

focus on REPRODUCTION

Helsinki highlights



- Endometrial scratch: The story so far
- Freeze-all oocytes or freeze-all embryos?

// SEPTEMBER
2016



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SEPTEMBER 2016

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CHAIRMAN'S INTRODUCTION

Summer is coming to its close, and most of us are now back at work, hopefully after a relaxing holiday, though I guess that many of you – like me – still keep track of e-mails. It's a practice which is both reassuring and stressful at the same time.

Looking back now, I once again see the Annual Meeting as this year's main event: an attractive venue, with efficient and friendly staff, in a beautiful and hospitable Nordic capital, so I want to give a big thank you to Juha Tapanainen and his local team, as well as to ESHRE's Central Office, for their excellent organisation. I also wish to thank the SIGs, the Scientific Committee and all speakers and poster presenters for putting together yet another scientifically outstanding meeting.

Today, for a society like ESHRE, instant communication is increasingly important - and that largely means social media. ESHRE is already quite active on Facebook, Twitter and LinkedIn, but this year we also engaged five young ESHRE members from different parts of the world to tweet their experiences in Helsinki. The '@theESHRE5' group were very active, sending out immediate tweets of highlights from different sessions, including new findings, questions and discussions. Their input represented 362 tweets in total, which certainly increased the instant coverage of their chosen sessions. So a big thanks to the ESHRE5!

This news magazine too featured a new *Focus on Reproduction* blog during the congress, where short but very informative reports were posted. A very nice initiative which I hope we can repeat next year. One especially interesting blog - 'ESHRE in the headlines' - was posted by Nick Macklon, where he describes the difficulty of communicating a message to the press, and how the media can twist words for the sake of a headline. Take a look at www.focusonreproduction.eu

So we are constantly working on our communication skills, not least with our website and apps. The website is currently being upgraded with a new and more user-friendly style, and it's here that you'll find our updated and fully interactive *Atlas of Human Embryology* and our new e-learning platform. In addition we have the ESHRE apps - for the Annual Meeting (still active), for guidelines, and for the journals, which can be accessed both on- and offline.

And on the subject of journals, I hope you all are aware that we are now in the process of launching our fourth journal, *HROpen*. The platform and the format are currently receiving their finishing touches, and the first articles are due at the start of 2017.

We hope all these new developments will enhance communication with our members, and indeed with everyone else interested in teaching, learning and discussing what's new in reproductive science and medicine.

Kersti Lundin
ESHRE Chairman 2015-2017

// SEPTEMBER
2016

Bonjour Genève



Invited scientific programme now in place; abstract submissions for free communication must be with ESHRE by 1 February 2017

For a city of just 200,000, Geneva punches well above its weight; it is home to the European HQ of the United Nations and the World Health Organization, as well as to many multinational companies, the European Organization for Nuclear Research (CERN) and the International Red Cross.

And for four days next year, Geneva will also be home to ESHRE, for its 33rd Annual Meeting which takes place from 2-5 July. The majority of the invited scientific programme is already in place and confirmed, and the oral communication sessions will be selected from abstracts submitted before 1 February next year. All abstracts must be submitted online via the ESHRE website.

This year's meeting in Helsinki attracted a participation of almost 10,000, and expectations are that Geneva next year will prove equally attractive. The city itself, located between the nearby Alps and Jura mountains, is at the heart of French-speaking

Switzerland. The quayside of Lake Geneva, the city's many parks, and the alleyways of the old town will prove big attractions outside the congress programme.

Geneva is a truly international city and is linked to Europe's capitals by an international airport (just 6 minutes from downtown), motorways and a high-speed and efficient rail network. Switzerland is part of the Schengen Area, while Geneva itself is also one of the greenest cities in Europe: 20% of its area is covered in parks and green space.

The scientific programme for next year promises to explore many hot topics, including in the opening keynote session non-invasive prenatal testing with cell-free maternal DNA. Monday will also feature an invited session on gene editing in the human germ line in which Robin Lovell-Badge of the Francis Crick Institute in London (which is now home to the UK's MRC National Institute for Medical Research) will discuss its possibilities and its risks. The genome

DIARY DATES AND DEADLINES

ESHRE's 33rd Annual Meeting will take place at the Geneva Palais Exhibition and Congress Centre (PALEXPO) from Sunday 2 July to Wednesday 5 July 2017. The site is located immediately adjacent to the airport and is in easy reach of the city centre and all hotels. Trains operating at regular intervals take only 10 minutes between the airport and the congress centre. All visitors staying in Geneva hotels receive a Geneva Transport Card, which allows free public transport in the city for the duration of stay.

- All abstracts must arrive at ESHRE's Central Office no later than 1 February 2017.
- Early bird registration - for the lowest participation fee - must be completed before 30 April 2017 - for ESHRE members, non-members, paramedical members and students.
- All practical information on next year's Annual Meeting can be now found on the dedicated website www.eshre2017.eu.



editing technique of CRISPR was named as the scientific 'breakthrough of 2015' by the journal *Science*.

As ever, there will be a packed programme of pre-congress courses scheduled for Sunday. Fifteen have been planned, including one by the Cochrane group on how to prepare a systematic review in

reproductive medicine. In addition to two exchange courses staged by the ASRM and Middle East Fertility Society, one course on scientific authorship and one for the Paramedical Group, 11 focused courses have been planned by ESHRE's SIGs.

Anis Feki

On behalf of the local organising committee

Design, architecture, culture and green spaces are all great city interests



The next 'Best Of' ASRM and ESHRE meeting set for Paris in February



Registration for the next 'Best Of' ASRM and ESHRE meeting is now open. Full details of the meeting can be found at www.eshre.eu/thebestof.

Our joint meetings highlighting the best of ESHRE and ASRM have quickly established a tradition for bringing together world authorities in the science of reproductive medicine, with updates on the latest concepts and developments presented in a framework of lectures, debates and back-to-back sessions. The meeting is now set on a biannual track, with venues alternating between North America and Europe. The fifth 'Best Of' meeting will be held in Paris from Thursday 23 to Saturday 25 February next year at the city's Palais de Congrès. The programme for 2017 brings together sessions on gene editing, artificial gametes, energised oocytes, preconceptional genetic testing, diagnosis by RNA, and sperm DNA fragmentation. More established topics include uterine disorders, automation in the IVF lab, male infertility, and access to fertility care.



Many hot topics, but few emphatic answers

- Almost 10,000 take part in ESHRE's first Annual Meeting in Finland
- New work presented in 230 oral presentations and 800 posters

THERE WERE MANY hot clinical questions asked at this year's Annual Meeting in Helsinki, but few were answered with the cold certainty of unequivocal evidence. Endometrial scratching, supplements in poor responders, freeze-all embryos, individualised dosing for ovarian stimulation . . . There were studies presented on all these topics, but most without categorical conclusions.

One long debated topic, however, does now seem to be terminal, and there now seems little benefit to be gained from adding recombinant LH to the FSH protocol of poor responders. A randomised parallel-group study (ESPART) presented by Peter Humaidan of Skive Regional Hospital, Denmark, found no significant difference in the number of



Allan Pacey at this year's opening keynote lecture: Little effect of lifestyle on sperm morphology.

oocytes retrieved between poor ovarian responders receiving FSH plus LH and those receiving FSH alone. This was a study of 939 women meeting two of the three Bologna criteria for poor ovarian response, and said by Humaidan to be the largest trial to date in poor responders. Although oocyte retrieval was the study's principal endpoint, results also showed no significant difference between the two groups for clinical pregnancy rate (14.1% vs 16.8%), ongoing pregnancy rate (11.0% vs 12.4%) and live birth rate (10.6% vs 11.7%).

Similarly, there seemed little equivocation in the results of a large multicentre Dutch study - the OPTIMIST trial - of individualised dosing in predicted

2016 HONORARY MEMBERSHIPS



Honorary membership of ESHRE was awarded to Finland's Markku Seppälä, pictured left after receiving his award, and to Henry Leese, who, above, received his award from Chairman Kersti Lundin and Chairman Elect Roy Farquharson. Seppälä's major research interests have been in embryonic, fetal and placental proteins in early development, while Leese, from the Hull York Medical School in UK, in pursuing the nutritional requirements of the early embryo, has helped lay the foundations for a non-invasive assessment of embryo viability.



poor and hyper-responders in IVF. The predicted normal responders (529 women with an AFC between 11-15) were simply treated with 150 IU FSH. However, those with AFC scores under 11 were randomised in two groups to individualised or standard FSH dose protocols - ie, AFC 0-7 to 450 or 150 IU FSH, and AFC 8-10 to 225 or 150 IU FSH. The second OPTIMIST trial involved women only with an AFC above 15, and as predicted high responders were all randomised to either 100 or 150 IU FSH.

Presenting results from the first individualised vs standard trial in predicted poor responders, Charine van Tilborg reported no difference in first-cycle live birth rates in both groups of poor responders (either AFC 0-7 or 8-10) when randomised to standard or individualised dose protocols. A Kaplan Meier analysis reflecting cumulative pregnancy rate leading to live birth within the 18 month study period revealed comparable rates for standard (39.8%) and individualised (38%) dosing. 'So individualised dosing does not seem to be more effective in this group of patients,' said Van Tilborg. Her colleague Simone Oudshoorn reported similar findings from the second trial in predicted high responders (AFC >15) - an ongoing pregnancy rate leading to live birth over 18 months of 63% in the individualised (100 IU) group

and 66% in the standard (150 IU) group. This study also found no difference in incidence of severe OHSS in either group. Thus, taken together, individualised FSH dosing based on predicted ovarian response did not improve live birth rates, but disappointingly did neither prove an obvious safety benefit for high responders.

This, however, was not the congress's last word on individualised dosing in IVF. A well attended invited session asked if 'all patients are the same' or whether protocols should be adapted to individual cases. Ernesto Bosch from IVI in Valencia built a case for an individualised approach on the huge degree of heterogeneity among patients and argued that AMH will allow personalised dosing in IVF. Citing the ESTHER trial (also reported at this congress), Bosch argued that an individualised dose based on ovarian reserve testing and body weight would extend the 'optimum' response of 8-14 oocytes and narrow the number of hyperresponders, with inherent benefits in safety. While Bosch argued that adapting IVF procedures to each patient is 'crucial to optimise efficacy and safety', his fellow speaker Julius Hreinsson was emphatic that adopting the same laboratory strategies to all patients makes no sense. He argued that evidence-based medicine and best practice have



Individual or standardised dosing protocols were high on the agenda of this year's meeting. The Dutch multicentre OPTIMIST trial, whose results were part presented by Charine van Tilborg, found that individualised dosing based on AFC does not improve cumulative LBR in either predicted poor or high responders. Ernesto Bosch speaking in an invited session argued the case of a personalised approach based on patient heterogeneity.

Developments in the IVF lab



Elpida Fragouli: 'Robust' results from a prospective study of mitochondrial DNA levels in blastocyst trophoderm cells.

As ever, developments in the lab were a strong feature of the congress and many thought this year's highlight came from Elpida Fragouli's report on the role of mitochondrial DNA levels in embryo implantation.

Fragouli, from Reprogenetics UK and the University of Oxford's Nuffield Department of O&G, explained that around one-third of chromosomally normal embryos fail to implant after transfer. However, a new approach to embryo assessment based on the quantification of mitochondrial DNA found in the trophoderm cells of a blastocyst sheds light on why so many of these apparently healthy embryos are actually not viable. And it's this approach in combination with aneuploidy screening which may now represent the most accurate measure of embryo viability we have ever had – and with it great potential for improving IVF outcome.

Results from a prospective study of 280 chromosomally normal blastocysts presented by Fragouli showed that, of the 111 single blastocyst transfers whose outcome was so far known, 78 (70%) led to ongoing pregnancies, and

every single one of them (100%) had levels of mitochondrial DNA known to be normal. The remaining 33 blastocysts failed to implant, and eight of these (24%) had unusually high levels of mitochondrial DNA. 'The results confirm that embryos with elevated levels of mitochondrial DNA rarely implant,' said Fragouli, who described her results as 'very robust'.

Another high-scoring study from the same group found, with evidence from cytogenetic testing, that advancing male age has a significantly adverse effect on the outcome of IVF and specifically on the DNA integrity of sperm cells. The study, presented by Araz Raberi from Oxford, examined 14 markers of male fertility and treatment outcome in almost 600 male partners of infertile couples. Not all these parameters – such as sperm concentration or sperm abnormality – showed deteriorations with age, but damage to sperm DNA integrity and sperm motility did increase significantly. As a result, increased male age in this study was significantly associated with a decrease in the average number of fertilised eggs and final birth rate.

been the drivers to standardisation, citing as its best example the move towards single embryo transfer. However, while 'a la carte IVF may not be very professional,' said Hreinnsson, there are many cases in IVF where an individualised approach will help a centre's success rates and maximise treatment outcome. ICSI for all, for example, irrespective of indication, has very little support from the evidence, while blastocyst culture may well benefit from an individualised approach.

Few other topical themes raised at this congress were able to clarify their own heated

debates. Again in poor responders (a recurring theme in Helsinki), a randomised trial presented by Rob Norman from the University of Adelaide found that live birth rates were no better in poor-responding patients (under the age of 41) given growth hormone as a supplement than in those given placebo. Norman disclosed that the study, to achieve sufficient statistical power for a strong conclusion, required an enrolment of 390 women, but after four years only 136 had been recruited – partly because many prospective recruits had bought growth hormone themselves outside the trial.



Nevertheless, results showed a clinical pregnancy rate of 14% in the growth hormone group and 11% per started cycle in the placebo group. There were equal comparisons between the two groups in the number of eggs collected, quality of embryos and duration of treatment.

Another study of supplements in predicted poor IVF responders - this time a meta-analysis of DHEA - also found no benefit of the

supplementation in this difficult patient group. 'The information is important,' said presenter Stratis Kolibianakis, 'for appropriately counselling poor responders without offering them unrealistic expectations regarding their prognosis.'

There were similarly unpromising results for endometrial scratch (explored more fully in this issue of *Focus on Reproduction* on page 26). A Cochrane review presented as a poster by Susan Lensen from Auckland did suggest that endometrial scratching may well be beneficial in couples trying to conceive naturally or with IUI, although with the strong caveat that the quality of the available evidence was 'very low' (a complaint also noted in a previous Cochrane report on endometrial scratch prior to IVF).

Similarly, in an invited session devoted exclusively to endometrial injury, Edinburgh consultant Hilary Critchley concluded that there was still insufficient evidence for it to make any biological sense, while Christophe Blockeel from the Brussels group drew the same conclusion about clinical benefit.

However, there was an emphatic conclusion in a large cohort linkage study from Denmark presented by Sara Malchau. After analysing the birth records of almost 20,000 women having fertility treatment between 2007 and 2010, she found that three out of four of them had had a baby within five years. The majority of these women (57%) had their baby as a result of treatment, but a significant proportion (14%) conceived



Both Hilary Critchley and Christophe Blockeel concluded there was as yet insufficient evidence to make a biological or clinical case for endometrial scratching. Results of randomised trials now under way are eagerly awaited.

Sara Malchau presented results of a cohort study in which 20,000 fertility treatments in Denmark were linked to the national birth registry and found that three in four of these patients had a baby within five years



A Cochrane review performed by Susan Lensen and colleagues from New Zealand found that evidence in favour of endometrial scratch before IUI and natural conception was 'very weak'.



spontaneously without treatment. More than half (57%) gave birth within two years. Describing the results as 'robust', Malchau said that 'we are now able to provide couples with a reliable, comprehensible, age-stratified long-term prognosis at start of treatment'.

Sperm quality - as reflected in morphological assessment - was the subject of the opening keynote lecture, given this year by Allan Pacey from Sheffield, author of the most downloaded recent original paper from the three ESHRE journals. Before an audience of more than 3000, Pacey proposed that few lifestyle factors make any difference to sperm morphology, and he advised couples not to defer fertility treatment on the basis of lifestyle changes in the male partner. The study did find a doubling of the risk for poor sperm shape and size if sample production occurred in summer, and if accompanied by the use of cannabis in

the three months prior to sample collection (but only in younger men). But no significant association was found with BMI, type of underwear, smoking, alcohol consumption or mumps. Use of mobile phones was, unfortunately, not one of the variables measured.

- For the record, this year's Annual Meeting had a total of 9711 registrations, which included 1680 'exhibitors'. There were 20 media registrations, with the congress's usual broad press coverage derived from eight press releases (and press podcasts).

The UK, Italy, India and Spain were the most represented countries at the congress, each providing more than 400 participants. More than 50% of those attending were clinicians, and almost 20% embryologists. Gender differences among attenders are now almost equal, with men (53%) only just more numerous than women (47%).

'AWARDS TO SEVEN PRIZE WINNERS AT THIS YEAR'S ANNUAL MEETING

Six presentations were rewarded with a prize of €2000. One additional presentation was selected for the Fertility Society of Australia Exchange Award. Committees of senior scientists and clinicians made the selection for each award.

Basic Science Award for oral presentation

ABVD chemotherapy for lymphoma affects number and morphology of primordial follicles in the adolescent and adult ovary

Evelyn Telfer (United Kingdom)

Clinical Science Award for oral presentation

Hysteroscopic intratubal Essure® device placement versus laparoscopic salpingectomy, as treatment for hydrosalpinges prior to in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI): a randomised controlled trial

Kim Dreyer (The Netherlands)

Basic Science Award for poster presentation

Unique geometry of sister kinetochores in human oocytes during meiosis I may explain maternal age-associated increases in chromosomal abnormalities

Jessica Patel (United Kingdom)

Clinical Science Award for poster presentation

Miscarriage risk in women with twice, once and never poor response in two consecutive IVF treatment cycles

Talita Honorato (The Netherlands)

The Fertility Society of Australia Exchange Award

Trends over time in congenital malformations among children conceived after assisted reproductive technology (ART)

Anna-Karina Henningsen (Denmark)

The Nurses Award

Reproductive options for transmen

Sara Somers (Belgium)

The ART Laboratory Award

The relation between cell size and developmental stage in human day 2/ day 3 embryos is a predictor for blastocyst formation on day 5

Vanessa Muyschond (Belgium)



ESHRE Chairman Kersti Lundin presents the Basic Science Award for oral presentation to Evelyn Telfer.



The Fertility Society of Australia Exchange Award went to Danish investigators of the CoNARTaS study for their linkage study of congenital malformations in ART children.

Annual Assembly of Members

Membership at a record high, finances in good order

ESHRE's Annual Assembly of Members took place at the Messukeskus Expo and Convention Centre, Helsinki, on 5 July 2016 at 18.00. The minutes of the meeting are recorded below. Matters arising and their approval will take place at next year's Annual Assembly in Geneva.

1. Minutes of the last meeting held in Lisbon

- The minutes of the 2015 Annual Assembly of Members (AAM), having been circulated to all members in *Focus on Reproduction* (September 2015), were approved.

2. There were no matters arising.

3. Membership of the Society

- Membership of the Society now stands at 6741, an increase on last year's figure of 6448 (December) and an all-time record membership. The top European membership countries are UK (456 members), Italy (351), Netherlands (310), Spain (306), Germany (298), and Belgium (283). The USA is represented by 327 members, India 315 (an increase of almost 50 on last year) and China 157.

- The Chairman reported that disciplines most prominently represented (according to SIG membership) are embryology and reproductive endocrinology, but there is strong membership presence in andrology, early pregnancy and reproductive surgery.

4. Society activities

Annual meetings

- Last year's Annual Meeting in Lisbon attracted 10,088 participants, the highest number ever recorded. Feedback, said the Chairman, was generally positive about both the organisation and scientific programme. This was ESHRE's first fully paper-free congress.

- Attendance in Helsinki was already approaching 10,000, with a total of 9844 registered (which included 1808 exhibitors and 21 press).

- From a record total of almost 1800 abstracts submitted, 234 had been selected for oral presentation and 800 for poster. The greatest number were from embryology (358), female infertility (237) and reproductive endocrinology (230). The majority (53%) were submitted from Europe, but there were high representations from Asia (31%) and the Americas (12%). The Chairman said that efforts continue to improve the abstract review process.

- Next year's event will be at the Palexpo centre, Geneva, from 2-5 July, with 15 pre-congress courses organised by the Special Interest Groups and exchange partners. The invited programme is already available online.

- The Annual Meeting of 2018 will be held in

Barcelona, Spain, from 1-4 July.

- The 'Best of ASRM and ESHRE' meetings have now been revised to take place every second year. Next year's event will be held in Paris from 23-25 February.

Educational activities

- The Chairman reported that nine Campus courses had been held in 2015 and eight already in 2016.

- The Chairman also announced introduction of e-Campus, the Society's e-learning platform available to members via the website, and an updated version of the very successful ESHRE *Atlas of Human Embryology*. This latest version is interactive, amenable to future expansion and freely accessible to members.

Data collection

- The Chairman praised the work of the European IVF Monitoring Consortium (EIM) and PGD Consortium. The EIM group, now under the chairmanship of Carlos Calhaz-Jorge, has been collecting data retrospectively since 1997 from around 30 European countries and is now monitoring around 600,000 European ART cycles each year and representing a cumulative total of more than 1 million babies born since the EIM began its work.

- Data collected for 2012 has now been published in *Human Reproduction*; preliminary data for 2013, which were the first to use a new online data collection system, were presented in Helsinki. Data collection for 2014 has a deadline of 31 October 2016.

- Data reported for 2012 (from 1111 reporting clinics) indicate that the number of frozen cycles has reached that of fresh cycles

(139,558 FER vs 139,978 fresh), with pregnancy rates from FER rising from 14.1% in 1997 to 23.1% in 2012. The majority of transfers are with two embryos, while SET continues to rise (to almost 30% of all cycles in 2012). Multiple delivery rates continue to decline, while pregnancy rates increase (now at around 30%, from 26% in 1997).

- Data XVI, XVII and XVIII (for 2013, 2014 and 2015) from the PGD Consortium were presented in preliminary form in Helsinki. They mark the interim phase between former retrospective data collection and the new online prospective system just introduced.



Swedish embryologist Kersti Lundin continues as Chairman of ESHRE until next year's Annual Meeting.

ESTEEM trial

- The ESHRE Study into The Evaluation of oocyte

ESHRE's Executive Committee remains in place until 2017: from left, Borut Kovacic (SI), Basak Balaban (TR), Andres Salumets (EE), Grigoris Grimbizis (GR), Mariette Goddijn (NL), Roy Farquharson (GB, Chairman Elect), Helen Kendrew (Paramedical Board), Kersti Lundin (Chairman), Tatjana Motrenko (ME), Juha Tapanainen (FI, Past Chairman), Cristina Magli (IT, SIG Committee), Rita Vassena (ES), Petra De Sutter (BE), Nicholas Macklon (GB) and Georg Griesinger (DE).



Euploidy by Microarray analysis (ESTEEM) continues as a multicentre RCT with two primary aims: to estimate the likelihood of having no euploid embryos in future ART cycles and to improve live birth rates in women of advanced maternal age.

- There are eight centres in the study, with presently some 345 patients randomised. The target, said the Chairman, is 560 cycles. Professor Karen Sermon (UZ Brussels) was appointed as the new chairman of the steering group last year, and the estimated completion date has been extended to the end of 2016.

ESHRE research grant

- ESHRE's first research grant scheme introduced in 2014 had 259 applications and was awarded to a joint UK/Italy project to prevent ovarian damage from chemotherapy.
- The Chairman noted several changes to the scheme, and explained that ESHRE will award two grants in 2016, one of 50,000 euro and one of 150,000 euro. The grants will be awarded to projects that will run for up to three years and will be selected on the basis of scientific excellence, originality and feasibility. Applications for 2016 were asked to focus on the theme of 'endometrial receptivity'. ESHRE received 40 proposals for the smaller award, and 51 proposals for the larger. A second evaluation round will take place in September-November, with the winners announced in December.

Guidelines

- The Chairman reported that guidelines are becoming an increasingly important activity of ESHRE. Two were published in 2015, *Routine psychosocial care in infertility and medically assisted reproduction* and *Management of women with premature ovarian insufficiency*. Also, revised guidelines for good practice in IVF laboratories were developed by the SIG Embryology.
- ESHRE is also collaborating with other societies in the development of guidelines - notably on key performance indicators for ART, on the surgical management of endometriosis, and in PCOS.
- All ESHRE guidelines are developed according to an

established methodology and are published as a full version, in summary format in *Human Reproduction*, and as a lay version. They are freely available to everyone. They may also be produced as pocket guidelines and as an app.

ESHRE accreditation and certification

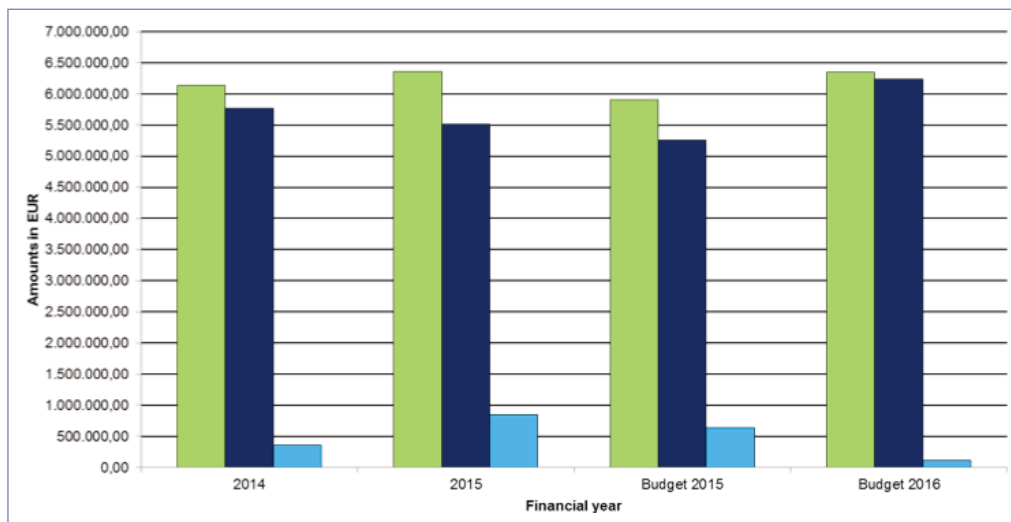
- Certification is now available to ESHRE members in embryology, reproductive endoscopy, and fertility nursing.
- By the end of 2015 the cumulative total of certified clinical embryologists was 1266 (with 701 certified at the senior level).
- Certification for reproductive endoscopic surgeons (ECRES), introduced in 2013, is on two levels, level 1 (bachelor) and level 2 (endoscopic surgeon), and assesses both practical and theoretical skills. In 2015 ten candidates applied and seven passed at level 1.
- The first examination for nurse and midwife certification took place in Lisbon in 2015; 63 took the exam, and 51 passed, a pass rate of 81%.
- Eleven centres have so far been accredited under ESHRE's joint programme for accreditation of subspecialist training programmes with the European Board and College of Obstetrics and Gynaecology (EBCOG).

Special Interest Groups

- Changes to the titles and interests of four Special Interest Groups were announced in 2016: the newly named SIG Global and Socio-cultural Aspects of Infertility absorbed the interests of the disbanded Task Force Developing Countries; the SIG Safety and Quality in ART absorbed the interests of the Task Force Viral Disease; and there were redefined interests for the newly named SIG Endometriosis and Endometrial Disorders and SIG Implantation and Early Pregnancy.

Committees

- The affairs of ESHRE are now in the hands of an Executive Committee and nine further committees: Finance, Publications, Communications, SIGs, Scientific, Research Grant, European Affairs, Certification & Clinical Management, and Ethics.



Income
Expenditure
Balance

Income in 2015 (€6,362,608) was ahead of expenditure (€5,516,613), leaving a favourable accounts balance of €845,994. The source differential of ESHRE's income is shown in the chart below.

5. ESHRE journals

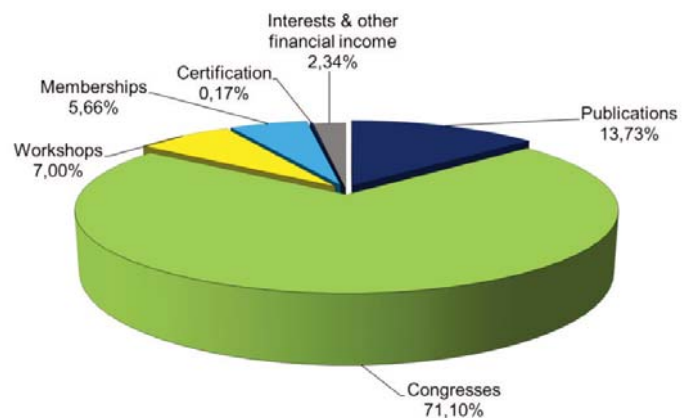
- Speaking on behalf of the Publications Committee, Hans Evers, Editor-in-Chief of *Human Reproduction*, reported that manuscript submissions to *HR* in 2015 totalled 1211, somewhat fewer than in 2014 (1325), with acceptance rate relatively steady at between 20 and 26% depending on category. Reviewing time for new submissions to a first decision is now down to 24 days.
- Last year's impact factors ranked *Human Reproduction Update* and *Human Reproduction* as the top two journals in the categories of Obstetrics and Gynaecology and Reproductive Biology, with *MHR* fourth in the latter category. All three ESHRE titles, *HR Update*, *HR* and *MHR Molecular Human Reproduction*, increased their impact factor, to 11.2, 4.6 and 3.8 respectively
- Evers reported several recent innovations, notably short alerts and editor's highlights via the website.
- The editor of ESHRE's forthcoming open access journal, Siladitya Bhattacharya, said the new title, *HR Open*, will follow a current trend in digital communication. Its aim, he said, is 'to improve the understanding of reproductive medicine and improve the quality of clinical care by making scientific research freely accessible to those providing or seeking treatment'. Initial publication will be in January 2017, with submissions welcome from September 2016.

6. Paramedical group

- Helen Kendrew, Chair of the Paramedical Board, reported that paramedical members comprise nurses, midwives, lab technicians (the largest group), counsellors and psychologists, and clinical embryologists up to BSc level. The Board meets three times per year.
- The group's training and pre-congress courses, as well as Helsinki paramedical sessions, were all well attended. Also progressing with enthusiasm was the certification course for nurses and midwives.

7. Financial report

- The Chairman presented the balance sheet (income and expenditure) for 2015 and the budget for 2016. Income in 2015 (6,362,608 euro) was ahead of expenditure (5,516,613 euro),



leaving a favourable balance of 845,994 euro. Expenditure in 2015 was slightly higher than forecast in the budget. A budget similarly constructed to 2015 - to provide a positive balance - has been set for 2016.

- The Annual Meeting continues to provide the Society's greatest source of income (71%) and expenditure (52%). Educational activities are the major source of SIG expenditure.
- The 2015 value of ESHRE's assets in capital and reserves was put at 13,298,731 euro.
- The financial report for the year ending 31 December 2015 and the budget for 2016 were approved by the members.

8. Election of honorary members for 2017

- The two nominees proposed by the Executive Committee for honorary membership in 2017 were Professor Marc Germond from Lausanne, Switzerland, and Professor Rob Norman from the University of Adelaide, Australia. Both nominations were ratified by the AAM.

9. Any other business

- There were no matters raised.

- The next Annual Assembly will be on 4 July 2017 in Geneva at 18.00.

ESHRE's e-learning platform now available to members

● More than 250 hours of slide sets, presentation videos, and reports assembled

e-Campus, ESHRE's much anticipated e-learning service, is up and running and available to Society members via log-in at the website. Already, more than 250 hours of educational items are available to ESHRE members, mainly in video and slide format, with many more promised over the coming months.

Presentations from complete Campus meetings and pre-congress courses dating back to 2014 have been recorded by video, with captions and commentary available with each. Each recording is accompanied by a short written introduction explaining its educational relevance and range.

Topics for coverage are those defined by interests of the SIGs, plus a section on academic authorship. The programme also gives users the chance to save items and develop personalised



playlists of interest.

A menu button at the top of the site page will take users to a drop-down of functions, which includes a 'Topic Overview' where subjects are arranged according to SIG interests. Thus, endometriosis carries more than 50 presentations from meetings held between 2014 and 2016; andrology carries 40 presentations, and reproductive genetics more than 80, and so on. Those hoping to produce better manuscripts for publication can access seven presentations from the editors of the ESHRE journals, including the principles of study design and manuscript composition.

Presentations are also listed by calendar date and can be re-assembled in the form of individual playlists.

Access is via the website at www.eshre.eu/ecampus.

91 project proposals for ESHRE research grant

Ninety-one proposals were received for the ESHRE research grant scheme for 2016, for which two awards are available: the first for a sum of €50,000 (with 40 submissions) and the second for €150,000 (with 51 submissions). In a bid to keep this year's proposals focused, all applicants were asked to make applications on the theme of 'endometrial receptivity'.

Collaboration between research groups is encouraged but not obligatory.

The first round of blind evaluation is now complete, with applicants notified of their fate in July. A second round of evaluation will start this month, with final decisions made public in December. The grants will be awarded to projects that will run for up to three years and will be selected by an evaluation team on the basis of scientific excellence, originality and feasibility.

ESHRE's first research grant scheme, which runs every two years, was introduced in 2014 and had 259 applications. The single grant was awarded to a joint UK/Italy project led by Professor Norah Spears of the University of Edinburgh to prevent ovarian damage from chemotherapy.

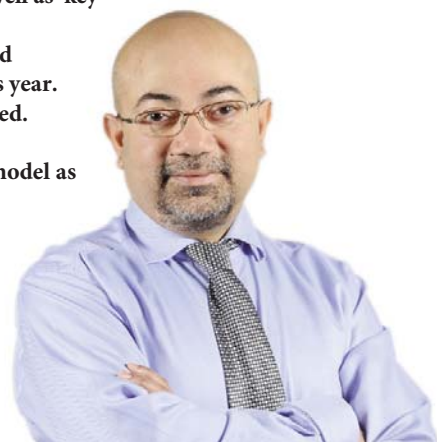
HROpen now ready for business

The new editor of ESHRE's open-access journal *HROpen* has spelled out its mission and editorial aims. Speaking in Helsinki, Siladitya Bhattacharya described *HROpen* as a high quality journal which aims to 'harnesses the full potential of the internet to deliver scientific scholarship which is current, personalised and fit for purpose' - and 'make scientific research freely accessible to those providing or seeking treatment'.

He added that the journal's scope would be wide, covering 'clinical, biological, environmental, ethical, and social aspects of reproductive medicine'. Such a range would include laboratory research, randomised or observational studies, systematic reviews or even pilot studies, with editorials and comment as well as 'key messages in plain English for lay readers'.

HROpen will launch in January 2017 and welcome submissions from September this year. Thereafter, four issues per year are planned.

In an interview with the publishers, Bhattacharya described the open-access model as 'the currency of research dissemination', adding that 'scholarship should not be the preserve of a few'. *HROpen*, he said, will be able to 'initiate and maintain a dialogue between authors and readers in real time and will hopefully encourage patients to access lay summaries of research relevant to their care'.



The highest ever impact factor in O&G

- *Human Reproduction Update* impact factor advances from 10.165 to 11.194
- All three ESHRE titles increase their individual impact factor scores

The advance of ESHRE's review journal *Human Reproduction Update* continues to break new ground in the impact factor fields of Reproductive Biology and Obstetrics & Gynaecology. Last year, after assessment of citations in 2014, the journal passed into the exalted realm of double-digit impact factor to join a catalogue of leading journals deep in the mainstays of science and medicine. Now, having long held its place at the head of both categories, *Update* has stepped forward yet again with an impact factor of 11.194, the highest ever recorded in the categories of Reproductive Biology or O&G. As a review journal, *Update* is now in a league of its own in terms of status and influence.

'It's a wonderful achievement, and a credit to everyone involved,' said *Update*'s Editor-in-Chief Felice Petraglia. 'It is a big step forward on last year, and a real landmark.'

All three of ESHRE's journal titles increased their impact factors from last year. *Molecular Human Reproduction* rose from 3.747 to 3.943, and *Human Reproduction* itself, ESHRE's flagship title, from 4.569 to 4.621. 'This is another important step towards an impact factor of 5 for *Human Reproduction*,' said Editor-in-Chief Hans Evers. 'For a journal with almost exclusively original scientific articles, this is indeed a great achievement.' The citation index also indicated another real advance for *MHR*, which is not just firmly established in Reproductive Biology but is also now in the top ten of O&G (and ahead of *Reproductive Biomedicine Online*).

In raising its impact factor, *Human Reproduction* regained its second place in the Reproductive Biology category ahead of *Fertility and Sterility*, whose impact factor fell back a little from 2014.

HR Update's 5-year impact factor increased to 11.366, and Petraglia said editorial commissioning would concentrate on hot topics and subjects 'which require consideration'. Such a policy is reflected in the journal's continuing list of most cited papers - on female reproductive ageing, ovarian reserve, WHO semen values, and ultrasound assessment of PCOS.

'It was Bob Edwards who had the vision to see the potential of a review journal in reproduction,' said Petraglia, 'and it's a matter of great pride to me that I can follow in his footsteps - and those of former editors John Collins and Bart Fauser - to make the promise of that vision so real and successful.'



Update editor Felice Petraglia: committed to further progress.

Reproductive biology

Title	Total cites	2014 Imp Factor	2015 Imp Factor
Human Reproduction Update	7239	10.165	11.194
Human Reproduction	27872	4.569	4.621
Fertility & Sterility	31421	4.59	4.426
Molecular Human Reprod	5158	3.747	3.943
Biol Reprod	21894	3.318	3.471
J Reprod Immunology	2447	2.815	3.202
Reproduction	7654	3.174	3.184
Placenta	7551	2.71	2.972
Am J Reprod Immunol	4116	2.438	2.916
Reprod Toxicol	5295	2.771	2.85

Obstetrics and gynaecology

Title	Total cites	2014 Imp Factor	2015 Imp Factor
Human Reproduction Update	7239	10.165	11.194
Obstet Gynecol	28520	5.175	5.656
Am J Obstet Gynecol	35156	4.704	4.681
Human Reproduction	27872	4.569	4.621
Fertility & Sterility	31421	4.59	4.426
Gynecol Oncol	20449	3.774	4.198
Ultrasound Obstet Gynecol	9482	4.254	4.197
BJOG	13960	3.448	3.943
Molecular Human Reprod	5158	3.448	3.943
Menopause	4632	3.361	3.172

TROPHY study published in The Lancet

● Hysteroscopy of no benefit before further IVF attempts

The TROPHY study of hysteroscopy in recurrent IVF failure, a large-scale randomised trial funded jointly by ESHRE and the European Society for Gynaecological Endoscopy, has been published in *The Lancet*.¹ The results, which showed that hysteroscopy does not improve IVF outcome in women with recurrent implantation failure, will lay to rest many of the conflicting conclusions emerging previously from underpowered studies and meta-analyses.

This, however, was a large eight-centre trial (in UK, Belgium, Italy and Czech Republic) in which more than 700 women under 38, without known uterine pathology and with a history of at least two to four unsuccessful IVF treatments, were randomised to outpatient hysteroscopy or no hysteroscopy one month before starting a further IVF cycle. Live birth rate in both groups was 29%.

The preliminary results were reported at



Tarek El-Toukhy, first author of the TROPHY study

ESHRE's 2014 Annual Meeting in Munich, when first author Tarek El-Toukhy from Guy's and St Thomas's Hospital, London, proposed that 'outpatient hysteroscopy before IVF cannot be considered essential for women with recurrent IVF failure'. El-Toukhy explained that outpatient hysteroscopy is performed routinely in many fertility clinics before further IVF, first diagnostically to visualise the uterus and check for abnormalities, and then operatively during the same procedure to remove any growths. Several studies had suggested that this can be beneficial prior to further IVF. However, the TROPHY study has now found such benefit to be less than previously suggested.

1. El-Toukhy T, Campo R, Khalef Y, et al. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. *Lancet* 2016; 387: 2614-2621.

Platelet-rich plasma for ovarian rejuvenation

A study of just eight subjects presented as a poster during the Annual Meeting in Helsinki may yet turn out to be the most talked about controversy of the congress. The study, presented as Poster 401 by a group from Athens, investigated 'ovarian rejuvenation and folliculogenesis reactivation' in perimenopausal women after autologous platelet-rich plasma treatment. The latter, the investigators explained, is a concentrated source of growth factors and cytokines, which in numerous studies have demonstrated beneficial effects on tissue and angiogenesis regeneration.

In this study the plasma preparation was infused into the ovaries of eight perimenopausal women who were without menstrual cycles for around five years. Successful ovarian rejuvenation was confirmed by menstrual cycle restoration around three months after treatment. Oocyte retrieval was successful in all cases, resulting in 2.50 ± 0.71 follicles and 1.50 ± 0.71 MII oocytes. All mature oocytes were inseminated by ICSI and the resultant embryos cryopreserved. No embryo transfers had been performed.

The study was taken up by the magazine *New Scientist*, whose report sparked widespread interest. The results, investigator Konstantinos Sfakianoudis told *New Scientist*, offer 'a window of hope that menopausal women will be able to get pregnant using their own genetic material'; he added that the platelet-rich plasma had now been given to around 30 women all aged between 46 and 49.



Screening for clotting mutation and heparin treatment found effective in recurrent implantation failure

A study reported by Elpida Fragouli in Helsinki highlighted the indeterminate fate of chromosomally normal embryos transferred in IVF; around 30%, said Fragouli, fail to implant, which in her study was explained by high levels of mitochondrial DNA.

Now, a study from the Care UK group of Simon Fishel suggests that a little known gene mutation transmitted by either partner may cause blood clotting in the female partner sufficient to cause placental complications and pregnancy loss. The investigators say the mutation is on chromosome 4 and, identified as the 'Annexin 5 M2 haplotype', can be tested as a marker for failed implantation and miscarriage.

A study in the *Lancet* online journal *EBioMedicine* suggests that those couples shown by screening to be 'ANXA5 M2 positive' are associated with an adverse IVF outcome.¹ However, a multicentre prospective study of ANXA5 M2 haplotype screening and

antithrombotic treatment with low molecular weight heparin following embryo transfer in 103 IVF couples ANXA5 M2 positive found live birth outcome similar to that of 103 matched controls.

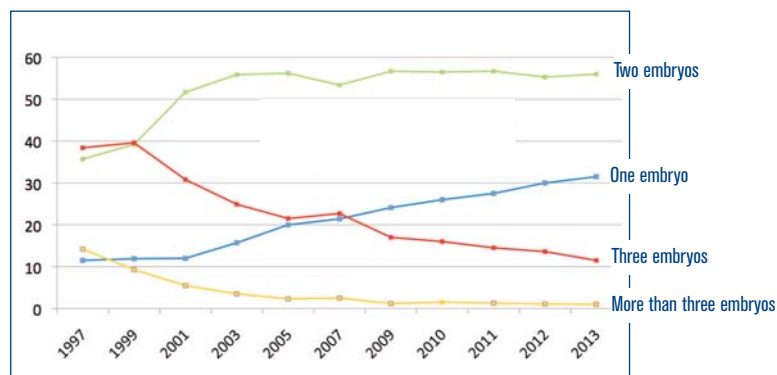
The authors say that the identification and treatment of M2 carrier pregnancies by screening both partners for the M2 haplotype in IVF may identify an adverse prognostic factor which may benefit from antithrombotic treatment.

1. Fishel S, Baker D, Elson J, et al. A multicenter observational cohort study of the annexin A5 M2 haplotype as a biomarker for antithrombotic treatment to improve pregnancy outcome. *Ebiomedicine* 2016; doi.org/10.1016/j.ebiom.2016.06.024

Pregnancy rates in IVF and ICSI now stable at 28% per aspiration

- Preliminary results reported for 2013
- European twin delivery rate steady 17.3%
- Highest pregnancy rates in egg donation
- Greatest availability in Belgium and Denmark

The data collection and monitoring of ESHRE's EIM Consortium have grown more complex with the progress of ART. IUI was added to the techniques monitored in 2002, while present data collections must include PGD, IVM, and frozen oocyte replacement. Collecting data on a procedure such as 'egg donation', for example, is no longer a simple matter of recording a cycle, but must now acknowledge oocyte and/or embryo cryopreservation, transfer in a fresh or future



Number of embryos transferred in IVF and ICSI - % per year.



EIM Chairman Carlos Calhaz-Jorge: Success rates have now been generally stable since 2008.

(non-stimulated) cycle, and outcome, which may well be several years after the initial egg collection cycle.

These demands have been made somewhat easier by the introduction last year of an online data collection system which is already simpler than the previous time-consuming paper version. The current requirement is based on eight data modules comprising ten pages and 20 tables, and, according to EIM Steering Committee chairman Carlos Calhaz-Jorge speaking in Helsinki, the total data provided now represents around 80% of ART activity in Europe and is more than a realistic snapshot of what's going on.

Among the trends identified in 17 years of data monitoring Calhaz-Jorge singled out an increase in SET (from 11% in 1997 to more than 30% in 2013), a major decrease in triplet rates (from 3.8 in 1999 to 0.5% in 2013), improving success rates from frozen embryo transfers, but a stabilisation of pregnancy rates in IVF, ICSI and egg donation. Also stable is the number of two-embryo transfers (at around 55% of all ETs); the increase in SETs seems to be driven by the decline in three-embryo and higher ETs.

The distribution of IVF and ICSI remains much in favour of ICSI, despite EIM evidence of a slightly higher pregnancy rate per aspiration from IVF (28.9%) than from ICSI (27.6%). It was this continuing overuse of ICSI, which sees ICSI applied in almost every cycle in some countries, which prompted a recent editorial

ALMOST 80% OF EUROPEAN CYCLES MONITORED

ESHRE's EIM Consortium has now been active for over 17 years and has reached the remarkable data milestone of more than 1.3 million babies recorded. In 2013 alone the Consortium's coverage was derived from 35 countries, 1144 treatment centres, 684,065 cycles monitored, and 143,957 babies born. 'Numbers are going up every year,' said EIM chairman Calhaz-Jorge, noting that the total number of cycles submitted for 2013 increased by 6.9% over 2012, meaning that the Consortium has monitored a cumulative total of more than 7 million cycles since its formation in 1997 and 1.3 million children born.

	1997	2001	2008	2011	2012	2013
IVF	21.9%	25.1%	28.5%	29.1%	29.4%	28.9%
ICSI	24.3%	26.2%	28.7%	27.9%	27.7%	27.6%
FER	14.1%	14.3%	19.3%	21.3%	23.5%	26.9%
ED	-	30.8%	38.3%	49.5%	51.7%	49.4%

Pregnancy rates per aspiration 1997-2013.

ICMART PUTS GLOBAL ART BABY TOTAL AT AT 6.5 MILLION

The total of IVF babies born throughout the world has now risen from a remarkable 5 million three years ago to 6.5 million, according to the USA's David Adamson presenting global results for 2012 on behalf of ICMART. His figures were based on an estimated 1.9-2.2 million cycles now being performed each year and the delivery of around 480,000 babies.

Among other findings, Adamson also reported a global delivery rate of 19.5% per aspiration and a cumulative rate of 28.9%. The mean number of embryos transferred in 2012 was 1.88, a slight decrease of 0.22. However, Adamsom also noted 'huge differences in availability, practice and results', with North America still responsible for the world's highest delivery rates (currently at 32% for fresh ETs), and

Australia/New Zealand for the highest rate of one/two embryo transfers.

As in Europe, global trends continue to show ICSI favoured over IVF by about two cycles to one.

Japan is the world's most prolific ART country (323,047 cycles reported in 2012), followed by USA and France. However, Adamson noted the undisclosed contribution of China to the ever rising number of cycles reported from Asia, which already represents the world's second most active region after Europe.

● Also included in this ICMART report were data submissions from ten African countries, Ghana and Nigeria for the first time. Africa, which now accounts for 1% of the global ICMART total, now has its own ART registry which, for 2013,

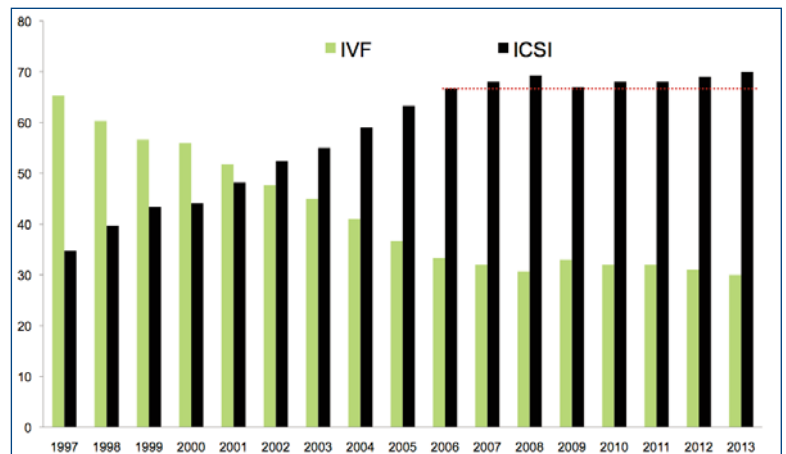


David Adamson presented global data on behalf of ICMART.

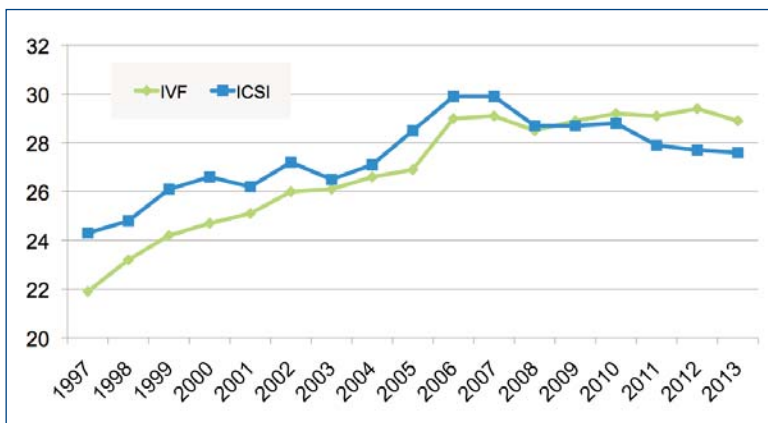
was able to collect data on 4659 cycles with a pregnancy rate per aspiration of around 30%.

from the editor of *Human Reproduction* denouncing the trend. 'The majority of the patients who will get pregnant with ICSI will also do so with IVF,' wrote Hans Evers. '[Although] intending to improve their patients' pregnancy probability by preventing fertilization failure, well-meaning doctors actually decrease their chances.'

According to cycles reported to the EIM Consortium, France remained Europe's most active ART country in 2013 (84,214 cycles), followed by Germany (76,422 cycles) and Spain (78,152). However, recent requirements for all Spanish clinics to refer their data to the Spanish Fertility Society's registry may well mean a huge increase in cycles reported from Spain and the elevation of Spain to Europe's most prolific ART country (see next page). However, for the time being Belgium and Denmark



ICSI's preferential use over IVF appears to have stabilised but not reduced.

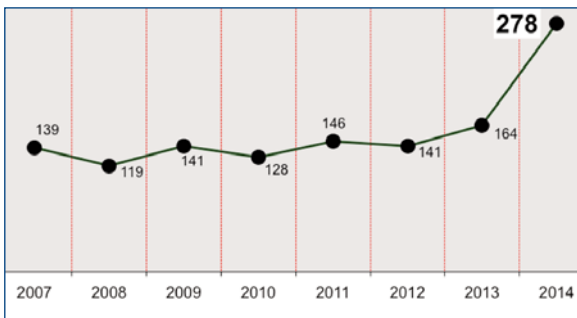


% pregnancy rates per aspiration with IVF and ICSI, the former more successful.

had the greatest provision of ART in 2013, with more than 2000 cycles of IVF/ICSI per million population. Leading countries such as France, Netherlands and UK were each below 1000 cycles per million. A health economics report in 2002 put the 'global need for ART' at 1500 cycles per million.

The highest ART pregnancy and delivery rates are now seen in egg donation, either fresh (49%) or as embryo transfers from cryopreserved oocytes (27%), while delivery rates from frozen embryo transfers are also rising. However, IUI delivery rates remain steady - at around 12% with donor sperm and 9% with partner sperm. Twin deliveries in IVF remained at around 17%, although some countries - notably Moldova, Serbia and Greece - continued to have very high rates of three or more embryo transfers.

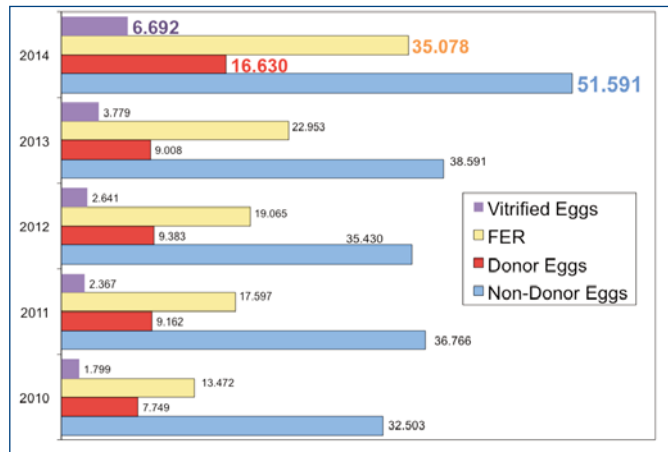
Spain now the most active European country in ART



A new requirement for all Spanish clinics to submit cycle data to a Ministry of Health ART registry run by the Spanish Fertility Society has seen a huge escalation in the number of clinics reporting data and in the number of cycles recorded in Spain.

Provisional EIM data presented in Helsinki for 2013 recorded just 78,152 cycles submitted from Spain (and 164 clinics). Now, in the latest figures for 2014 calculated by the Spanish Fertility Society for the national registry, the number of clinics reporting (ART and IUI) has risen to 278 and the number of ART cycles performed to a remarkable total of 116,688. The extent of the increases in reporting clinics and cycles prompted by the new registry requirement can be seen in the two graphs above.

The majority of these cycles (51,591) were IVF or ICSI with non-donor eggs, but more than 16,000 were for treatment with donor eggs. Frozen embryo transfers accounted for more than 35,000 cycles. The year-on-year data also show how treatment with vitrified oocytes is slowly increasing in Spain, in 2014 accounting for



Fernando Prados: 'Data aggregated centre by centre and externally validated'.

more than 6000 cycles and almost 6% of all treatments.

Madrid embryologist Fernando Prados, who runs the registry for the Spanish Fertility Society, told *Focus on Reproduction*: 'Our registry is now the official Spanish Ministry of Health registry. It is compulsory, with data aggregated centre by centre and externally validated to make sure the information provided is correct. We also require each centre to provide us with data on more than 50% of the evolution of their pregnancies.'

The newly assembled figures mean that Spain is now by far Europe's most prolific ART country, taking over from France (84,214 cycles) in the EIM data list. In global terms without China, Spain now ranks third, behind Japan (323,000 cycles in 2012) and USA (145,000 cycles) in ICMART data monitoring.

While the rate of triplet pregnancies has fallen markedly in recent years, twin pregnancy rates are now falling by only small annual amounts. The twin rate fell below 20% for the first time in 2009, but since then has steadied at around 17% - in fact there was a slight increase in 2013 over 2012.

While overall pregnancy rates remain fairly static, cumulative delivery rates - deliveries from fresh and frozen transfers per aspiration - are still calculated as the highest in the Nordic countries, with Finland and Sweden recording cumulative delivery rates of 36% in 2013 and with multiple rates of below 5%.



National representatives of the EIM Consortium pictured in Helsinki.

Fertility preservation in boys

... all approaches except sperm banking are 'experimental'

Total body irradiation and chemotherapy with alkylating agents pose greatest treatment threat to fertility

The question of fertility preservation in prepubertal and adolescent boys was addressed in a far-reaching best-practice review by a Task Force of ESHRE in 2015, and among its many conclusions was that the development of treatment strategies and consideration of ethical issues are best kept in the hands of multidisciplinary teams.¹ This multi-focus was clearly reflected in the organisation of a well attended Campus meeting in May in which five of ESHRE's SIGs set out an agenda for fertility preservation in young boys and adolescents; rarely has such wide collaboration been evident. The meeting took place in Münster, Germany, under the direction of Stefan Schlatt, a former Co-ordinator of ESHRE's SIG Andrology.

That ESHRE report of 2015 indicated that around half the centres contacted in 2012 were actively offering testis tissue cryobanking for the future fertility preservation of boys and adolescents, and the remaining centres were considering a tissue-based programme for boys facing oncological treatments. A year or two later, according to Sabine Kleisch from the Center of Reproductive Medicine and Andrology of the University Clinic Münster, the cryopreservation of immature testis tissue for spermatogonial stem cells remains experimental, and only the cryopreservation of spermatozoa in late pubertal boys and adults is 'accepted standard of care'; there are still no established options for prepubertal boys.

Yet the need, as many of her fellow speakers indicated, is great and getting greater. Claudia Rossig, head of paediatric oncology at the University Clinic Münster, reported an 80-90% cure rate for boys with cancer (the most common of which are leukaemia and Hodgkins lymphoma, with a cure rate of about 90%), although treatment is long and intense, with substantial toxicity and serious late effects - including secondary cancers, neuro-cognitive defects and osteonecrosis.

'We don't really know about fertility,' she said. 'Here, we follow the course of disease empirically at different time points, but believe we should offer fertility preservation to all.' The biggest treatment risks for



This well attended meeting was held in a minimally converted brewery in Münster, Germany, and organised by five of ESHRE's SIGs.

infertility are total body irradiation and intense chemotherapy with alkylating agents.

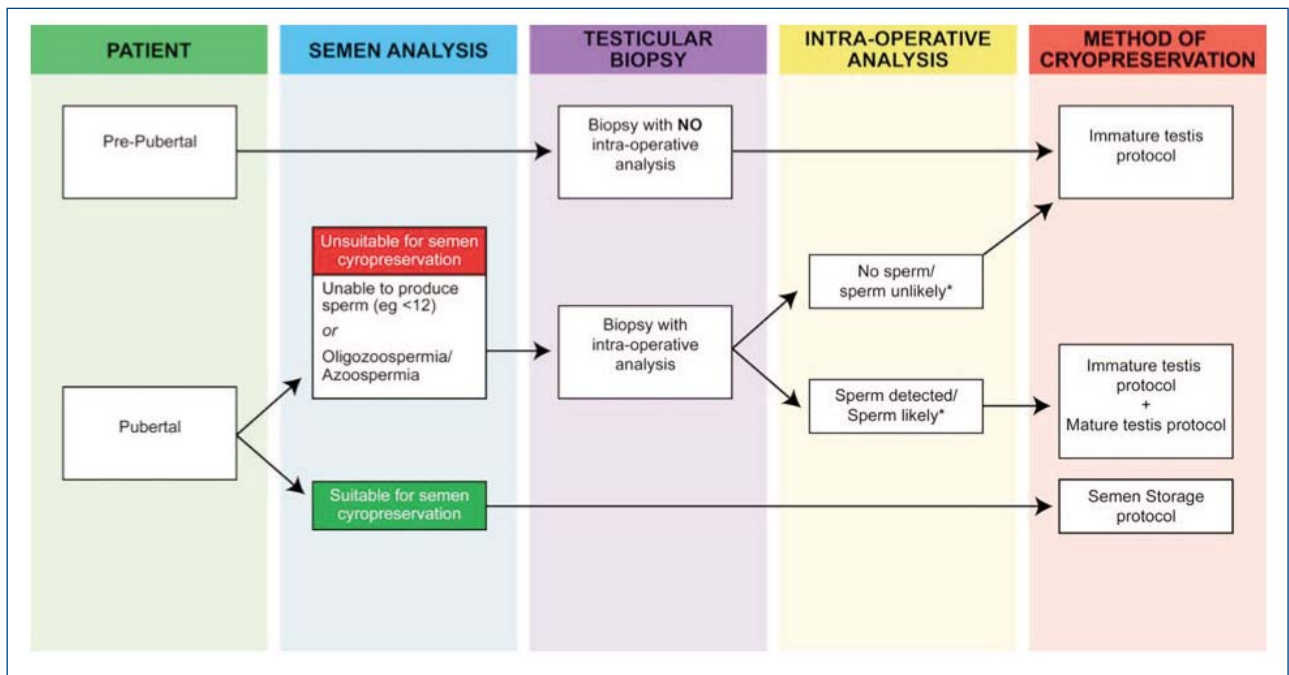
In prepubertal boys experimental approaches include the propagation and autotransplantation of spermatogonial stem cells, the autotransplantation of testicular tissue, and in vitro spermatogenesis. Such techniques, she said, are theoretically able to restore the patient's individual germ line, but efficiency and safety are not yet proved. The ESHRE Task Force proposed the treatment algorithm illustrated opposite

Rossig added that a project in Germany - Androprotect - founded in Münster had been licensed by the university ethics committee for fertility preservation in prepubertal boys and was expecting approval from the German authorities this year. The programme would involve three small biopsies from one testicle, one for cryopreservation, one for histological analysis, and one for research.

Annelise van Pelt from the Academic Medical Center of Amsterdam and a member of the ESHRE Task Force described successful experiments of SSC propagation in animal models, and some evidence of successful propagation in vitro in humans. However, concerns remain over cancer relapse after transplantation and the genetic stability of SSCs in vitro. However, after concluding that cultured human SSCs maintain their characteristics for migration after transplantation and can survive and

The Campus course was organised by Münster andrologist Stefan Schlatt





Algorithm for the cryopreservation of testicular tissue/sperm in prepubertal and adolescent patients at high risk of infertility.¹

proliferate in long term culture (with elimination of leukaemic cells and genetic stability), she described SSC transplantation as ‘a good future clinical option to restore fertility in infertile male childhood cancer survivors’.

However, this meeting was not just about the scientific and clinical challenges of preserving fertility in young boys. Christine Wyns, from the St Luc University Hospital in Brussels and another member of the Task Force, described numerous factors complicating indication and referral for treatment, including the lack of any sure predictive factor for infertility itself. There still remains a need for a good clinical pathway, she said. And she too emphasised the need for collaboration in development of a pathway which recognised information, decision and consent (with specific regard for children) in its application.

A survey at her own hospital of 348 boys (aged 0 to 18 years) diagnosed with cancer between 2005 and 2013 found that one-



Task Force member Christine Wyns: Still a need for an appropriate clinical pathway.

third had had no discussion of fertility preservation. And of those who had discussion around three in four (in both under and over 12s) had accepted the treatment. Such discussion, she added, should provide full and understandable information and place emphasis on the future as a positive decisional factor.

For Belgian bioethicist Veerle Provoost, there were two overriding decision considerations: that the decision to store tissue or gametes should be made freely and without pressure; and the decision to use stored samples should similarly be made freely and without pressure, regardless of decisions at the time of the fertility preservation.

Simon Brown
Focus on Reproduction

1. Picton HM, Wyns C, Anderson RA, et al. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. Hum Reprod 2015; 30: 2463-2475.



Stratis Kolibianakis, Deputy Chair of ESHRE's SIG Committee, believes that the patient's best interests are served by the evidence of properly conducted studies. A study will always provide a conclusion, but, he tells Focus on Reproduction, the important thing is to know if that conclusion is valid.

More facts, less opinion

'We have to be critical in evaluating research before accepting its conclusions'

FoR: Tell us a little about your working life in Greece.

SK: I have been working at the Unit of Human Reproduction of the 1st Department of Ob/Gyn at the Medical School of Aristotle University in Thessaloniki since 2006, but I also work in the private sector.

So IVF is not funded in Greece?

There is a little funding, which covers part of the cost of medications for ovarian stimulation. The state funds medication for up to four cycles, with up to 5000 IU gonadotrophins for each cycle.

And government regulation in IVF?

Legislation in ART was introduced back in

2005. Its main aim then was to reduce our multiple pregnancy rate by restrictions on the number of embryos transferred. But it has also regulated every aspect of assisted reproduction and is now considered one of the more liberal legislations in Europe.

You personally, Stratis, have been a big supporter of evidence-based medicine . . . meta-analysis, systematic reviews. How did that come about?

When I started working in assisted reproduction in early 2000, I felt there was something missing between clinical research and clinical practice. There seemed to be no solid answers to many important questions, despite the fact that research on many of

these subjects had been published. At the same time this research was not always of good quality, with unclear or contradictory messages. So the importance of synthesising the evidence was obvious. In theory it would allow a safer transition from clinical research to clinical practice - or would at least stimulate further research in those areas where it was needed.

So how would it work?

Evidence-based medicine needs to follow certain rules, a specific methodology, to reach a clear answer to the question asked - or admit that at a certain point there is no such answer or only an incomplete answer. Unfortunately, however, where there are no solid answers, it's not unusual for clinical practice to adopt strategies that are not proven. So it's of paramount importance for clinicians to understand the quality of evidence which supports their choices in clinical practice.

Are you saying that some results are more valid than others?

Yes. Knowing how to do the technical part of data synthesis will always give you a result, an answer to the question asked. The important thing, however, is whether that result is valid. Practically, this means we

need to be very careful in reading systematic reviews and meta-analyses. It's not just about conclusion. Every statistical test, every meta-analysis will lead to a conclusion, but this doesn't mean that the conclusion is valid. We need to be aware of how it was reached.

But because reproductive medicine is a relatively small discipline, doesn't that make any meta-analysis fairly risky?

Yes, that might be true. But to some extent this is also the case with any type of research in reproductive medicine, whether an RCT or just an expert consensus statement. We need to be aware of the limitations. A large RCT may try to measure an important difference between two techniques in live birth rates, say 5% or more. Yet such a study would need more than 2500 patients to accept or reject the hypothesis tested. This is clearly very difficult, and would only be feasible in a multicentre study - and they in turn have their own problems and limitations.

But doesn't meta-analysis aggregate the findings of these smaller RCTs?

Yes, this is true in most cases in reproductive medicine. So it's important to know the criteria for eligibility in a meta-analysis. In Helsinki I presented a meta-analysis of DHEA in poor responders. There have been six published meta-analyses on this topic in the past five years, which is more or less equal to the number of eligible RCTs - and they all have contradicting conclusions. The lesson is that we have to be critical in evaluating research before accepting its conclusions in everyday practice.

So who should decide about new treatments? You or the patient?

Patients must be presented with facts, not personal opinions or what is vaguely called 'experience'. Most of the time our patients don't have the knowledge to differentiate between a fact and a clinician's opinion.

If we can move on to ovarian stimulation, do you think there is a place for an individualised approach, enough evidence?

Well, it depends what you mean by individualisation. In the early 2000s we used a relatively wide range of FSH dose - from 100 to 600 units for ovarian stimulation. So determination of the optimal dose was much more meaningful then - to prevent OHSS yet at the same time retrieve enough oocytes. Now, however, in realising that an FSH dose over 300 IU - or even lower - doesn't probably offer much in increasing ovarian response, determining an optimal dose has

become less important. This has happened alongside the introduction of GnRH antagonists and agonist triggering where an excessive ovarian response is expected or met. All this has been facilitated by ovarian reserve testing. So 'individualisation' is an evolving term. Yes, it is still a valid concept today, but it is a less demanding task than it was in the past.

Are you saying we can respond to a predicted excessive response, but really there's nothing we can do about poor response, at least with FSH dose.

We all recognise that the aim of ovarian stimulation is to salvage a few oocytes from their destiny, atresia. If the number of oocytes is great, the patient is considered at high risk of OHSS. But actually these patients are not at risk, even with an excessive ovarian response, provided that we apply the recommended protocols. On the other hand, it is not feasible to create oocytes in the case of poor response. All published interventions for increasing ovarian response are either ineffective or of debatable clinical significance.

So nothing we can do about poor response?

Well, based on a limited number of published RCTs, one field which requires more research is the use of androgens, either in the form of testosterone pretreatment or DHEA. However, so far the overall increase in the number of oocytes appears to be small.

Vitamins, antioxidants . . . is there no evidence in favour of any strategy?

I am afraid the answer is fairly negative. Growth hormone is an expensive intervention but has not been shown to increase ovarian response, although it has been associated with an increase in live birth rates. However, the existing evidence is very unstable, and not supported by data recently presented in Helsinki. Similarly, the addition of recombinant LH was not effective in another big RCT in Helsinki.

I gather that ESHRE is planning a guideline on ovarian stimulation?

Yes, it's an initiative of the SIG Reproductive Endocrinology, which is one of the Society's largest SIGs. So we'll assess the available evidence and provide guidance endorsed by ESHRE. The kick-off meeting took place in Helsinki and the relevant questions were defined. We hope to have the guideline ready by the end of 2017. Such guidelines are missing at present and I hope they'll give authority to our conclusions. Hopefully, clinical decisions in the future will be less.

PROUST QUESTIONNAIRE*

● **What trait do you most dislike in yourself?**

Most of the time I quite like myself

● **And in others?**

I tend to focus on things I like

● **What's your greatest extravagance?**

Extra time with my family

● **Which phrases do you most overuse?**

'It appears that . . .'; 'I am not convinced that . . .'

● **Your greatest achievement?**

There's still plenty of time for that

● **If not Greece, where would you most like to live?**

I guess the question for a Greek should be, could you live happily outside Greece?

● **Where did you spend your latest vacation?**

Crete

● **What is your favorite pastime?**

I am very happy as a reproductive endocrinologist

● **Your most treasured possession?**

My family - if you can call them a possession

● **And your favourite writers?**

Nikos Karantzakis, Milan Kundera

● **The last film you saw?**

Spectre

● **Your preferred last supper?**

I could never be so organised

● **Your greatest regret?**

I tend not to have regrets if plans were well thought out, whatever the final outcome

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



In the last issue of *Focus on Reproduction*, Christophe Blockeel reviewed the evidence for a freeze-all embryo protocol in IVF. Now, French embryologists Debbie Montjean and Pierre Boyer propose an alternative - oocyte cryopreservation which, they say, has distinct advantages over embryo freezing.



Freeze-all oocytes

An alternative to freeze-all embryos

The negative impact of controlled ovarian stimulation on endometrial receptivity and implantation prompted the development of a freeze-all protocol for embryo transfer. This approach comprises the elective cryopreservation of embryos obtained after oocyte pick-up for delayed transfer in a subsequent natural cycle or during a cycle regulated with hormone replacement. The aim of the freeze-all strategy is to create a physiological environment and primed endometrium suitable for embryo transfer.

Although fresh embryo transfer is still the standard in most IVF centres, freeze-all is gaining interest and popularity and is now being used in a wider range of situations. In the last issue of *Focus on Reproduction*, Christophe Blockeel reviewed the advantages and drawbacks of freeze-all policy - both for the prevention of complications of OHSS and in everyday routine practice. However, an answer to one major question was missing: why should we choose to cryopreserve embryos rather than oocytes? We summarise our views on oocyte freezing which, to us, present many advantages over embryo freezing.

1. Embryo freezing: ethical considerations

Embryo freezing raises moral questions in couples

faced with a choice. Couples might express confusion about 'freezing babies and question the impact of cryopreservation on their baby's health.¹ Next, the prevention of OHSS using embryo freezing in a segmentation approach implies that all collected oocytes, no matter how many, are fertilised. This means unfavourable technical conditions (a large number of oocytes to microinject) and surplus embryos, many of which will be discarded. Indeed, the Agence de la Biomédecine has estimated that up to 50% of all embryos created during IVF are never transferred or frozen: they are simply destroyed.

Taken together, these two features of a freeze-all embryo policy add up to confusion for couples and more uncertainty in the ongoing ethical debates about embryo freezing. It's partly for these reasons that embryo freezing has been variously regulated by governments throughout the world, ranging from a request to IVF centres to limit the number of cryopreserved embryos to a complete ban on the procedure. A freeze-all policy for the prevention of OHSS involving large numbers of embryo is inconsistent with the political will to limit our stock of frozen embryos. Oocyte vitrification, on the other hand, does not generate the same ethical debate, appears a satisfactory alternative to embryo freezing.

2. Embryo freezing: lowering the odds?

A conventional freeze-all approach involves elective embryo vitrification either at day 3 or day 5. However, studies of this strategy do ignore the percentage of embryos which are not eligible for freezing and are eventually discarded. A recent study has shown that, among poor morphology embryos commonly discarded at day 3, some may have evolved favourably at day 5 and, when transferred (after freezing) may increase cumulative delivery rate by 4%.² Similarly, our results show satisfactory success rates from day 5 embryos displaying a slight morphokinetic delay when assessed by strict criteria for embryo grading (see table opposite). These embryos are usually not selected for fresh transfer or for freezing and are thus discarded.

In the context of OHSS, a large embryo cohort is usually available, suggesting that stringent selection of embryos for freezing is necessary in order to avoid extensive stocks of cryopreserved embryos. Based on these observations, a freeze-all policy constitutes a poor outlook for lower morphology embryos (with a lower but superior to zero chance of implantation) and a likelihood of being discarded.

Oocyte vitrification followed by gradual oocyte thawing leads to the creation of smaller embryo cohorts, fewer surplus embryos, and fewer repeat embryo transfers - including the transfer of those which would otherwise be discarded. A proposal to vitrify oocytes in a freeze-all policy thus appears an appropriate strategy worthy of full evaluation.³

3. Embryo vs oocyte freezing: Equivalent results

Recently published data showed that cryopreserving oocytes or embryos provides similar results in terms of live birth rate.⁵ Indeed, both frozen/thawed embryos and embryos produced from vitrified/warmed oocytes are transferred in identical conditions: during a natural cycle or during a cycle with hormone replacement. We have shown in sibling oocytes that vitrification does not affect the morphokinetics of embryos.⁶

Overall, data demonstrating the safety and reliability of oocyte vitrification indicate that oocytes can be efficiently frozen instead of embryos in a freeze-all approach with no impact on success rates.



Pierre Boyer and
Debbie Mountjean:
'Undeniable'
advantages from
oocyte freezing in
the prevention of
OHSS.

Success rates from embryos of three morphological categories

	Embryo category			P value
	1	2	3	
N	257	233	53	NA
Transfer rate post thaw (%)	88	88	93	0.55
Implantation rate (%)	16	14	26	0.21
Clinical pregnancy rate/ET (%)	16	16	24	0.17
Miscarriage rate (%)	9.1	16	6.3	0.12

Outcome from embryos belonging to three morphology categories. Category 1, compacted morula or blastocyst with early forming blastocœle (n=257), Category 2, early blastocyst with clear blastocœle occupying less than half the embryonic volume (n=233) and Category 3, late blastocysts displaying a blastocœle occupying more than half the volume of the embryo and/or increased size (n=53).⁴

4. Embryo freezing and adverse perinatal outcome

The health of children born after frozen embryo transfer is still the matter of debate and the object of cautious survey. Danish data show an increased incidence of macrosomia in children born after frozen embryo transfer. Freezing oocytes rather than embryos thus not only enables repeated fresh (non-frozen) embryo transfers, but may also avoid the perinatal risks so far associated with FET. Indeed, to date no increase in birth weight has been observed in children born after donor or autologous oocyte vitrification.^{7,8}

Based on these results, cryopreserving oocytes for the prevention of OHSS appears a reasonable alternative to embryo freezing, at least in terms of perinatal outcome. However, further investigations in a large cohort of children are still required to draw a definitive conclusion regarding perinatal outcome and the health of children.

5. Oocyte freezing for the prevention of OHSS

Data on oocyte freezing for the prevention of OHSS are scarce and the disadvantages of such a strategy have not yet been clearly identified. We have put our finger on two potential flaws, namely, cost and efficiency. A study evaluating and comparing the human and material cost of both oocyte and embryo freezing strategies is required to answer these questions; an embryo freeze-all strategy has been assessed for its impact on resources, but oocyte freeze-all remains to be investigated.

Although it is accepted that oocyte quality is diminished when high numbers of oocytes are retrieved, it is not known how OHSS might additionally affect embryo quality. Interestingly, our own preliminary data from freeze-all oocytes in cases where immediate embryo transfer was contraindicated are encouraging and show satisfactory outcomes in terms of oocyte survival, fertilisation, and pregnancy.

Continued on page 29

The tale of the rapid introduction into clinical IVF of endometrial injury (or, euphemistically, 'scratch') is a salutary one. It tells us much about the challenges and frustrations felt by clinicians and patients alike when faced with implantation failure after IVF. It reflects the lack of other effective clinical interventions, and it reveals many of the drivers for implementing innovative practices into modern fertility medicine. The frustrations are real and well founded. Despite spectacular advances in embryology, ongoing pregnancy rates after IVF appear to have plateau'd, and in recent years the endometrium has increasingly become the focus of efforts to identify new ways to improve outcomes.

Up to now, however, the story has not been very encouraging. Complex and expensive medical therapies, based largely on the two premises that thrombophilia and disrupted immune responses to the presence of an embryo can be successfully modulated, have failed to deliver any real benefits. New insights into human endometrial biology and embryo-endometrial signalling offer promising new avenues for research, but sometimes serendipity is as important to advancing care as fundamental research. And there begins the story of the endometrial scratch.

At the end of the last millennium an Israeli group was investigating endometrial protein markers in 12 women who had previously suffered failed IVF treatment.¹ However, observing that 11 of these women who had had endometrial biopsy went on to conceive in the following cycle, the group moved quickly to investigate the possible therapeutic benefit of endometrial trauma, and in 2003 published the first case series, reporting an apparent doubling of IVF pregnancy rates in those having a biopsy in the previous cycle.² So here was a simple clinical intervention, already within the skills and practice of trained clinicians, that promised to revolutionise IVF outcomes.

Initial clinical reports were very promising, and, with a frustrating lack of therapeutic options for improving



Endometrial scratch

A tale with a happy ending?

A recent survey found that 92% of physicians questioned support the concept of endometrial 'injury' before IVF in women with recurrent implantation failure. Ying Cheong and Nick Macklon explore the science behind the technique and ask if the magic wand will yield a fairy story.

endometrial receptivity and patient-driven pressure to 'try something', the scratch seemed to offer clinicians a magic wand. No wonder it was rapidly adopted. In a recent survey, 83% of clinicians were found to recommend a scratch prior to IVF and 92% to endorse the technique in women with recurrent implantation failure.³ Yet we still await confirmation of its efficacy from large randomised studies.

So is the tale of the endometrial scratch a fairy story destined to disappoint? Or will it after all have a happy ending?

Does it work?

The endometrial scratch distinguishes itself from other receptivity interventions in at least two ways. Firstly, it has been a wholly empirical intervention searching for a biological explanation for its efficacy. Even the more creative branches of reproductive immunotherapy can refer to some degree of mechanistic plausibility to justify their interventions. Secondly, it is counter-intuitive and even anti-Hippocratic. 'First do no harm' is exactly the opposite of what the scratch requires. So, if we are to justify

'harming' the patient, we need to be well assured that it works, and preferably that we know why.

Since Barash et al described in 2003 the 'doubling' of pregnancy rate in their retrospective case-control study, there have been 15 randomised controlled trials and five meta-analyses evaluating the impact of endometrial scratching on reproduction. The conclusions from these studies are conflicting. While there is support for the beneficial effects of the procedure, other studies and authors have suggested the opposite.^{4,5,6} This has led to a lively controversy played out in our journals and conference halls, particularly as personal experience conflicts with data from more recent well designed but conflicting studies.^{7,8}

As clinicians, we are frequently challenged to devise sound treatment strategies in the face of inconsistent findings from studies and systematic reviews, and often the patients will try to guide us with information from the lay press. This is reflected in the ongoing uncertainty over the efficacy of acupuncture to improve pregnancy rates after IVF.⁹ Such non-consensus may often arise because the reviewers differed in their choice of methods, their assessment of the quality of studies for inclusion, and their summing-up evidence.

Analysis of the studies included in the major meta-analyses of endometrial scratch shows them to be heterogeneous in design - with pooled studies of participants having first-time IVF, or with one or more failures or 'recurrent' implantation failure, itself a condition characterised by various causes and definitions.

The studies included in these reviews also vary considerably in the timing of the scratch. Some involved intervention in the preceding month, some within the month of ovarian stimulation, some during oocyte retrieval and others during hysteroscopy. The method of scratch also varies, from not being specified to more than one scratch; from using the Pipelle to the Novak curette. Furthermore, the control groups were non-standardised. For example, some used a sham-type intervention, while others continued with routine

care, simply omitting a scratch procedure.

Most studies, therefore, while concluding that there is a clinical benefit of endometrial scratch in improving pregnancy rates, were judged to suffer from a high risk of bias. As a result, almost all the authors of the reviews have concluded that more evidence is required to make their conclusions robust. Conversely, some reviewers who adopted a strategy which limits heterogeneity within the meta-analysis concluded that there is no clinical benefit of endometrial scratch, or that it is possibly only useful in a subgroup of women with recurrent implantation failure.^{7,8}

The interpretation of conflicting results to help inform and implement clinical practice requires a common sense approach. The field is still uncertain, and this equipoise provides the opportunity to carry out definitive, well powered randomised controlled studies. It is reassuring to report that these are now under way.

How does it work?

From the molecular perspective, the over-arching belief is that endometrial scratching induces an inflammatory response which encourages implantation. Pro-inflammatory factors are implicated in eliciting a receptive endometrial phenotype and the increase of pro-inflammatory cytokines, chemokines, and immune cells after endometrial scratching has been observed.¹⁰ Our own group has reported increased implantation rates when a pro-inflammatory cytokine profile is identified in endometrial secretions aspirated immediately prior to embryo transfer.¹¹ However, the ability for endometrial scratch to simply invoke inflammation and thereby result in better implantation could be deemed overly simplistic and unconvincing.

As mentioned earlier, extensive research in reproductive immunology has not yet yielded any significant therapeutic leads for improved implantation rates. The accurate prediction of endometrial receptivity and prediction is an ongoing challenge in the field of reproductive medicine, and the most promising strategies are only on the cusp of clinical validation.¹² An endometrial biopsy is a prerequisite part of 'receptivity testing' using gene array tests but surprisingly this has not been associated with better pregnancy outcomes in this cohort of patients.¹³

In recent years the importance of endometrial decidualisation as a determinant of successful implantation has become increasingly apparent.¹⁴ It has been hypothesised that endometrial injury may induce or enhance endometrial decidualisation, and thus could assist implantation. Those seeking experimental evidence to support this concept can point to the induction of decidualisation by embryo implantation and the efficacy



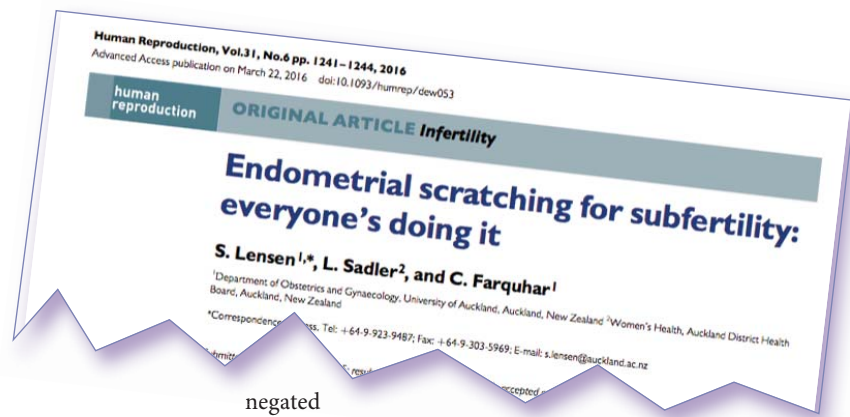
Ying Cheong and Nick Macklon: 'Robust trials to possibly undo the introduction of an "unproven" procedure rather than vice versa.'

of mechanical and irritant stimuli in inducing decidualisation in laboratory animals.

Mechanistically, however, there are distinct differences in the way endometrial stromal cells differentiate between commonly employed animal models and higher primates. In the latter group, which includes humans and apes, decidualisation is not triggered by the implanting embryos but is hormonally regulated. In humans, decidualisation occurs in every ovulatory cycle irrespective of conception or implantation. So, while a mechanical stimulus (taken here to be synonymous to a 'scratch') has long been known to provoke rapid growth of decidual cells in guinea pigs and rodents (and there may be an element of evolutionary conservation of this mechanism in humans), the story is likely to be more complex. For instance, the clinical effect relies on decidualisation being modulated in the cycle following the intervention rather than in the scratch itself.

Despite this rather unpromising landscape, recent work by the Brosens group points to a possible plausible mechanism by which endometrial injury might increase stem cell numbers in the endometrium, and encourage the removal of excessive senescent cells by stimulating NK cell activity.¹⁵

In addition, clinical evidence for the propensity of implantation to occur in uterine fibrosis or a scar niche, resulting in the ongoing challenges in the management of 'scar' pregnancies, would support an element of decidual enhancement distant in time to the episode of trauma. Indeed, in humans, the process of menstruation can be viewed as a hormonally orchestrated monthly 'injury' necessary for recruitment of the endometrial stem cell system and subsequent implantation.¹⁶ This development of an endogenous control through the hypothalamic pituitary axis for menstruation may have evolutionarily



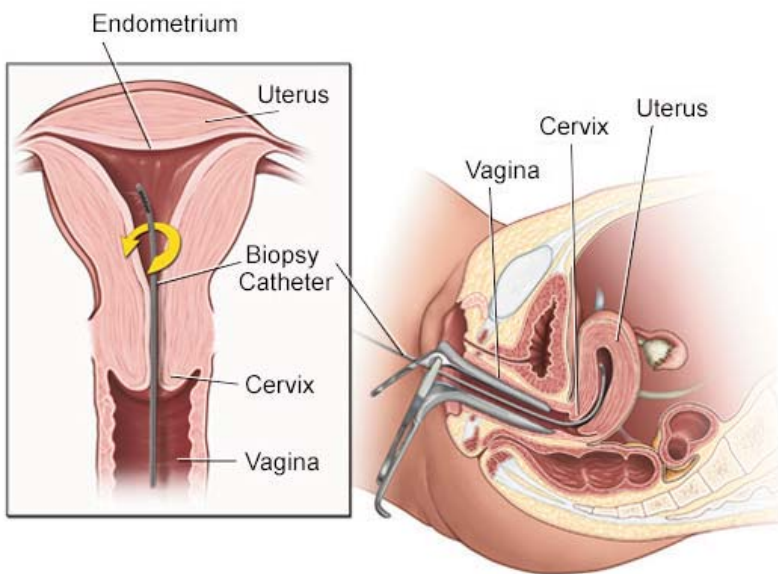
negated the need for a 'trigger factor' (presence of embryo or mechanistic injury) for decidualisation.

From an evolutionary perspective, the notion of reproductive tract injury and its association with conception is a familiar concept. Lost in human lineage due to the deletion of an otherwise highly conserved sequence, but preserved in many animals (eg, chimpanzees, cats and mice), is the presence of penile spines. These appendages are crucial for effective mating, probably through the generation of reproductive tract injury, induction of spontaneous ovulation, or via the removal of 'mating plugs' that may prohibit effective fertilisation. Hence, the proposed mechanistic hypotheses around how the scratch works should be expanded to include the processes involved in conducting a scratch rather than focusing on the endometrium alone. However, development secondary to evolution need not necessarily always confer reproductive advantages, and it could be that in a selected population a mechanical stimulus by way of endometrial injury reconstitutes a missing evolutionary link. In seeking mechanistic explanations as to how the scratch works, it is therefore important to adopt a systems approach in conjunction with investigating local factors.

Conclusion

Primum non nocere dictates that clinicians be honest with patients. At this juncture, endometrial scratch remains an unproven procedure, without full knowledge of its potential implications (or risks). This should be clearly explained to patients to ensure they are fully informed and consented for treatment. Last but not least, clinicians should audit outcomes of the scratch procedure when used in clinical practice, as this could inform us of the 'unintended' but practical advantages of the procedure.

To scratch or not to scratch, that is still the question. There are no quick answers, other than to pursue good-quality clinical trials. These are happily ongoing and we find ourselves in the scientifically unorthodox, yet not uncommon, situation of engaging in robust trials to possibly undo the introduction of an 'unproven' procedure rather than vice versa. As Lensen et al tell us, 'everyone is doing it' and it is now being offered well beyond the initial indication to women having IUI and even trying to conceive spontaneously.³ Will we look back at this phenomenon as a well meaning but misguided fairy



Endometrial biopsy procedure.

tale or will the story of the endometrial scratch have a happy ending? The answer will become apparent 'all in good time' (Horace, 65-8 B.C).

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Freeze-all oocytes

Continued from page 25

7. Task force needed

Freezing oocytes instead of embryos for the prevention of OHSS presents undeniable advantages. However, this strategy still needs careful evaluation to rule out potential disadvantages before extending its application to other situations, such as increased progesterone level on the day of triggering. Therefore, prospective studies are required to assess the efficiency this approach.

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Use of PGS continues to rise ‘despite the debates’

- New data submission system will be prospective and based on analysis, not cycles
- Data presented in Helsinki from three-year ‘interim’ period 2013-2015

Data collected and presented by the PGD Consortium in Helsinki was derived from a three-year interim period between cycle-based retrospective data (as collected up to 2012) and the newly introduced prospective analysis-based data to be collected from 2016. The two data systems, said PGD Consortium chair Edith Coonen, pictured right, were ‘incompatible’ but the figures, presented in Helsinki as a three-year summary snapshot, were no less interesting in this very fast-moving field.



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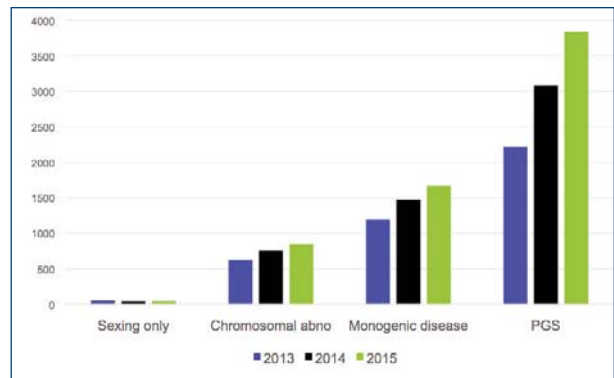
This summary data of 2013-2015 was not ‘definitive’ said Coonen, and was derived from just 50 participating centres representing only 75% of the Consortium’s full membership. Efforts over the next few months, she added, would be to encourage missing centres to complete their data returns, though much, she feared, might be lost to follow-up.

The most striking trend over these brief three years was - as expected - in PGS, which despite a paucity of robust data continued its irrepressible increase in application. As the graphs show, uptake approached 4000 cycles in 2015, considerably more than in 2013 - and that from just a limited number of centres returning data. The larger PGS chart shows how usage stalled in 2006 and even fell in 2013, only to revive over the next two years, presumably with the introduction of more efficient complete chromosome screening technologies. ‘Despite the debates,’ said Coonen, ‘the use of PGS just keeps on rising.’

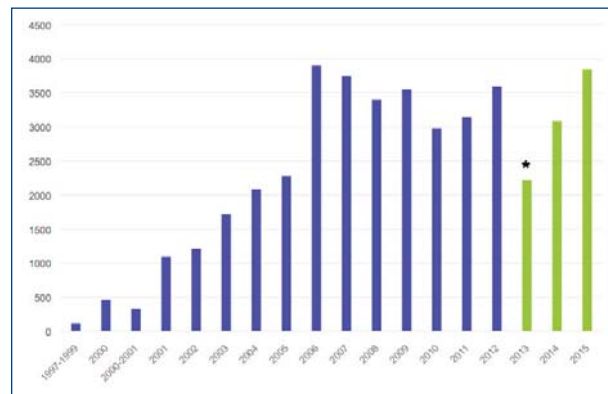
The data presented also showed a steep decline in FISH and an upturn in array CGH over the three-year period, with a decline in cleavage stage biopsy in favour of blastocyst stage. However, in PGD for monogenic disease PCR with cleavage-stage biopsy was used in more than 80% of cycles throughout the three years.

Now, the Consortium will look forward to a new data collection system which, said Coonen, will be prospective, accurate, reliable and effective. Presently, she said, there are 126 centre members of the Consortium, the majority (89) in Europe (and just seven in the USA). Full completion of the data from all members will next year provide the first detailed picture of what’s really happening in this progressive field.

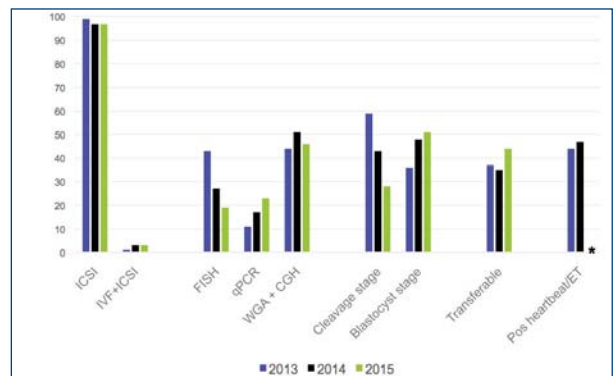
All PGD indications increased in application over the three-year interim period.



After stalling in 2012, the uptake of PGS increased to its 2006 level, with almost 4000 cycles reported in 2015.



How PGS technologies and techniques changed between 2012 and 2015.



Atlas of Embryology now online and interactive



European Society of Human Reproduction and Embryology

ATLAS OF HUMAN EMBRYOLOGY:

from Oocytes to Preimplantation Embryos

ESHRE's *Atlas of Human Embryology* in PDF format has been a reference for embryologists for many years. So we are delighted and proud to announce that a web version of the *Atlas* was launched at the Annual Meeting in Helsinki (<http://atlas.eshre.eu>). This is freely and easily accessible from laptops, desktops, tablets and smartphones.

There is no new content in the online edition, but the web format does represent the starting-point of a new development phase. Thanks to the versatility provided by its web design, the *Atlas* is now amenable to future and continued expansion. Time-lapse microscopy, cryopreservation, micromanipulation, ultrastructure and cytoskeleton are possible new sections, but the *Atlas* has the potential to become a continuously evolving entity.

As ever, our pre-congress course in Helsinki was well attended. Our theme was **The multiple choices (sides) of IVF**, the title reflecting the multiplicity of options, and sometimes dilemmas, that embryologists face in the IVF lab to achieve the best possible treatment. Arne Sunde discussed the use of sequential and single-step culture media while giving an overview to a much larger question - that irrespective of the culture strategy, embryologists have no access to information on the composition of their media. Sunde concluded that a difference in performance between sequential and single-step media does not seem to exist, but thought the whole question of culture media deserved 'more serious' attention.

The theme of David Edgar was the pros and cons of cryopreserving oocytes or embryos. Clearly, these approaches have different significance for fulfilling different needs of individual cases. However, very

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convincingly he demonstrated that, with optimal methodology, oocyte and embryo (cleavage stage and blastocyst) cryopreservation can achieve comparable results. He also argued that 'there is no longer justification for creating embryos merely to ensure successful cryopreservation'. In the final talk,

Aisling Ahlstrom presented her view on

the dilemma of using morphology or genetic testing for embryo selection, addressed by analysing safety, clinical evidence, cost-effectiveness and ethical concerns. She closed her talk with the crucial point of why PGS is growing.

Business matters

Helsinki marked an important change in the co-ordination of the SIG Embryology. Carlos Plancha completed his term as Basic Science Officer, in which role he has been a driving force for our group, and indeed for ESHRE, for many years. On behalf of the SIG Embryology, I wish to express our thanks to him. However, the arrival of Roger Sturmey, the newly appointed science advisor, is exceptionally good news. Roger is currently Senior Lecturer of Reproductive Medicine at the Hull York Medical School, and above all an extremely talented scientist with a keen interest in oocyte and embryo metabolism.

Next year (11-13 May) we will host a Campus meeting in Milan on **The fourth dimension: the time factor in human IVF**. Time is a crucial dimension in all processes, including embryo development, and Milan, the most dynamic and fast-changing city in Italy, is the ideal place to host this event.

Giovanni Coticchio
 Co-ordinator SIG Embryology

Five events planned for a busy 2017

Development group under way for next endometriosis guideline

Annual Meeting Helsinki

Our pregress course in Helsinki, titled **Endometriosis – getting research from bench to bedside**, was a huge success attended by over 100 delegates. The course proved an excellent start to the main meeting and included an overview of current treatment approaches for endometriosis, a review of current laboratory techniques used to identify new treatments, and a review of specific therapeutics currently in clinical research. The speakers were all leaders in their field – and included both clinical and basic science researchers, as well as those from the pharmaceutical industry. We heard about the EPHeC initiative that has led to harmonised biobanking protocols, molecular mechanisms which underlie pain and offer new openings in drug discovery, and mouse models that mimic the human endometriosis phenotype that are now being used to test new treatments. The course closed with an extremely thought-provoking and informative lecture on the challenges of moving endometriosis research from the laboratory into the clinical setting.

Highlights from the main scientific programme, included presentations which described the complex network between the brain and endometriosis in pain signalling and pain amplification, and further explored the association of endometriosis with mental distress and anxiety. During the oral communication

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Krina Zondervan (UK), Basic Science Officer
Lone Hummelshoj (UK), International Officer



session on endometriosis, we learnt about the implementation of integrated genome-wide approaches (DNA methylation and mRNA expression) and their implications in endometriosis research; about novel insights into the role of the estrogen receptor proteins and variants; and the regulation of angiogenesis and hypoxia during menstruation. Our session on endometrial receptivity gave an

interesting overview of classical receptivity markers such as 'endometrial thickness', promising new receptivity tests, and novel molecular mechanisms underlying the decidualisation process. The main programme also offered further stimulating sessions on the use of ART for women suffering from endometriosis and their surgical management (laparoscopy vs. robotic surgery), plus several exciting posters. For extra information you can also read the congress report of one of the 'ESHRE 5', Nilufer Rahmioglu from the University of Oxford, available at <http://endometriosis.ca/news/article/endometriosis-highlights-from-eshre2016>.

ESHRE Endometriosis guidelines

In April Christian Becker was appointed the new chair of the guideline development group (CDG) for endometriosis. The members of the CDG remain the same, except for Carla Tomassetti who replaces Thomas D'Hooghe. The first literature searches began in May and the aim is to have the guideline published by April 2018.

Research priorities in endometriosis

Research recommendations from a global consortium of investigators, agreed at the 3rd International Consensus Workshop on Research Priorities in Endometriosis held in São Paulo in 2014 following the 12th World Congress on Endometriosis, have now been published. Fifty-three new research recommendations were made at the meeting, which was attended by many ESHRE members, which in addition to the 13 updated recommendations have resulted in a total of 66 new recommendations for research.¹ New areas included in the recommendations include infertility, patient stratification, and research in emerging nations, in addition to an increased focus on translational research. See: www.endometriosis.ca for more information.

The EndoKey project

Following the publication of the ESHRE guideline on



Members of the SIGEED team, Andrea Romano, Andrew Horne and Carla Tomassetti, outside the Congress Centre in Helsinki.

the management of women with endometriosis, ESHRE noted a need for insight into the application of the guideline in daily practice (ie, actual clinical care) and the potential barriers to guideline adherence. The EndoKey group has now taken the first steps in the development of quality indicators by starting a process of selecting key recommendations on which to focus. They published the first stage of this work in April in *Human Reproduction*.²

Future activities: mark your agenda

We have a full and exciting programme of events for 2017. From 27-28 January 2017, we are holding a Campus meeting on the **Effects of ART and endometriosis on pregnancy outcome** in Sofia, Bulgaria. This is a joint venture with the SIG Early Pregnancy.

On 17 May 2017 we are running a joint ESHRE/ASRM pre-congress course at the 13th World Congress on Endometriosis in Vancouver, Canada. This is a half-day course titled **Unravelling the mystery of infertility and endometriosis**. Abstract submission for the World Congress - the largest world event in endometriosis - is open until 9 October 2016.

Then, on 2 July 2017, we will be holding our own annual pre-congress course prior to the ESHRE meeting in Geneva on **Endometrial receptivity**.

From 18-19 September 2017 we are running a Campus workshop on **Methodological approaches for investigating endometrial function and endometriosis** in Edinburgh, another joint venture

with the ASRM. The course aims to update the methodological aspects of biobanking (to facilitate large-scale, cross-centre, epidemiologically robust, biomarker and treatment target discovery research in endometriosis), genomics (micro-RNAs and their role in the aetiology of endometriosis, genome wide association studies and next generation sequencing), cell biology (cell populations regulating endometrial function with a putative role in endometriosis), intracrinology (role of the steroid microenvironment), epidemiology, clinical trials (the importance of trial design), biomarkers (serum, urinary, imaging) and animal models (murine and primate).

To close the year, we are running a 'hands on' Campus workshop on **Ultrasound in ART and early pregnancy: a blended training approach** on 16-17 November 2017 in Cardiff, a joint course with the SIGs Early Pregnancy and SIG Safety and Quality in ART.

Andrew Horne
Co-ordinator SIG Endometriosis and
Endometrial Disorders

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SIG PSYCHOLOGY & COUNSELLING

Proposals for certification in counselling now under consideration

Our pre-congress course in Helsinki, on complex cases in infertility counselling, proved exciting for clinicians and researchers. We learned of the ethical and psychosocial consequences of posthumous conception, findings during the fertility work-up, and also medical and psychosocial aspects of fertility preservation for transmen and donor conceived children. We also reviewed the potential of fertility and sexual counselling for infertile couples.

Certification

We are now developing a proposal for certification in skills in counselling in third-party reproduction.

Guidelines

The pocket and patient versions of our guidelines on *Routine psychosocial care in infertility and medically assisted reproduction* are now available on the ESHRE website. Patients can now know what psychological

STEERING COMMITTEE

Sofia Gameiro (GB), Co-ordinator
Mariana Martins (PT), Deputy
Giuliana Baccino (ES), Deputy
Juliana Pedro (PT), Junior Deputy
Uschi Van den Broeck (BE), Past Co-ordinator



support they should receive at their fertility clinics.

Future activities

With professional and researcher feedback, we are preparing new courses on information and communication at fertility clinics and on third-party reproduction. A

course on transgenderism and reproduction has been proposed in collaboration with the SIGs SQART, Ethics & Law, and Socio-cultural aspects of infertility and we hope to announce the venue and date soon. Our pre-congress course in Geneva will be on fertility awareness and its role in preventing infertility.

And please don't forget our next Campus meeting **Basic training for infertility counselling: from theory to practice** which will be held in Vienna on 29-30 October 2016. We are waiting for you!

Juliana Pedro
Junior Deputy SIG Psychology & Counselling

Managing the 'difficult' IVF patient optimally

Precongress course Helsinki

Our precongress course in Helsinki, **Managing the difficult IVF patient: Facts and fiction** provided outstanding lecturers and intense audience interaction in a fully packed lecture room of 500 participants. The course aim was to critically review what is already available in literature and identify what is still needed to support the optimal management of a

consistent proportion of women undergoing IVF. Highlights included recurrent implantation failure, a challenging condition still under debate regarding definition, etiology and clinical significance. The possible solutions discussed (embryo selection and donation, endometrial scratch, uterine surgery, adjuvant medical treatments) stimulated a lively discussion. The endometrium - that is, the 'thin endometrium' - took the spotlight in the presentation by the SIG Co-ordinator Frank Broekmans, who emphasised that the ultrasonographic diagnostic criteria, pathophysiology and clinical relevance all still need to be elucidated.

The potential of surgery in the presence of

More than 500 took part in the SIG RE's precongress course in Helsinki on difficult IVF patients, the second year that so many have attended. Questions, right, for presenter Juan Garcia Velasco, who spoke on endometriomas.



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Frank J. Broekmans (NL), Co-ordinator
 Daniela Romualdi (IT), Deputy
 Peter Humaidan (DK), Deputy
 George Lainas (GB), Junior Deputy
 Efstratios Kolibianakis (GR), Past Co-ordinator
 Roy Homburg (GB), International Advisor
 Jenny Visser (NL), Basic Science Advisor



endometriosis and leiomyomas was also discussed. But, with well designed RCTs still lacking, it was accepted that the opportunity to treat these conditions surgically must be weighed on the balance of benefit and risk of uterine and especially ovarian damage.

Efstratios Kolibianakis reviewed the poor IVF outcomes in women over 40, the prognostic role of AMH measurement, and the debatable utility of preimplantation genetic screening.

A further challenging topic was the management of choice for infertile patients presenting with extremely high or extremely low BMI, as well as for women with more general health concerns, from thrombophilia to cystic fibrosis. Speakers agreed on the need for a multidisciplinary approach in considering how IVF treatment, pregnancy and the background condition may influence each other and in assessing risk for the patient and the offspring. The very active discussion at the end of these lectures focused on practical issues, as well as on the ethical challenge to be undertaken in such circumstances.

The programme ended with a valuable contribution from Jacky Boivin on the importance of psychological support to the infertile couple, both for compliance with treatment and for dealing with possible IVF failures and permanent childlessness.

Guidelines

We have now initiated a new ESHRE guideline project on ovarian stimulation for IVF/ICSI. After a few preparatory rounds of telephone conference, the guideline development group finally got together in Helsinki under the guidance of Nathalie Vermeulen and finalised the questions which will form the basis of the work in subgroups. Our plans are that the working groups complete their review and analysis in the summer of 2017, so that a first draft will be available for peer review early in 2018.

The first meeting of the development group for the collaborative guidelines on PCOS took place in Helsinki. They will be produced in partnership with the Australian Centre for Research Excellence (CRE) in PCOS in partnership with ESHRE and will be published as an update and expansion of the international guidelines for PCOS.

Unfortunately, our Campus meeting on reproductive ageing scheduled for Istanbul in December has had to be postponed again. In view of the political situation in Turkey, ESHRE's Central Office has taken the difficult decision to relocate the meeting, and updates will soon be announced on the ESHRE website.

*Daniela Romualdi
 Deputy SIG Reproductive Endocrinology*



Despite doubts, surgery contributes to the success of ART

The Campus workshop organised in Thessaloniki in May by the SIGs Reproductive Endocrinology and Reproductive Surgery was a beautiful example of how two distinct fields with different views can share ideas and opinions. The subject - on the benefits and limitations of surgery in reproductive medicine - raised topics which have prompted much debate.

PCOS

Developments in new agents for ovulation induction may come from aromatase inhibitors as a possible replacement for clomiphene citrate, as suggested in a recent Cochrane review.¹ Second-line treatment in clomiphene-resistant PCOS may find step-up low-dose FSH balanced by laparoscopic ovarian drilling, as the NICE guidelines have clearly indicated. Studies have made clear that the effects of LOD remain valuable for the long term, with low costs and low multiple rates. The uptake of LOD in daily practice may increase, as reduction of ovarian mass by any method will allow for improvement of cycle regularity and spontaneous fertility without affecting long-term issues such as the timing of menopause.²

Endometriosis

Fertility preservation could become a future tool in endometriosis, to increase the chance of reproduction in those with known endometriosis at a young age. This may be of value, as current fertility strategies do not seem very successful. There is a possibly lower performance in ART, and surgery may not offer a clear solution in the more severe stages, with the added risk of affecting ovarian reserve. In addition, surgery may have a high rate of disease recurrence and/or dysmenorrhea.

Options for fertility preservation include egg cell vitrification, embryo freezing, ovarian tissue banking and heterotopic transplantation.³ Currently, few studies have been presented in this field, possibly because IVF still provides first-line treatment for this group. It was reported that worldwide 39 women with endometriosis have had oocyte vitrification, and three women ovarian issue freezing and transplantation. Fertility preservation may be considered if the severity of disease may lead to extensive ovarian surgery, specifically when pain accompanies infertility.

Tubal surgery

Current evidence suggests that surgical removal of hydrosalpinges or terminally occluded fallopian tubes is indicated before IVF. Where there are surgical difficulties in removing the tube, proximal tubal (isthmic) occlusion may be an alternative, but both procedures will need laparoscopy. PTO may be not as effective as salpingectomy, so there is need for a robust trial. The DESH study clearly failed to find a beneficial role for hysteroscopic proximal occlusion by intratubal devices, with pregnancy rate half that at one year of classical salpingectomy.⁴

Fibroids

Submucosal myomas are long known for their effect on fertility, but the effect of myoma resection remains unproven, although

highly plausible. The effect of intramural myomas without distortion of the cavity is highly variable in studies. The putative effect could be exerted by reduced perfusion, increased uterine contractility or paracrine disturbances. Size and number of the myomas could also play a role, as could the proximity of the endometrium. Is it therefore advised to remove these fibroids? Will removal restore the supposedly reduced live birth rates? Comparative trials will be necessary to substantiate this.

Uterine cavity

For many years it has been thought that those small, unexpected uterine abnormalities such as septa, polyps, and adhesions affect the prospects of pregnancy in ART. The recent publication of the INSIGHT and TROPHY trials has demonstrated that this effect is not evident, as live birth rates in the hysteroscopy screen-and-treat arm were the same as in the direct IVF/ICSI arm. However, to the surprise of many, a recent study in ICSI patients came to an opposite conclusion.⁵ A small unsuspected abnormality was found and treated in 23% of the screened group, arriving at an ongoing pregnancy rate of 41%, significantly better than the controls (32%).

Surgery and ovarian reserve

It is clear that LOD in PCOS will damage ovarian reserve, but will prevent conditions such as ovarian failure. Ovarian surgery for endometriomas will frequently imply ovarian damage unless more atraumatic approaches are chosen. Salpingectomy prior to ART for the prevention of fluid leakage in hydrosalpinx has clearly demonstrated not to harm ovarian reserve.

Resumé

The conclusion of this well attended workshop (170 participants) was that reproductive surgery clearly contributes to the successes of ART. The challenges lie especially in the field of endometriosis and myoma surgery, where well designed RCTs are the only route for amplification of knowledge and wisdom.

Frank Broekmans

Co-ordinator SIG Reproductive Endocrinology

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Stem cell research continues its rapid advance

Looking back at Helsinki

Our well attended pregress course on **ART in 2020: the next frontier** was organised with the SIG Safety & Quality in ART and covered a variety of state of the art topics such as uterine transplantation, artificial gametes from stem cells and even e-health and social media.

During the main congress we heard from Jacob Hanna more about the naïve state of pluripotency in the human and how this affects derivation efficiency for gamete precursor cells, an ongoing hot topic in our field. Recent developments in full spermatogenesis in vitro, using a co-culture system with neonate testis and starting in a mouse model from naïve embryonic stem cells, represented a major step forward and the question now remains whether this process can be translated to the human in the future. A lot of research and safety testing still needs to be done over the next few years before we might consider any clinical application.

Myriam Hemberger also described the recent generation of induced multipotent trophoblast stem cells in the mouse as a model to study the early steps of placental development.

Finally, five young and ambitious junior researchers were able to present their data during the meeting's oral presentation stem cell session. This covered several interesting topics which included the development of genetic aberrations in human embryonic stem cells and induced pluripotent cells, the development of models of endometrial mesenchymal stem cells, and human trophoblast stem cells that could be useful to study infertility problems. This session showed that there is certainly a place for both fundamental and more clinical translational stem cell research within ESHRE.

Looking ahead

We are now looking forward to our Campus event on **Novel gamete manipulation technologies in ART: SEEM (safety, ethical, efficient, moral) OK?**, which will be held in Amsterdam on 22-23 September organised with the SIGs Safety & Quality in ART and Ethics & Law. We are very pleased to have as presenters so many distinguished experts on topics such as nuclear and mitochondrial transfer, stem cell derived gametes and genomic editing in the germ line by CRISPR. These hot topics are highly investigated right now as possible treatments for some rare genetic disorders or infertility. And although some of them are controversial or raise sensitive ethical concerns, it is necessary to at least discuss them with an emphasis on safety before clinical use. There are some places available, so please register!

Our pregress course in Geneva will focus on the

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Rita Vassena (ES), Past Coordinator



crosstalk between 'human embryology' and 'human embryonic stem cells'. We now have greater insight into the nature of embryonic and pluripotent stem cells in general, and how different states of pluripotency can be established by comparing them to late pre-implantation stage embryos. This provides valuable information for

possible stem cell therapies - knowledge of the basic stem cell characteristics is a first prerequisite before even thinking of possible future therapies. It is also because of studying human pluripotent stem cells that we know more about signalling pathways and those media components which play such crucial roles in human embryo development. So our pregress programme should appeal to both fundamental embryologists as well as stem cell researchers.

The course will also feature new state of the art molecular screening methods enabling single cell transcriptomics, for example on a genome-wide scale. Lectures will consider the application of these next generation sequencing technologies on both human embryos and human pluripotent stem cells and how we can use both to obtain greater insight into the process of early human development.

Finally we are planning a new Campus symposium in late 2017/early 2018, whose content will depend much on what is happening in this rapidly progressive field. Almost every week there are important new publications in the high impact factor journals, many of which are often related to combined research on human embryos, which makes the whole subject now very relevant for ESHRE members.

Steering Committee changes

A new basic science officer for the SIG Stem Cells was proposed in Helsinki, Sarita Panula, who is working now as a post-doc in the lab of Fredrik Lanner at the Karolinska Institute in Stockholm. Sarita began her PhD research in late 2009 with Renee Reijo Pera at Stanford University, and continued the work in 2010 in Shinya Yamanaka's lab in Kyoto before moving back to the Karolinska..

I am also happy to announce that Cristina Eguizabal will take over as our new Co-ordinator in Geneva. I am sure she will do a great job given her endless enthusiasm and her great expertise in different aspects of stem cell research. As Cristina steps forward, new elections will be organised for the position of Deputy, so please follow the announcements - or put yourself up as a candidate if you have interest in stem cells and/or in early human development. A new Junior Deputy will be selected by our Steering committee, so a lot of new vibes for the coming few years.

*Björn Heindryckx
Co-ordinator SIG Stem Cells*

A new beginning with an extended new scope

Interests of the viral disease Task Force absorbed by SIG SQART

The coming year will be a year of transition for the SIG SQART as we merge with the Task Force on viral diseases. This is an exciting natural progression approved by both boards and ESHRE's Executive Committee. In such new circumstances it was decided that Augusto Semprini, former Co-ordinator of the Task Force, will become our SIG International Advisor and Daniela Nogueira our Basic Science Officer. We warmly welcome these new members.

Annual Meeting Helsinki

Our pre-congress course on **ART 2020, the next frontier**, chaired by Arianna D'Angelo, Björn Heindryckx, Rita Vassena and Kelly Tilleman and organised with the SIG Stem Cells, attracted many delegates. The course was designed to consider many topical themes and their multiplicity of options, dilemmas and challenges when introducing new techniques to our daily practice in a safe way. A panel of outstanding speakers discussed PET/CT as a new non-invasive approach to the evaluation of testicular function (Lawrence Dierickx); or stem cells for artificial gametes (Bjorn Heindryckx) or as therapies for reproductive tract defects (Filippo Zambelli). All indicated that, while efforts are in place to develop these new techniques, their real objectives still lie far ahead for now.

We also had the pleasure of hearing from Mats Brännström, who described and reviewed his own group's ground-breaking uterine transplantation procedures, and Anne Marie Vinggaard, who presented a review of reproductive toxicology. Angelique van Dongen discussed the potentials of e-health and social media, while Heidi Mertes closed the programme with the technological imperatives of reproductive medicine. Arianna D'Angelo, SIG SQART Co-ordinator, had opened the course with a

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Kelly Tilleman (BE), Deputy
Ioana Rugescu (RO), Deputy
Zdravka Veleva (FI), Junior Deputy
Willianne Nelen (NL), Past Co-ordinator
Augusto Semprini (IT), International Advisor
Daniela Nogueira (FR), Basic Science Officer



presentation on ultrasound training with a simulator and suggesting that those with simulation training supplementary to their clinical training actually achieve higher scores and skills acquisition than those receiving clinical training alone. Webcasts of these interesting talks are now available for viewing on the ESHRE e-Campus learning platform.

Several members of the SIG SQART steering committee chaired sessions and gave invited presentations in Helsinki. Our Deputy, Kelly Tilleman, spoke in the Paramedical session on fertility preservation for transgender patients prior to transition surgery, highlighting her own centre's approach and legal requirements of different countries.

In addition, many abstracts were submitted and reported in the two sessions allocated to the SIG. Both had good attendance and generated interesting exchanges from the audience.

Forthcoming events

In September (22-23) the SIG SQART will take part in a very exciting Campus course in collaboration with the SIGs Ethics & Law and Stem Cells on **Novel gamete manipulation technologies in ART: SEEM (safety, ethical, efficient, moral) OK?** This multidisciplinary course will target some of the recent breakthroughs in gamete manipulation as possible new treatments for infertile patients.

Those interested in oncofertility will wish to attend a Campus course in Paris on **Innovative care and technologies for female fertility preservation** on 17-19 November 2016. The course will discuss the target populations of women and female children diagnosed with cancer who can benefit from fertility preservation. It will have a pragmatic emphasis and will describe the development of multidisciplinary cryobiological platforms and the use of different approaches dependent on gonadotoxic urgency. Different fertility preservation strategies appropriate to specific patient groups and oncology conditions will be described along with their risk/benefit balance and ethical considerations.

We are anticipating more exciting collaborations with other SIGs for state-of-the-art Campus courses in 2017/2018, so watch this space!

Finally, we warmly welcome comments or further ideas, so please do not hesitate to e-mail me on dangelo@cardiff.ac.uk.

Arianna D'Angelo
Co-ordinator, SIG Safety & Quality in ART



Arianna D'Angelo and Björn Heindryckx, Co-ordinator of the SIG Stem Cells, chairing their joint pre-congress course in Helsinki.

Preparation nears completion for multicentre study of subtle tubal abnormalities

We have been very active over the past few months with two Campus workshops followed by the pregress course in Helsinki, where we spent the whole day in discussion about the impact of fibroids on fertility and the indications and risks of morcellation.

Our pregress course was also very well attended, with much discussion after every presentation.

It was also in Helsinki that we held our now 'traditional' live surgery session. The surgical procedures were carried out in Lyon (Hôpital Natercia) and transmitted via satellite to one of the session halls in Helsinki. We had three operators: Rudi Campo for hysteroscopic procedures, Filipa Osorio (our Junior Deputy) for myomectomy and endometriosis, and

STEERING COMMITTEE

Antoine Watrelot (FR), Co-ordinator
Michelle Nisolle (BE), Deputy
Razvan Vladimir Socolov (RO), Deputy
Filipa Beja Osório (PT), Junior Deputy
Tin-Chi Li (HK), Past Co-ordinator

Antoine Watrelot for fertiloscopy. The chairmen and co-ordinators were TC Li, Stephan Gordts and Michelle Nisolle.

Once again the session proved a great success, with high attendance, and I take this opportunity to thank the Karl Storz company for their much appreciated support and the team of Mathy Vanbuel for organisation of the transmission.



Looking ahead

In November (23-25) we will hold our traditional but always well attended hands-on workshop in Leuven on **Endoscopy in reproductive medicine**. This will be followed by a further edition in April next year and a workshop in Romania on tubal pathology organised by our Deputy Razan Socolov.



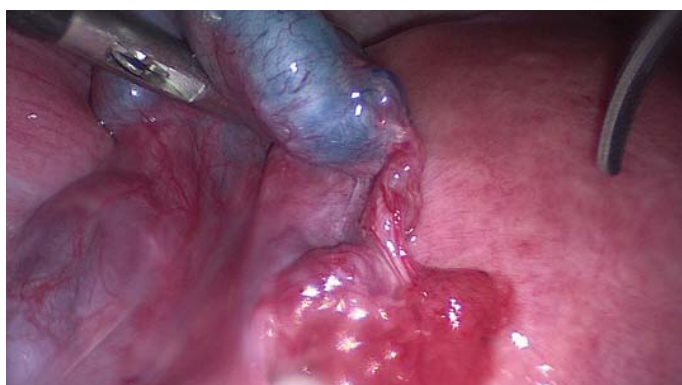
The SuTuBa project

We are now in the final stages before starting the SuTuBa study, an investigation of subtle tubal abnormalities. These abnormalities are not well known and their impact on fertility is probably underestimated. They are usually not obstructive lesions and thus tend to be considered as having negligible impact on fertility. Not surprisingly, since 1955 fewer than 15 publications have been devoted to them. And that's why this study should be able, firstly, to evaluate the frequency of such abnormalities and establish a thorough classification, and secondly to study their influence on fertility outcome. The SuTuBa study, which is an initiative of the SIG RS but is not sponsored or funded by ESHRE, will

be a prospective and multicentre trial, and those interested in participating may contact me, who will be the trial's co-ordinator (watrelot@orange.fr). Recruitment should start before the end of 2016.

Antoine Watrelot
Co-ordinator

SIG Reproductive Surgery



Live surgery continues to be an appealing feature of the Annual Meeting, above, and this year proceedings were transmitted direct to the congress hall from Lyon.

Subtle tubal abnormalities will be defined and classified in the SuTuBa study. Pictured left is an ampullary sacculation with 'reactional' phimosis.

Another active educational programme planned

Those attending our pregress course in Helsinki, **Genetics and epigenetics behind subfertility and reproductive system disease**, enjoyed very high quality presentations followed by lively discussion on epigenetic alterations in male infertility, chromothrypsis and oocyte aneuploidy, inheritance of epigenetic modifications and implications for ART, genome editing approaches and limitations, genomic imprinting and epigenetic reprogramming during gametogenesis and early embryo development. The course was very well attended and the talks well received. It was indeed a very good start to the main conference programme, where the topic of epigenetics was prominent in several sessions. As always, the syllabi are available for participants on the ESHRE website, and some recordings of contributions hopefully can be incorporated in the new e-learning programme.

Future meetings

Our next pregress course in Geneva on **Mitochondria in human reproduction** will aim to combine basic with applied science, and we hope to attract researchers as well as embryologists, clinicians and other scientists working in ART and reproductive genetics. Some of the topics to be covered include the impact of mitochondrial DNA mutations and how to prevent their transmission, the role of mitochondria in male and female infertility as well as their role in ART. We look forward to much participant interest - and a similarly large audience as this year!

We are currently in the process of finalising our activities for 2017, which include a Campus meeting planned for autumn 2017 in Sofia, Bulgaria. Details will be announced shortly. Together with SIG Embryology we will also contribute to another Campus meeting on **Basic human embryology** which will take place in Edinburgh, with a cutting edge discussion on 'The genetic basis of embryo development' (dates to be announced).

Steering committee

Our business meeting, which took place after the pregress course, was not well attended. We will address this problem in the future and hope to provide opportunities for more members to attend by shifting the time into the main conference programme. Despite that, some important announcements were made.

STEERING COMMITTEE

Claudia Spits (BE), Co-ordinator
Tania Milachich (BG), Deputy
Georgia Kakourou (GR), Deputy
Signe Altmäe (EE), Junior Deputy
Ursula Eichenlaub-Ritter (DE), Past Co-ordinator



Ursula Eichenlaub-Ritter (Past Co-ordinator) announced the changes to our Steering Committee that will take place in 2017, when Claudia Spits, our current Co-ordinator, and Tania Milachich, our Deputy, both step down.

Claudia will remain as Past Co-ordinator for another two years.

Georgia Kakourou will take over as Co-ordinator and Signe Altmäe (elected in 2015) will remain our Junior Deputy. Following these changes, two new Deputies will need to join the committee following nominations and elections in 2017. Notice for applications and details of the election procedure will be sent out by Central Office in the autumn and we look forward once again to active experts joining our group.

We are pleased that Stephane Viville has accepted the invitation to be the SIG's new basic science officer following proposal and agreement by all members of the Steering Committee. His input and expertise in the field will be invaluable for planning future activities.

Campus reports

This year, the SIG RG was involved in the organisation of two ESHRE Campus meetings: **Oocyte maturation – from basics to clinic** organised jointly in March with the SIG Embryology and TF Basic Science, and **All about preconception, preimplantation and prenatal genetic testing** organised in collaboration with the European Society of Human Genetics in Maastricht in April, which was very well attended.



Georgia Kakourou
Deputy
SIG Reproductive Genetics

Oocyte cryopreservation data from 27 countries

Annual Meeting Helsinki

First of all, thanks to all those who took part in our joint pre-congress course in Helsinki on the interface between pre-pregnancy care and socio-cultural aspects of infertility. The course was organised with the SIG Early Pregnancy and raised ethical and legal issues relevant to the mother and her future child as well as clinical questions, such as uterine scar pregnancy. We also learned a lot about the importance of nutrition and of social disparities, including poverty, which still affects outcome for a future child, whether conceived by ART or spontaneously.

This, the course showed, is an important epidemiological lesson, that such problems are not only a global issue, but a national one too for most countries. This very question was reiterated during our joint session in the main scientific programme, which also highlighted the importance of economics in society with the example of the high relative cost of ART for South African patients.

Business matters

Having now started my final year as Co-ordinator of our SIG, I now wish to draw everyone's attention to the need to appoint a new Deputy to the Steering Committee, who should be in place from the next Annual Meeting in Geneva. There I will become Past Co-ordinator and Willem Ombelet will take on the role of Co-ordinator. We would thus like to receive applications for this Deputy position. ESHRE's rules state that any applicant for all SIG steering committees must have been a member of the Society for five consecutive years. Candidates should submit a CV to ESHRE's Central Office, and applications will be reviewed by the SIG Steering Committee and listed for election by SIG members. We will also select a Junior Deputy (under 35 years old) who should be a member of the Society for the past three consecutive years.

We already have plans for 2017 in collaboration with SIG SQART and the EIM Consortium, with a Campus meeting on **ART disparities in Europe: from regulation to practice** to be held in Helsinki in September 2017. More details will be available later this year.

Our pre-congress course in Geneva next year, which we are hosting with the SIGs SQART, Ethics & Law

STEERING COMMITTEE

Françoise Shenfield (GB), Co-ordinator

Willem Ombelet (BE), Deputy

Paul Devroey (BE), Deputy

Virginie Rozée (FR), Junior Deputy



and Psychology & Counselling, will focus on the fertility options and reproductive rights of transgender and sex reassignment individuals.

Transgender people who wish for transition to their desired gender have to undergo hormonal and surgical treatments, which leads to irreversible

loss of reproductive potential. It is thus important to discuss fertility preservation options with these patients and to present and counsel them about any future child wish. This course will provide an insight into what these possibilities and options for fertility preservation are. It will also provide information on counselling this specific patient cohort and discussion on the ethics of certain controversial topics. The aim of the course is thus to raise an awareness of transgenderism and fertility, provide information on treatments and counselling from centres of excellence on transgender care, present a transgenders perspective on fertility, and deliver guidance for qualitative and safe treatment options in ART centres

Last but not least, you should read very soon about the outcome of our study on oocyte and ovarian tissue cryopreservation in Europe. Here we will describe legislation and access in 27 European countries, where just over half now provide state funding for oocyte cryopreservation for medical reasons. We also analyse data comprising 9078 specific aspirations in 17 countries for oocyte cryopreservation, showing the rise in numbers between 2010 and 2014 and detailing the proportion of cycles performed for medical indications (both for serious disease and as part of ART treatment), and non-medical or 'social' (age-related ovarian reserve decrease) reasons. The aim is to promote full national oocyte cryopreservation data in European countries in order to contribute to an accurate European register on use and efficiency of the method. Ultimately, this will be an important information tool for all stakeholders, including women and funders - such information has been scarce until now. We hope our survey results will encourage the collection of data in each of your countries .

*Françoise Shenfield
Co-ordinator SIG Global and
socio-cultural aspects of infertility*

Hello (again) Dolly

● It was 20 years ago in July that the world's most famous sheep was born

It was in February 1997 that a UK Sunday newspaper broke news of the birth of a domestic animal conceived not from an egg and sperm but from DNA removed from a cell of a mature sheep. By now Dolly - as the world had come to know her - was seven months old and getting used to the quiet life among her fellow animals at the Roslin Institute in Edinburgh.

The head of the Roslin's programme, Professor - later Sir - Ian Wilmut, had hoped that news of Dolly's birth could be kept under wraps until the group's letter to *Nature* was published; but *The Observer* newspaper beat them by a week.¹ And then it only took a few minutes for the Roslin phones to start ringing, and just a few hours before the TV trucks were lined up outside.

'They were all there wanting interviews with Ian, wanting to see the sheep,' the Roslin's scientific director later told *Nature*. 'It was chaos. I don't think you can ever appreciate the intensity of the media in full flight unless you've experienced it yourself.'

Next day's stories, of course, were verging on the hysterical, truly astounded that such a scientific achievement was possible, and fearsome that from now on life would never be the same again. The predictions were dire and extreme. Even ESHRE, which awarded honorary membership to Ian Wilmut in 2012, convened a hasty ExCo meeting and declared a moratorium on reproductive cloning. Yet here was Dolly, photographed happy in her Edinburgh pen and apparently no different from any other sheep.

Of course, reproductive cloning was never on the Roslin Institute's agenda; somatic cell nuclear transfer was simply one of the steps necessary for the creation of genetically modified animals able to open up completely new therapeutic avenues. Indeed, in the year after Dolly's birth, several transgenic sheep were produced to secrete the human blood-clotting factor IX into their milk to be harvested as treatment for haemophiliacs - although the most productive of these transgenic animals, Polly the sheep, didn't produce enough



factor IX for commercial viability.

Today, 20 years after her birth (on 5 July 1996), Dolly is remembered as the first mammal to be cloned from an adult cell. Her birth proved that adult cells could be used to create an exact copy of the animal they came from and thus paved the way for the creation of personalised induced pluripotent stem (iPS) cells. Indeed, the Nobel prize winning discoverer of iPS cells, Shinya Yamanaka, told the magazine *Scientific American* that Dolly's cloning motivated



Dolly's first lamb, Bonnie, was conceived naturally and born in April 1998, twins Sally and Rosie were born the following year, and triplets Lucy, Darcy and Cotton, pictured left, the year after.

The team responsible for Dolly's birth was led by Professor Sir Ian Wilmut, above, who in 2012 was made an honorary member of ESHRE. All pictures courtesy of the Roslin Institute, University of Edinburgh.



Dolly as a lamb with her surrogate mother, clearly a different breed of sheep.

him to begin his work on stem cells derived from adult cells. 'Dolly the sheep told me that nuclear reprogramming is possible even in mammalian cells and encouraged me to start my own project,' said Yamanaka. Since then the accumulation of iPS cells has reduced the need for embryonic stem cells - a cause of ethical concern for many - and they now form the basis for most of today's stem cell research.

Dolly died six years after her birth of a lung infection, apparently common in sheep without access to outdoor life, and 'probably nothing to do with her being a cloned animal', according to Wilmut. Today, Dolly can still be seen as a taxidermic specimen in the National Museum of Scotland in Edinburgh, a tribute to her creators and testimony to Scotland's place in reproductive science.

*Simon Brown
Focus on Reproduction*

1. Wilmut I, Schnieke AE, McWhir J, et al. Viable offspring derived from fetal and adult mammalian cells, *Nature* 1997; 385: 810-813.

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