte competence during the maturation phase.

DIFFERENCES BETWEEN IN VIVO AND IN VITRO CONDITIONS

In vivo	In vitro
* Constant temperature	* Thermal variations
* Darkness	* Variations of light
* Controlled O_2/CO_2	* Variations in O_2/CO_2
* Volume of fluids	* Volume of media
* Osmolality (unknown)	* Osmolality 260-290 mosm
* Cumulus-oocyte-complex connections and dynamic changes in secretions	* No cumulus-oocyte-complex connections
* Free radical scavengers	*Vulnerability to ROS → DNA fragmentation
* Gentle mechanical stimulation	* Static platforms

be upregulated in oocytes that produce healthy live births.[3] Should these findings be confirmed by further data, this approach would represent an extremely valuable non-invasive marker of aneuploidy and general oocyte competence.

Proteins are the product of the activated genes. Assessment of the embryonic proteome is of particular interest since proteins, including those that are secreted, represent a reflection of cell function and physiology. Given that embryo metabolism is a critical determinant of viability, it seems reasonable to propose that a viable embryo has a unique metabolic fingerprint. Based on this hypothesis, the spent culture media of IVF embryos have been analysed and a clear relationship between the reproductive potential of these embryos and the modification of their culture media has been demonstrated. Unfortunately, however, when tested in a randomised trial, the clinical application of this strategy did not show any improvement in the chances of achieving a viable pregnancy.[4] This was a really disappointing result, especially as other scientific studies using different targets (measurement of the amino acid turnover in the spent culture medium, or oocyte/embryo respiration rate) had also supported a non-invasive approach to the selection of embryos with the highest implantation potential. Hopefully, it will be just a question of perfecting the technology before considering the specific profiles of the secretome and metabolome as an objective marker of viability.

Thus, from revisiting the current data on embryonic intrinsic constituents, we can start to design the first features of the new generation embryo in the laboratory of the future. They should be:

→ Screened for aneuploidy

→ Tested for viability markers

Metabolic activity

The embryo undergoes complex changes during the transition from the zygote to blastocyst stage which are accompanied by different nutrient requirements and metabolic pathways. During the early stages of this transition the embryo is metabolically quiescent, with low metabolic rate and biosynthetic activity. Unable to metabolise glucose, the embryo relies on its mitochondria to produce energy via the oxidative phosphorylation of pyruvate. At later stages, complete activation of the embryonic genome occurs, which is associated with increasing transcription activity. At this point, the preimplantation embryo begins compaction to form a morula, and then to form a blastocyst. Because of its high energy requirements, the embryo now consumes glucose.

These profound changes in the embryo are mirrored by changing environments along the female reproductive tract, with the uterus providing higher levels of glucose and amino acids than in the oviduct.

It was these findings which led to the design of sequential culture media, which were then tailored to meet the metabolic and nutritional requirements of specific stages of embryo development according to the natural condition. Several media are now commercially available, but there is still no agreement on the optimal formulation of culture media for human embryos. What is worse, not only do the great majority of producers fail to supply information on the exact composition of their media (some do not even provide a list of components!), but new culture media are still admitted into clinical care without properly designed trials. This is unacceptable, especially when considering that every developmental step which occurs during the preimplantation phase is the result of a precisely co-ordinated event. The surrounding environment - of which the culture medium represents the closest environment for the embryos - may cause important changes in epigenetics, gene transcription, metabolism and cell allocation.

Therefore, in the laboratory of the future, new generation embryos should be:

→ Cultured in a 'safe' medium causing no alterations in the pattern of gene expression with potential long-term consequences

Physical requirements

There are undeniable differences between in vivo and in vitro conditions whose effect on embryo viability could be relevant. As an example, it is now well known that oocytes and embryos are highly temperature sensitive, particularly at those stages of meiosis involving delicate spindle formation. Similarly, extended exposure to inappropriate CO2 levels may result in altered pH, with consequent negative effects

on embryo growth. This is especially true for cleavage stage embryos, which appear to be more susceptible to stress exposure. They actually lack many key homeostatic mechanisms routinely found in almost all somatic cells, resulting in a limited ability to regulate against alterations in pH, osmotic stress and reactive oxygen species.

Although in vitro culture should not be regarded as a substandard copy of the in vivo process but as an artificial process with its own frames, limitations and possibilities, the maintenance of stable conditions seems to be extremely important for embryo viability.

Advanced incubation systems now offer strictly controlled incubation conditions, even during embryo scoring. With time-lapse imaging, it is possible to detect the start of cell cleavage and to determine the time interval between cell divisions. Morphokinetics has been reported to be important for embryo viability, but, while waiting for robust clinical data to confirm the preliminary results, the embryo culture in semi-closed systems providing strict control of temperature, air, humidity and light, seems to represent the preferred approach.

Hence, in the laboratory of the future, new generation embryos should be

→ **Cultured in stable, controlled conditions**

Novel culture devices and strategies

In natural conceptions, the preimplantation embryo is constantly moving as a result of muscle contractions and epithelial cell cilia movement. This exerts a mechanical influence on the embryos, resulting in a constant renewal of the surrounding fluid. In static cultures, none of these features are present.

These considerations have encouraged the development of dynamic culture systems based on different approaches, such as shaking-rotation, tilting, vibration, and controlled fluid flow. The data available up to now remain very preliminary and several factors still need to be investigated and optimised, but these strategies might provide a pathway towards a significant improvement of culture systems.

Another aspect of human embryo culture which deserves the highest attention is traceability, especially in the prevention of mismatching errors of reproductive samples, commonly known as mix-ups. Different preventive measures have been set in place in fertility clinics, but none has proved totally effective. More recently, electronic witnessing systems have been proposed, which automatise sample recognition by labelling all lab-ware used for each single case with bar code stickers. A novel approach proposes the direct tagging of an oocyte, in which the tag is attached directly to the zona pellucida. Thus, the identification rate from the oocyte to the blastocyst stage is 100%, even after micromanipulation or vitrification, provided that the oocytes and embryos are rolled at the microscope for observation.

This adds another characteristic to the culture system of new generation embryos in the laboratory of the future:

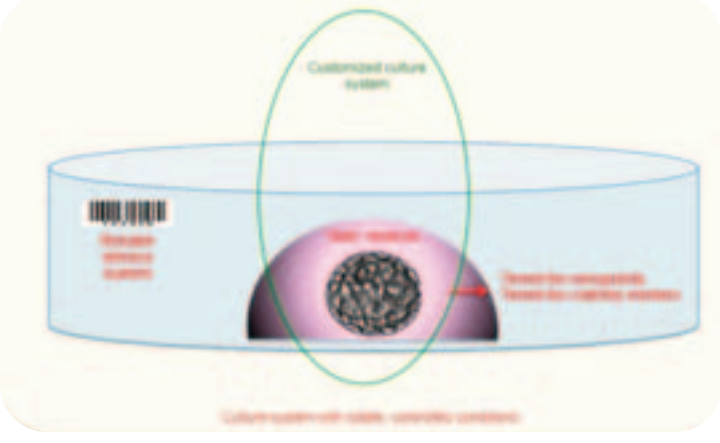
→ **Use of a reliable witnessing system**

Considering the present in relation to the past, there is no doubt that the IVF laboratory is constantly renewing and improving its performance. So how far away is the future? How much can we add to the current status to reach a new generation of embryos?

Realistically, all IVF embryos should now be tested for aneuploidy and viability markers; they should be cultured in a 'safe' medium, in stable and controlled conditions, and under reliable witnessing. As further improvement, each embryo should be approached individually and treated individually - embryos, like patients, are individual entities.

Even if perfection is our dream, improvement is still a reasonable hope. Thus, while full robotic automatisation as a likely futuristic advance might bring more objectivity and control to all phases of the embryology process, none and nothing but the embryologist can make the observations, draw the conclusions, detect the problems and propose the solutions. Only the embryologist's superior knowledge can take advantage of the technological advances to ensure the arrival of new generation embryos.

New generation embryos defined by a customised and controlled culture system, 'safe' culture media, assessment for aneuploidy and other markers of viability, and a reliable witness system.



Cristina Magli is an embryologist and Laboratory Director at the SISMER centre in Bologna, Italy. She is a member of ESHRE's Executive Committee and a former Co-ordinator of ESHRE's SIG Embryology.

● This article is based on a presentation given at a SISMER meeting in September 2013.

1. Scott RT Jr, Upham KM, Forman EJ, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. Fertil Steril 2013;100:697-703.
2. Rubio C, Bellver J, Rodrigo L, et al. Preimplantation genetic screening using fluorescence in situ hybridization in patients with repetitive implantation failure and advanced maternal age: two randomized trials. Fertil Steril 2013;99:1400-7.
3. Fragouli E, Wells D, Iager AE, et al. Alteration of gene expression in human cumulus cells as a potential indicator of oocyte aneuploidy. Hum Reprod 2012; 27: 2559-2568.
4. Hardarson T, Ahlström A, Rogberg L, et al. Non-invasive metabolomic profiling of Day 2 and 5 embryo culture medium: a prospective randomized trial. Hum Reprod 2012; 27: 89-96.

Embryonic and fetal genomes considered 'most sensitive' to environmental effects

SIG's winter symposium puts emphasis on prenatal factors in determination of subsequent health and disease

The 'hypothesis' proposed by the epidemiologist David Barker in the early 1990s - that intrauterine and early postnatal nutrition are in part responsible for the risk of non-communicable diseases in later life - is now widely accepted as biological fact. He particularly noted that those with a low birth weight are at greater risk of coronary heart disease. The acceptance of the hypothesis now explains the 'life course' approach to health policy, whereby interventions at the maternal/infant stage of life, when developmental plasticity is at its greatest, are considered just as effective in disease prevention as interventions during adolescence and adulthood.

Such thinking lay behind most of the presentations at the Winter Campus Symposium of the SIG Early Pregnancy, which was organised jointly with the Task Force Basic Science and titled 'From early pregnancy to later in life'. There was indeed little disagreement that health in maturity is the consequence of a continuum that begins with the oocyte (and sperm cell) and that the embryonic and fetal genomes are most sensitive to environmental effects. Lurking in the background of this continuum were the mechanisms of epigenetics, whose modifications are assumed to mediate environment-gene interactions which cause persistent changes in gene regulation and metabolic pathways.

There was, therefore, a strong emphasis in this Campus programme on the effects exerted on the oocyte and embryo at their very earliest formative stages: genes expressed by cumulus cells (those predictive of competence); freeze-thawing and its damaging effects on 'trans-zonal' processes during antral follicle growth; optimal culture after freezing and thawing; oocyte vitrification (evidence so far that survival rates are better than after slow-freezing, without negative impact on oocyte integrity); and embryo culture in IVF (a 'real possibility' of an effect). These observations thus strongly implied that ART - with which all these functions are associated - is taking place at a very sensitive time for epigenomic reprogramming in the germline and early embryo.

'We should,' said Thomas Haaf from Wurzburg, 'be much more concerned about the long-term consequences of a sub-optimal environment around the time of conception and during pregnancy . . . The adaptive response of the fetus to the intrauterine environment influences the lifelong risk of metabolic and other diseases.'

SIG Co-ordinator Mariëtte Goddijn, with Carlos Plancha representing the Task Force Basic Science.

However, while most presentations concentrated on the germ-cell, periconceptional, prenatal and perinatal stages of development, there was also good evidence presented during the symposium that these effects may even have lasting consequences over several generations. Thus, while recent studies suggest, for example, that mothers with gestational diabetes and obesity have babies with epigenetic changes conducive to metabolic disease later in life, the well known and evolving Dutch famine cohort study now suggests that the effects of diet restriction 'might' be passed down to subsequent generations.

The proposal - that 'you are what your (grand)mother ate' - came from Dutch investigator Tessa Roseboom, principal investigators of the Fetal Origins Research group at the Academic Medical Center in Amsterdam, who confirmed from data from the Dutch famine study that 'prenatal nutrition has a 'huge influence on lifespan'.

The study was based on the consequences of food

During the Dutch famine of 1944-1945 the Netherlands suffered from substantial undernutrition (of around 1000 calories per day). The limited food intake of mothers who were pregnant during this period has been associated with direct effects on body weight, diabetes and cardiovascular disease. Some effects of the famine - epigenetic changes, for example - have been observed 60 years later.

shortages during the winter of 1944-45 and the full birth records later found in the Wilhelmina Gasthuis in Amsterdam (which would later become the AMC). The records covered the births of 2500 babies, all of whom have been traced by investigators. Inevitably, there have been many studies based on this natural experiment, but the single finding to emerge with consistency is that undernutrition caused by the famine did have a direct effect on birth weight, especially among those whose exposure to malnutrition was later in the famine period. As early as 1997 a study showed that second born babies in the cohort weighed less than first borns, and third borns even less again. Even then, said Roseboom, there appeared an intergenerational effect of famine.

More recently, when examined at the age of 50 by her group, the late and medium term exposures in the cohort had higher rates of obesity, diabetes, atherosclerosis and cardiovascular disease than those exposed early (or controls). Examined ten years later, the incidence of CVD mortality was also higher.

Right now, the investigators are seeing for the first time a fourth generation of subjects whose pedigrees trace back to the famine. But, said Roseboom, it's too early yet to see what the direct effects - if any - will be.

Nevertheless, the evidence from this Campus meeting pointed unequivocally to a critical effect of lifetsyle and environmental factors during the pre-pregnancy, conception and early pregnancy stages. And in the debate which closed the meeting there was clearly an overwhelming view that as a biomarker of successful pregnancy the embryo is far more predictive than the endometrium. Despite the emphatic case of the SIG's Deputy Co-ordinator Siobhan Quenby (that the endometrium determines implantation), it was the prevailing opinion of this meeting that the outcome of conception, whether pregnancy or later life health, was more dependent on factors affecting the oocyte and embryo in their formative stages, where intervention for disease prevention now seemed likely to be effective.

Evidence search next for the SIG's diagnostic and management guidelines for recurrent miscarriage

Our joint Campus meeting reported above was attended by a variety of reproductive scientists, clinical embryologists, reproductive gynaecologists, and reproductive physicians. Indeed, the concept of developmental origins of health and disease are now attracting an increasing amount of attention, and speakers made it obviously clear that the pre-pregnancy, early implantation and early pregnancy stages are critical periods in which environmental or lifestyle factors may adversely affect pregnancy outcomes and health in later life.

Steering committee SIG EP, l to r: Ole B Christiansen (DK) Past Co-ordinator, Emma Kirk (GB) Deputy Co-ordinator, Mariëtte Goddijn (NL) Co-ordinator. Siobhan Quenby (GB) Deputy Co-ordinator, Robbert van Oppenraaij (NL) Junior Deputy

New evidence has been reported on the treatment of women with recurrent miscarriage, which now demands an update of our 2006 guideline. The new version will be revised and updated according to ESHRE's latest guideline protocols. Our aim is to provide statements systematically developed to assist professional and patient decisions on appropriate care for couples with recurrent miscarriage. A guideline team has been established (with many European experts) and 20 key questions formulated. Following a literature search, evidence will be graded and recommendations formulated.

Guidelines

Our current ESHRE guidelines project involves the diagnostics and management of couples with recurrent miscarriage. New medical tests should be thoroughly evaluated before routine introduction, thereby avoiding erroneous diagnoses or the initiation of potentially harmful therapy. In addition, the increasing costs of healthcare demand the elimination of ineffective medical testing. In addition, women with recurrent miscarriage are vulnerable and easily attracted to unproven therapies to apparently increase their future chance of a healthy liveborn child.

Future activities

Our precongress course in Munich will be held in collaboration with the SIG Reproductive Endocrinology on **The contribution of endocrinology and early pregnancy management to the success of an ART centre**.

Later in the year, our traditional winter symposium, organised with the Paramedical Group in December in Copenhagen, will be on the evidence-based management of early pregnancy.

Mariëtte Goddijn
Coordinator SIG Early Pregnancy

Latest data collection report now ready for publication, with others moving ahead

The end is in sight for 'manual' data collection

Core members of the PGD Consortium steering committee meeting in Athens in October. From left to right, Edith Coonen (Chair Elect), Martine de Rycke, Jan Traeger-Synodinos (Chair), Sioban SenGupta, Celine Moutou.

Our data XII paper has been finalised and accepted for publication in *Human Reproduction*, while Veerle Goossens is now progressing with cleaning the cycle-entries for data XIII and XIV. In addition, we are now preparing for the next data collection, and the empty Filemaker Pro templates have been sent out to all centres for data XV. These data will be on cycles performed in 2012, with babies delivered up until September 2013. The steering committee hopes that data XV will be the last manual data collection and that for data collection XVI the on-line database will be available. Celine Moutou and Martine de Rycke are working on it!

At the end of October the paper summarising the results of our collaborative study to evaluate PCR-based PGD follow-up was accepted for publication in the *European Journal of Human Genetics* and should be published very soon.

Working groups

The working group to monitor new technologies in PGD, chaired by Martine de Rycke, has been initiated. A questionnaire was distributed to all Consortium member centres (125) in mid-October, with a deadline to submit completed questionnaires by the end of November. So far, around 50 PGD centres have responded. The working group and steering committee hope to evaluate the results and begin a written paper by the end of this year.

Activities for other working groups in 2014 include a plan to follow-up PGD cycles performed for HLA in order to evaluate outcomes and clinical utility of HLA-PGD (to be chaired by Jan Traeger-Synodinos), and another to look at collaborative working practices between genetics and IVF teams when delivering a PGD service (to be chaired by Sioban SenGupta).

With respect to the 'Education' aims of the PGD Consortium, some current and past members of the steering committee went to Brussels to record the first introductory webinars on PGD. Members of the Consortium will be notified when they are available for viewing. In a recent e-mail sent to all Consortium members the steering committee requested suggestions for suitable topics for the interactive webinars that the Consortium proposed to initiate. However, the response was very low and so we have decided not to give this activity high priority in the imminent future.

In October a survey was sent out to all Consortium members asking them for their preferred day and time for the annual PGD Consortium meeting from 2014 onwards. The three choices were Saturday afternoon (as it is now), after the PGD session in the main programme, or on Thursday (the day after the annual meeting closes). The majority vote was for directly after the PGD session in the main programme. ESHRE's Central Office is planning to make registration fee arrangements for Consortium members not registering for the whole annual meeting.

In collaboration with UK-NEQAS, CEQA, and many members of the PGD Consortium and wider PGD community, Eurogentest organised and supported a meeting in Athens, Greece, in October on PGD EQA and microarray best practice. The meeting was well attended, with positive feedback. As our picture shows, all five core members of the Consortium steering committee were present.

The PGD Consortium remains an important forum for all PGD practitioners to share and exchange data, experiences and valuable expertise. For everyone's optimal benefit, we strongly encourage the participation of all member centres in Consortium activities.

Jan Traeger-Synodinos
Chair PGD Consortium Steering Committee

SIG REPRODUCTIVE GENETICS

Steering committee reshuffle; recent meetings well attended

Changes to the SIG Steering Committee were confirmed at the latest business meeting of the SIG in London. Ursula Eichenlaub-Ritter became new Co-ordinator, while Stephane Viville stepped down as Past Co-ordinator to be replaced by Joyce Harper. Claudia Spits continues her second term as Deputy, while Tanja Milachich moved from Junior Deputy to become Deputy of the SIG. After announcing the position and asking for applications and proposals, the proposal for Georgia Kakourou as our new Junior Deputy was accepted. We wish to express our sincere thanks to all former Deputies and Co-ordinators and hope that they will still contribute to SIG activities with their interest and input.

STEERING COMMITTEE

Ursula Eichenlaub-Ritter (DE), Co-ordinator
Claudia Spits (BE), Deputy
Tania Milachich (BG), Deputy
Georgia Kakourou (GR), Junior Deputy
Joyce Harper (GB), Past Co-ordinator

Recent events

Our precongress course on **Genetic and epigenetic causes of infertility - can we minimize the risks?** at the annual meeting in London and a Campus workshop on **Application and challenges of emerging technologies in preimplantation and prenatal diagnosis** in Prague in September both attracted a large audience and encouraged much debate on their technical, clinical, ethical and social implications in reproductive medicine and ART.

Future events

Our next precongress course in Munich this year will focus on **The current status of PGD and PGS** and will hopefully attract another big audience with its attractive programme and an internationally recognised faculty of speakers.

Along with the SIGs Stem Cells and Andrology and the TF Fertility Preservation in Severe Disease, we are also involved in a Campus workshop in Brussels on 27-28th April on **Stem cells: Origins, genetics, properties and significance for fertility preservation**.

Another Campus on **Epigenetics in Reproduction** organised with the SIG Embryology and TF Basic Science will take place on 25-27th September in Lisbon. The speakers have been invited and the programme completed.

Another Campus - **An update on preimplantation genetic screening (PGS)** - is planned for Spring 2015 in Rome.

The first recordings of four introduction webinars by members of the PGD Consortium and the SIG Reproductive Genetics have been completed for the e-Learning programme.

Ursula Eichenlaub-Ritter
Co-ordinator SIG Reproductive Genetics

SIG EMBRYOLOGY

Time-lapse technology for this year's precongress course

Recent activities

Our busy agenda continues and our joint meeting with the Paramedical Group on the introduction of new technologies into the IVF lab attracted more than 150 delegates. The meeting, held in Barcelona in October, took a wide range of approaches, from the data of recent studies to more everyday practicalities, and generated great and valuable debates.

STEERING COMMITTEE

Maria José de los Santos (ES), Co-ordinator
Sophie Debrock (BE), Deputy
Giovanni Coticchio (IT), Deputy
Susanna Apter (SE), Junior Deputy
Kersti Lundin (SE), Past Co-ordinator

Forthcoming courses

Our next appointment will take place at the annual meeting in Munich when we address the hot topic of time-lapse technology and its application in IVF for embryo selection. This will be very interesting precongress course, with much to consider and discuss.

After Munich we meet again in Lisbon on 26-27th September for a joint Campus meeting with the Task Force Basic Science and SIG Reproductive Genetics on **Epigenetics and reproduction**.

Among topics discussed at a business meeting in December were plans to improve interactivity of the *Atlas of Embryology* and to update the current ESHRE guidelines for good practice in IVF laboratories.

Maria José de los Santos
Co-ordinator SIG Embryology

Certification in endoscopic surgery is up and running

The first international certification in reproductive surgery is proudly on the move. This year, the ESHRE Certification for Reproductive Endoscopic Surgery (ECRES) will be available on two levels: Bachelor in Endoscopy, and Reproductive Endoscopic Surgeon. For the former, psychomotor skills but no specific surgical skills are required, and certification will confirm that candidates have the required theoretical knowledge and practical skills to enter an endoscopic or training programme. For the second, specific psychomotor and surgical skills are required. These must be demonstrated in the form of submitted videos of specific endoscopic procedures performed by each applicant over a three year period. Candidates will be certified that they are able to practise endoscopic surgery independently within the field of reproductive medicine and will then have the title of Reproductive Endoscopic Surgeon. This certification programme is unique internationally and awarded only by ESHRE.

Recent activities

Following the joint publication of the new ESHRE/ESGE classification on female genital tract congenital malformations, a workshop on **Female genital tract congenital malformations: new insights in an old problem** was held in Thessaloniki, Greece, hosted by Grigoris Grimbizis. The workshop was attended by participants from all over the world (see photo below) and enjoyed fascinating and high quality lectures ranging from the genetic insights of female genital malformations to video presentations of hysteroscopic treatment of dysmorphic uteri. Most engaging was the debate amongst participants and members of the Task Force who proposed the new classification, and the quiz which tested the new classification against a series of anomalies..

It was apparent that, with the new classification, malformations will now be more accurately classified, which will be invaluable not only in terms of assessing their reproductive impact but also the effect of any surgical treatment.

It also transpired that the next most crucial step will be to determine how these malformations should be screened and diagnosed. A preliminary discussion was chaired by Professor Grimbizis and a strategy for the screening and diagnosis of female genital tract malformations prepared.

Future events

We have the pleasure of hosting two courses in the first half of 2014, one in March and one in April. The first, on **Endoscopy in reproductive medicine** will be held in Leuven, Belgium. It will consist of three parts: first, a series of theoretical lectures, second, live surgical teaching of 4-6 hours from expert centres, and third, hands-on training including suturing and an evaluation of laparoscopic skills. The course in April will be on **the impact of surgery on the cross talk between the embryo and the endometrium**, and will be held in Vienna. This will be an advanced course discussing the latest data and operative techniques used to increase pregnancy rates in women undergoing ART. The course will cover areas from genetics and immunology to microsurgical techniques employed to improve implantation rates.

Tin-Chiu Li
Co-ordinator SIG Reproductive Surgery

Participants in the SIG RS's workshop in Thessaloniki on congenital malformations in the female genital tract.

Standardised sperm analysis

The SIG Andrology welcomes Victoria Sanchez as new Junior Deputy. Victoria is from Venezuela and is currently in the third year of her PhD studies at the University of Münster working on RAMAN microspectroscopy for analysis of DNA damage in sperm. 'I am intending to create options for young scientists,' says Victoria. 'My main scientific interest is in sperm nuclear DNA damage which presents an exciting research area with many novel and innovative options for the future.' We are also looking forward to Christina Sanchez from Seville joining the steering committee. She is trained as a pathologist and clinical andrologist and has already acted as coordinator of andrology groups in her home country.

We are involved with the SIGs Reproductive Genetics and Stem Cells in a two-day Campus meeting in Brussels on **Stem cells: origins, genetics, properties and significance for fertility preservation** on 27-28th April. Andrological highlights are sessions on the future derivation of gametes from stem cells as well as epigenetic risks associated with manipulation of germ cells. This programme is highly recommended for all andrologists interested in fertility preservation and treatment with in vitro derived sperm.

A highly attractive programme is also offered in our precongress course in Munich. The course co-ordinators, Sheena Lewis and Rafael Oliva, have put together a programme with excellent speakers on such diverse topics as sperm RNA as future diagnostic tools, molecular markers of male health in the ejaculate, vulnerability of androgen production in fetal testes and on more clinically oriented topics such as the treatment of males with antiestrogens, effects of diet and dietary supplements on male fertility and the rationale for genetic testing prior to ART treatment. The programme is specifically relevant for clinical andrologists and will provide a critical, evidence-based assessment of therapeutic strategies for infertile men.

Other future activities focus on novel aspects of sperm analysis. In a continuation of the 2009 Campus workshop in Stockholm, plans for implementing standardised methods and multicentre external quality schemes in Europe, America and Australia will be developed. A work meeting is planned for Munich to compose a manuscript and propose an outline for a possible task force in collaboration with the SIGs Reproductive Genetics, Quality and Safety of ART and the Basic Science Task Force.

We are considering future activities for the critical evaluation of novel tests for DNA integrity and chromatin changes in sperm. As agreed in London, we are also committed to our andrological training activities and spermatology quality control programme. In conjunction with other organisations we hope to develop a curriculum for training in clinical andrology and spermatology.

Stefan Schlatt
Co-ordinator SIG Andrology

'Experimental' redefined

Our pre-congress course in London was organised jointly with the SIG Safety and Quality in ART. The topic was on responsible innovation in ART and prior to the meeting members of the steering committees of both SIGs had worked together on a position paper on the definition of 'experimental' in ART. This paper was presented during the annual meeting in London by the SIGs' two junior deputies and will be published shortly in *Human Reproduction*.

We are of course closely linked to the Task Force Ethics & Law, which last year published one new position paper on sex selection for non-medical reasons. We are currently working on three further documents, two of which will make new recommendations: one on genetic screening of gamete donors and the second on ART in singles, lesbian and gay couples, and transsexual people. We will also update our position paper on PGD.

Future events

Next on our agenda is a Campus course on **Fertility preservation, from technique to implementation in clinical practice** in March in Amsterdam. This is a collaboration of the Task Force Fertility Preservation, the Paramedical Group, the SIGs Psychology & Counselling, Safety & Quality in ART, and Ethics & Law. The aim is to understand barriers and facilitators for implementing fertility preservation in adult and paediatric cancer care involving both men and women, and boys and girls.

Our precongress course in Munich will address the ethics of gamete donation and information sharing between donors, parents and donor conceived children/persons. Whereas a number of countries have in recent decades decided only to allow open-identity donation, others continue to allow (or even require) anonymous donation. During this course we will discuss the ethics of these policies.

Veerle Provoost
Co-ordinator
SIG Ethics & Law

Guideline development programme now moving forward

In London we thanked Jan Kremer for his years on the steering committee of the SIG SQUART. Jan was one of the main founders of the current ESHRE guideline programme. Petra de Sutter also stepped down as Co-ordinator in London, and we wish her all the best as a new Executive Committee member. Finally, we were glad to welcome as Junior Deputy Daniela Nogueira, an embryologist in Toulouse and a valuable addition to our SIG.

Recent events

In 2013 we were involved in the organisation of Campus courses on **Ultrasound in reproductive medicine** in Maribor, Slovenia, and on **Infections from conception to birth: role of ART** in Berlin (Germany). In addition we participated in two precongress courses - on **Total quality management (TQM) in an IVF Centre** and, together with the SIG Ethics & Law **Responsible innovation in medically assisted reproduction**, an overview of issues, challenges and responsibilities relevant to the safety and quality of innovations.

We also collaborated with the SIG Ethics & Law in the development of a conceptual framework to identify and distinguish three types of treatment: experimental, innovative and established. We hope this tool will facilitate discussion on the classification of treatments in reproductive medicine. This instrument will soon be published in *Human Reproduction*.

Guideline programme

The first ESHRE guideline developed according to the systematic protocols of ESHRE's guideline programme was presented at the annual meeting in London. The guideline - on 'the management of women with endometriosis' - is published on the ESHRE website and as a summary in *Human Reproduction*. To facilitate implementation, ESHRE is now supporting the development of a patient version (in collaboration with the Dutch patient group Endometriose stichting) and an app for use on smartphones and tablet.

Other ESHRE guidelines in advanced development are on 'Psychosocial care in fertility units' and 'Premature ovarian insufficiency'. Both will be presented in Munich following review and comment in the Spring. Please send an e-mail to nathalie@eshre.eu if you wish to comment personally.

A fourth guideline on recurrent miscarriage has now been started, and this and all further guidelines will be developed according to the updated ESHRE manual.

Future events

Impaired fertility as a result of cancer treatment affects 20-80% of young cancer survivors. However, despite increasing fertility preservation options (sperm, embryo, egg and ovarian freezing), only a minority of the care providers discuss these options with their patients. A Campus meeting on **Fertility preservation: from technique to implementation in clinical practice** organised in a broad collaboration (SIGs SQUART, Ethics & Law, Psychology & Counselling, Paramedical Group and Task Force Fertility Preservation in Severe Diseases) will consider the barriers and facilitators for implementing fertility preservation in adult and paediatric cancer care. On the agenda are the psychological impact of fertility preservation and the dynamics of communicating with patients and their proxies. The meeting will be held on 14-15th March in Amsterdam.

In Munich we join the SIG Psychology & Counselling in a precongress course on **Seeking and finding the evidence**. We will consider the value of evidence for us as professionals and for patients, and the means by which evidence can be translated to patient behaviour.

Willianne Nelen
Co-ordinator SIG Safety and Quality in ART

Agonist triggering next on the agenda

As reported on page 12, the SIG RE's October workshop in Rome on PCOS proved extremely popular, with 194 participants from 36 different countries. Ovarian stimulation for IVF in patients with PCOS has, until recently, been problematic, characterised usually by excessive ovarian response. However, the use of agonist triggering instead of hCG in these patients represents a safe and effective mode of stimulation. Agonist triggering will be the focus of our next workshop, to be held in Thessaloniki in Q4. Agonist triggering is viewed as one of the major advances in ovarian stimulation, with the potential to eliminate OHSS, for which it creates a zero risk environment. Colleagues actively working in this field will cover all the aspects of this exciting approach.

Our 2015 precongress course in Lisbon will cover a very intriguing area in ART - recurrent implantation failure. Several treatment approaches have been tested so far for this difficult category of patients. The workshop will both enhance our understanding of the problem as well as provide a critical appraisal of management strategies.

Stratis Kolibianakis
Co-ordinator SIG Reproductive Endocrinology

SIG PSYCHOLOGY & COUNSELLING

A multidisciplinary perspective

In the face of an ever increasing interest in the psychosocial aspects of ART, the SIG Psychology & Counselling is continuing to offer ESHRE's members a multidisciplinary view on the latest developments. After teaming up with the SIG Andrology in 2012 on **The whole man**, we are joining four other SIGs to offer a holistic and comprehensive approach on fertility preservation. The meeting, titled **Fertility preservation: from technique to implementation in clinical practice**, will have contributions not only from our SIG but also from the SIGs Ethics & Law, Safety & Quality in ART, the Paramedical Group and the Task Force Fertility Preservation in Severe Diseases. Knowing how to inform these patients about their treatments and involve them in the fertility preservation decision-making process is crucial. This two-day course is taking place in Amsterdam, 14-15th March, and covers the impact of cancer treatment on reproductive functioning to follow-up results on pregnancies after treatment. It will also give the audience a chance to acquire tools on patient information and multidisciplinary collaborations.

Munich 2014

Our precongress course on **Seeking and finding the evidence** will be held jointly with the SIG Safety and Quality in ART. We will consider what exactly constitutes evidence and how it is perceived not only by academics, but also by professionals and patients. We will discuss the best approach to inform patients and transmit evidence, and how to balance evidence with patient preferences. There will also be an opportunity to learn more about the placebo effect and the role of suggestion - and about the mindfulness-based programme for infertility of Dr Ana Galhardo.

Mariana Martins
Junior Deputy SIG Psychology and Counselling

SIG STEM CELLS

Next, the application of basic research to fertility preservation

There have been some changes in the steering committee of the SIG Stem Cells and I am very pleased to introduce as our new SIG deputy Dr. Björn Heindryckx from Ghent. Björn is a very active researcher in the field of stem cell biology and ART. His research focuses on embryonic lineage segregation and the different states of stem cell pluripotency in mouse and human. In ART, his focus is on oocyte activation, developing diagnostic tests and applying the technology of artificial oocyte activation, an experimental procedure designed to help patients with complete fertilisation failure even after ICSI. He is also investigating the prevention of mitochondrial disorders and cases of oocyte maturation arrest.

Future activities

On 27-28th April we are involved with colleagues from the SIGs Andrology, Reproductive Genetics, and Task Force Fertility Preservation in a Campus event on **Stem cells: origins, genetics, properties and significance for fertility preservation**, a top-quality programme of cutting-edge basic and applied research in stem cell biology and epigenetics and their application to fertility preservation. This is an area of growing interest in reproductive medicine, given the growth of fertility preservation both for medical and non-medical indications.

Our precongress course for Munich is titled **Of stem cells and gametes: more similarities than differences**? in which we will hear the latest news on the production of in vitro gametes (both oocytes and spermatozoa), their drawbacks and advantages, and what we can expect to see in our practices. The course will address the different shades of stem cells, and what their potential for differentiation towards gametes are. We will discuss differentiation into primordial germ cells, starting from the preimplantation embryo, and current knowledge on differentiation into either male or female gametes. Alternative routes, such as from the adult ovary and testes, will also be discussed. This course has been designed mainly for scientists and clinicians, but clinical embryologists with an interest in fundamental embryology or clinicians interested in alternative ways to obtain donor gametes will also be attracted.

Rita Vassena
Co-ordinator SIG Stem Cells

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