

focus on REPRODUCTION



Another record-breaking Annual Meeting

- The first double-digit impact factor in O&G
- From assisted conception to artificial conception

// SEPTEMBER
2015



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SEPTEMBER 2015

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FOCUS ON REPRODUCTION is published by The European Society of Human Reproduction and Embryology, Meerstraat 60,
Grimbergen, Belgium // www.eshre.eu

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CHAIRMAN'S INTRODUCTION

This is my first introduction to *Focus on Reproduction* as Chairman of ESHRE. I am writing it in Sweden in the middle of a Scandinavian 'summer' (14 degrees, heavy winds, and rain . . .), and with the last days of my holiday approaching too quickly.

I have now spent two years as Chairman Elect of ESHRE, working with Anna Veiga as Past Chair and Juha Tapanainen as Chairman. It has been a rewarding and exciting experience - and one in which I have learnt in much more detail how ESHRE works. I have to say that I am impressed by the number of things in which ESHRE is involved, and to see the impact that we have in reproductive medicine. Not only on a day-to-day clinical and scientific level, but also at a European and international policy level, working together with EU and WHO as well as with other international societies and organisations. It is crucial that we are present when major decisions about reproductive medicine and science are being taken.

Alongside policy making, one of the most important objectives for ESHRE is scientific knowledge and education. We have a responsibility to acquire knowledge from the experts in our field and to collect data - and to extend this information into the community, by which I mean not only ESHRE members but also our politicians, regulators, patients, media and general public. And this should be done through all the channels we have available, through our workshops, our certification programmes, our journals, our website, our national representatives and our annual meetings. We do have a huge opportunity and a lot of tools at our disposal.

We also have the advantage of a very well running, hardworking and dedicated ESHRE machinery in the Executive Committee, the SIGs and Task Forces and working groups, and of course our Central Office under the direction of Bruno Van den Eede. For me the best part of ESHRE has always been the fantastic people one meets. This creates a lot of positive energy, that we all need in order to move ahead.

One place where we find a lot of these fantastic people is the Annual Meeting. And, although a little biased, my impression is that this year's meeting in Lisbon was very good indeed. I even heard a number of people saying it was one of the best. The scientific quality was high, the venue was very efficient, and Lisbon of course is a wonderful city. The app, having improved for each year, now received a lot of positive feedback, and, for the first time ever, I heard no complaints at all about the food! Many thanks to the organisers and to our Central Office for an excellent job. But there is never time to relax, and now planning for Helsinki next year moves into a more intensive phase.

So, thinking ahead to my task as Chairman of ESHRE, I am very much looking forward to the next two years. I know that it will be a lot of work, with a number of challenges to deal with, but I am also confident that it will be a very interesting - and fun - time.

Kersti Lundin
ESHRE Chairman 2015-2017

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Tchau Lisboa

Hei Helsinki



Invited scientific programme now in place; abstract submissions for free communication must be with ESHRE by 1 February 2016

ESHRE's next Annual Meeting will for the first time be held in Finland. Helsinki, the capital, is a lively and safe city offering multiple opportunities for spare time activities, and is easily explored on foot. Design, architecture, culture and shopping are all great city interests, and large park areas, forests, lakes, and a dramatic coastline with numerous islands ensure there's no shortage of natural attractions. The archipelago of Helsinki consists of around 330 islands, and many of them can be reached by regular ferry from early morning until late at night. Public transportation is efficient and in the heart of the city everywhere is conveniently within walking distance.

Geographically situated between the East and the West, Helsinki has a rich cultural heritage originating from both, which you can see in the old part of the city and taste in the restaurants. It's quite easy to take a train to St Petersburg or a ferry to Tallinn or a boat trip to discover the archipelago of Finland, lakeland

Finland with its 188,000 lakes, or even up north to Lapland.

The venue for our Annual Meeting is Messukeskus Expo and Convention Centre, which is located in a modern urban complex within easy reach of the city centre. All local trains stop at the Pasila railway station, a mere 300 metre walk from the congress centre. Trains from the city centre to Pasila take five minutes, and trams and buses stop at the southern entrance.

An outstanding scientific programme will include the usual mix of invited sessions and keynote lectures, beginning on the opening day with a presentation by Finland's Johan Eriksson on the long-term consequences of maternal obesity for the health of offspring. Other invited presentations include translational discoveries in stem cells for human reproduction, optimal monitoring of ovarian stimulation, cellular interactions in oocyte physiology, and anonymity in donor conception. Likely to prompt

*Design, architecture,
culture and shopping are
all great city interests*



*Venue for the congress is the
Messukeskus Expo and Convention Centre,
located in a modern urban complex within easy reach
of the city centre.*

interest is a session on the 'new frontiers' raised by modern genetics - sequencing of the embryo and personal genomic analysis. There are also strong practical sessions on standard or individualised protocols in IVE, 3D ultrasound in uterine diagnostics and in pregnancy, on insulin sensitisers in reproductive medicine, and on the risk of twins in ART. A session on endometrial injury asks if it makes sense scientifically or clinically, while the last of several hot sessions from the paramedical programme considers the controversy of transfer from frozen cycles only. An earlier paramedical session examines the competence of nurses and midwives to perform ultrasound monitoring in ovarian stimulation.

Thirteen Precongress Courses have been planned and, as a new approach, one will be a hands-on course on embryo transfer using the new embryo transfer simulator. Other courses include the surgical management of myoma, genetics and epigenetics in infertility, future directions for ART, early pregnancy care, complex cases in fertility counselling, and, in the age of Lance Armstrong, the effect of exercise, sport and doping on fertility.

We are also working to create a memorable social programme, which will begin with a Finnish touch at the Opening Ceremony. On Tuesday there will be an affordable get-together for all participants, with food, drinks and live music not far from the city centre. As usual, a charity run will be held during the congress - and don't forget that Finland is one of the world's most successful countries in long-distance running.

With this brief snapshot of what Helsinki 2016 has to offer, the local organising committee extends a warm invitation - to learn more about the many new developments now happening in reproductive medicine and to enjoy the country which brought you thousands of lakes, the sauna, endless forests, Santa Claus, the northern lights and . . . that uniquely resilient Finnish quality known as 'sisu'.

*Juha Tapanainen
On behalf of the local organising committee*

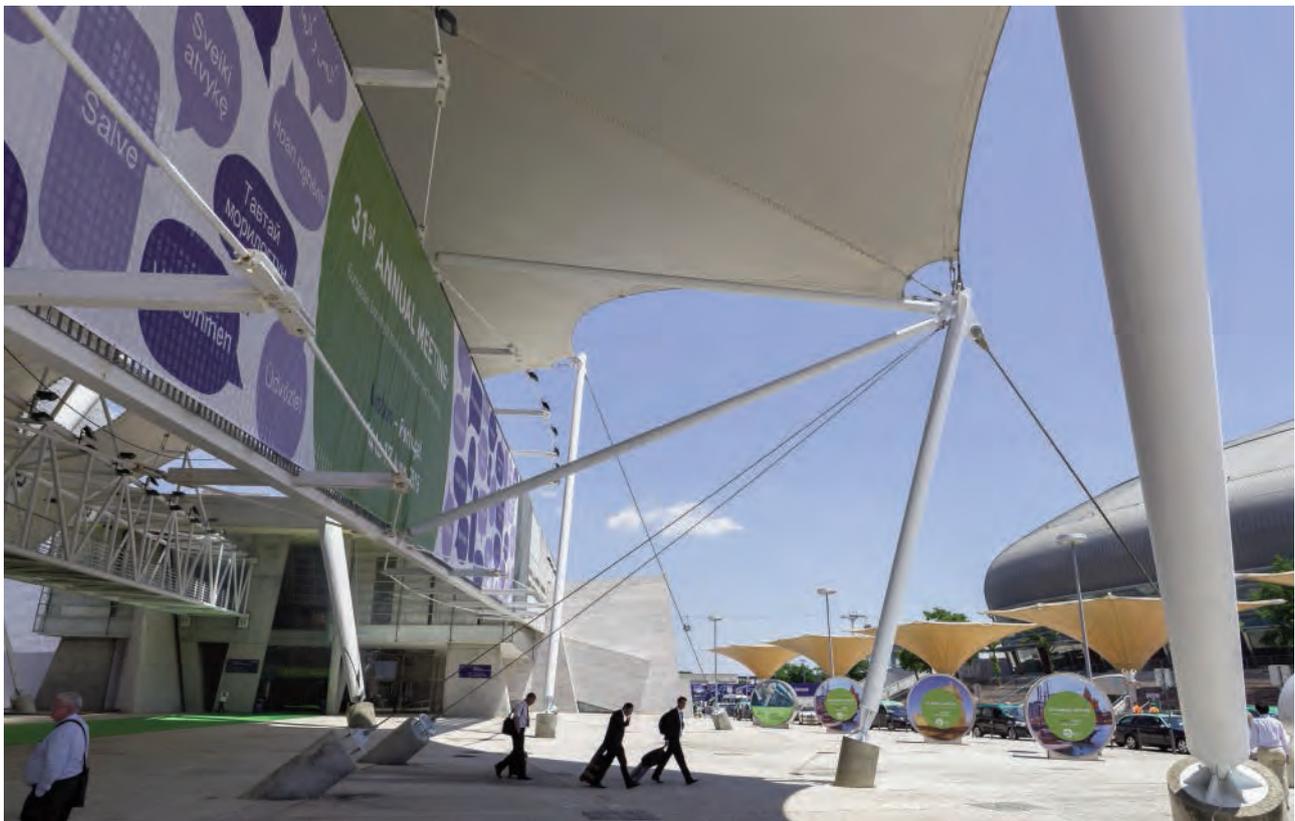
DIARY DATES: ABSTRACT SUBMISSION RESUMES NORMAL

ESHRE's 32nd Annual Meeting will take place in Helsinki from Sunday 3 July to Wednesday 6 July 2016.

- The deadline for abstract submission is back to normal. All abstracts must arrive at ESHRE's Central Office no later than 1 February 2016.
- Early bird registration - for the lowest participation fee - must be completed before 30 April 2016 - for ESHRE members, non-members, paramedical members and students.

All practical information on next year's Annual Meeting, as well as an early look at the invited scientific programme can be now found on the dedicated website www.eshre2016.eu.





Another record-breaking Annual Meeting

- Lisbon overtakes London, with more than 10,000 participants
- Welcome transition to ESHRE's first paper-free congress

IT LOOKED LIKE being a stressful congress. An opening keynote lecture on stress as a preconceptional risk factor, an entire Monday session on stress in infertility . . . yet by Wednesday, 279 oral and 800 poster presentations later, the stress threat had finally evaporated like the rain clouds over Lisbon.

In fact, Courtney Lynch, presenter of the Annual Meeting's Human Reproduction keynote lecture, concluded after a study following 501 couples trying to conceive and measuring levels of two stress-associated biomarkers that we cannot yet say with certainty that stress causes infertility ('more data needed') or that stress reduction will help women get pregnant faster ('need an RCT'). Her study, however, which had the highest



Courtney Lynch: Stress reduction 'a reasonable option' for women unable to conceive.

number of full-text downloads during the first six months of publication in *Human Reproduction* between January 2013 and June 2014, did show that higher levels of stress as measured by salivary alpha-amylase (but not cortisol) were associated with a longer time-to-pregnancy and an increased risk of infertility. After adjustments, women in the highest tertile measurement of alpha-amylase had a 29% lower fecundity than women in the lowest tertile (OR 0.71), which translated into a more than two-fold increased risk of infertility among these women. Despite her caution, Lynch did agree that 'stress reduction seems like a reasonable option' for women unable to conceive.

Stress in IVF was also reduced by

adopting a milder approach. Michael van Wolff from the University of Bern described a study in which 119 couples could choose between natural cycle and conventional IVF. Once in treatment, patients completed psychological tests at home (including FertiQuol), which showed that depressive symptoms were significantly higher in conventional IVF than in natural cycle. Results also indicated that in the three-cycle natural programme fertility-related stress decreased significantly once the first cycle was completed. As far as the patient is concerned, said von Wolff, there's more to IVF than just pregnancy rate per transfer - there's simplicity, low risk, low cost, low side effects . . . all features associated with natural cycle IVF. And outcome after up to three cycles (24.6% pregnancy rate) was comparable with one conventional cycle (25.8%).

Also in the stress department, results from the Danish National ART-Couple Cohort (n=37,913) showed that men with unipolar depression had a lower chance of becoming a father than men with no depression. Conversely however, Lone Schmidt reporting the results added that neither live birth nor male factor infertility were found to be risk factors for subsequent unipolar depression. Incidentally, this huge cohort showed that 1.2% of all men registered had been diagnosed as depressive.

These were not the only results in Lisbon derived from big-ticket cohort studies. Anne Lærke Spangmose Pedersen, a medical student at Copenhagen University Hospital Hvidovre, described as 'reassuring' findings from a nationwide analysis of more than 8000 ART children that conception by ART is not associated with reduced academic performance in adolescence. 'We were pleased to see the results,' said Pedersen. 'The higher rate of twins and preterm birth in ART singletons might have given rise to lower academic test scores. But our results now confirm smaller studies which have shown no difference in IQ between ART and non-ART children.'

The database of the UK regulatory authority is now open to other groups for study and an analysis of all ART pregnancies recorded by the HFEA between 2000 and 2012 found that the rate of ectopic pregnancy following IVF and ICSI progressively decreased throughout these 12 years, almost halving from an overall rate of 20 to 12 cases per thousand. Commenting on the findings,



This was ESHRE's first serious attempt at a paper-free Annual Meeting and it was made with considerable success and relatively few complaints. All congress essentials - navigation, programme, abstracts - were available in a variety of electronic formats, including a dedicated app downloadable to phones and tablets. The only concession to print was a pocket programme summary. The app, which was activated by more than 5500 individuals, will be upgraded further for next year.



Nicholas Polyzos from the VUB Brussels said that this decrease in incidence 'appears strictly associated with the reduction in the incidence of tubal factor infertility and the transfer of fewer embryos' in ART. Details from the database showed that the proportion of ART patients with tubal disease progressively decreased from 24% in 2000 to 12% in 2012. A recent analysis of national IVF data in the USA found that the rate of ectopic pregnancy was 1.6% when one embryo was transferred, and 1.7%, 2.2% and 2.5% when two, three, or four or more embryos were transferred.

However, complications in pregnancy were found to be higher in women with endometriosis in a nationwide cohort study using discharge data from all state hospitals in Scotland. The study compared the pregnancy



This was a congress of cohort studies, with large databases providing new registry evidence in safety and risk. Anne Lærke Pedersen, left, found no evidence of scholarly disadvantage in IVF adolescents, Nicholas Polyzos, centre, found that the incidence of ectopic pregnancies following IVF had halved since 2000, and Pim Ankum, right, reported that D&C for miscarriage or termination is linked to prematurity in subsequent pregnancies

2015 HONORARY MEMBERSHIPS



Honorary membership of ESHRE was awarded to Paul Devroey, pictured left receiving his award from incoming

ESHRE Chairman Kersti Lundin, and to Steve Hillier, who, above, received his award from outgoing Chairman Juha Tapanainen. Devroey himself was Chairman of ESHRE from 2005 to 2007, having developed ICSI more than a decade earlier with his Brussels colleague André Van Steirteghem. Hillier was Editor-in-Chief of *Molecular Human Reproduction* from 2007 to 2013.



outcomes in 5375 women with endometriosis with those of 8280 women without endometriosis who were pregnant at the same time. After adjustments for age and previous pregnancy, results showed that women with endometriosis had a significantly higher risk of early pregnancy complications than the controls. This risk was 76% higher for miscarriage (OR 1.76) and nearly three-times higher for ectopic pregnancy (OR 2.7). In women with a previous diagnosis of endometriosis the risks of adverse pregnancy outcomes, including ante- and postpartum haemorrhage and preterm birth, were also significantly increased. Principal investigator Lucky Saraswat from Aberdeen Royal Infirmary advised that women with a diagnosis of endometriosis should be counselled about the higher risks of miscarriage and ectopic pregnancy in the first trimester, 'which warrants increased monitoring by ultrasound scans, and greater vigilance to identify potential complications such as bleeding and preterm delivery'.

An even bigger analysis of 21 cohort studies which included almost 2 million women found that a dilatation and curettage (D&C) procedure performed in cases of miscarriage or induced abortion increases the chance of preterm birth (under 37 weeks) in a subsequent pregnancy by 29%, and of very preterm birth (under 32 weeks) by 69%. Presenting the results, Pim Ankum from the Academic Medical Centre of the University of Amsterdam called for a more 'restrained

use' of D&C. Indeed, this decline in use appears already to have begun, reflected in the increased popularity of misoprostol either as an alternative to D&C or for cervical priming prior to curettage.

Another large cohort study reported in Lisbon - from the Netherlands Cancer Institute - found that after a median follow-up of 16 years in an ART group (the OMEGA project) of almost 30,000 women having treatment between 1983 and 2001, no significantly increased cancer risk was observed in any of the offspring conceived by ART. The results, said Mandy Spaan, confirm another linkage study reported at ESHRE two years ago in which no increased cancer risk was observed in 106,000 ART-conceived children in the UK. Similarly, results from the Cancer Registry of Norway presented in Lisbon by Marte Reigstad, which included more than 25,000 children conceived by ART, showed no overall increased risk of cancer but a small increased risk of leukaemia and Hodgkin's lymphoma. These findings, said Reigstad, were in line with other studies.

Although the risk of ovarian damage following treatment for childhood cancers depends on its dose and



duration, Joop Laven from the Erasmus Medical Centre in Rotterdam confirmed that survival rates from these cancers are increasing 'dramatically', but with it an increasing likelihood of ovarian dysfunction and infertility. He described combination therapy of alkylating agents with abdominal or pelvic radiotherapy as 'especially gonadotoxic', with premature ovarian insufficiency a high risk, adding that an assessment of ovarian function in pre- and post-pubertal girls and young adult cancers is 'mandatory'. He recommended that fertility preservation should depend on a fixed protocol of risk assessment (such as the Edinburgh criteria) which recognised health status, ovarian reserve, treatment, and informed consent.



A study on cumulative live birth rate in IVF women over 38 presented by Marta Devesa proved exceptionally popular with the press. Ernesto Bosch in a study on freeze-all embryos found no benefit in normo-responder patients.

WITH MORE than 10,000 registered participants, ESHRE 2015 was yet another record-breaking congress, just surpassing the attendance of London in 2013. But record attendance means big crowds and, on day one especially, there were several sessions packed out well before the starting gun, with proceedings only visible on screens outside.

One such hot session was on 'endometrial receptivity', but interest lay unequivocally in the contentious practice of endometrial scratch and its effect on implantation and IVF outcome. A systematic review performed by Carol Coughlan and colleagues from Dublin and Sheffield, UK, included RCTs published up to September 2014 and suggested that endometrial injury in the cycle immediately preceding embryo transfer cycle does indeed improve clinical pregnancy rates in those with at least one previous unsuccessful embryo transfer. This conclusion, derived from an analysis of seven applicable RCTs, was not far away from an earlier Cochrane review which, based on 'moderate quality evidence', also found endometrial injury performed between day 7 of the previous cycle and day 7 of the transfer cycle associated with improved outcome in women with one or two previous transfers. However, with reference to her own study, Coughlan was 'not clear' on how many scratches might have a beneficial effect, nor precisely when they

might be performed. Aim for once in the luteal phase, she suggested.

Such lack of clarity paved the way for another presentation in the same session on the 'pitfalls' of judging endometrial injury by meta-analysis. One, raised by Jose Franco from Sao Paulo, Brazil, was a lack of biological plausibility, with no support in basic research for any increase in endometrial receptivity in the cycle following injury. And epidemiologically, the results of meta-analysis are no better than those of the trials included, and so far, said Franco, with so much heterogeneity and absence of credibility in those trials, endometrial injury has no support in reliable evidence-based ART.

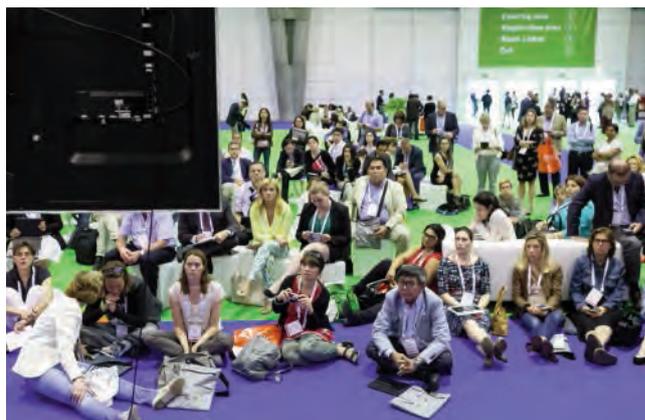
Another hot topic causing controversy is a freeze-all policy in IVF to delay transfer until a subsequent 'natural' cycle. However, an observational study of 882 first- or second-cycle patients at IVI Valencia found little encouragement for the policy in routine cases comparing 364 patients (41%) having embryo transfer in the initial fresh cycle, and 518 (59%) having all embryos frozen for later transfer. When the outcomes were compared, no differences were observed between ongoing pregnancy rate and live birth rate (36.2% freeze-all vs 33.8% fresh). All patients in the study were considered normal responders and were thus, said Ernesto Bosch, representative of a routine IVF population. 'These findings,' he said, 'do not support a change in IVF practice moving to a freeze-all strategy in normo-responders in IVF.'

However, a detailed review by Matheus Roque from Brazil, which covered efficacy and obstetric outcomes in frozen embryo transfers, found the prevalence of risk (such as OHSS, ectopic pregnancy, placental disruption and preterm birth) greater in fresh cycles - and thus favouring frozen transfers.

The question of reproductive ageing continues to be of interest, especially in the lay press, and one study included in the press programme made the front pages of several newspapers. The study quantified the age-related decline in fertility evident in all ART programmes by analysing cumulative birth rate at the

Record attendance meant some packed sessions were only watchable on TV screen outside the lecture hall.

One of this year's highpoints was the invited lecture by Mary Herbert on the prevention of mitochondrial disease by pronuclear transfer.



Hospital Universitario Quiron-Dexeus in Barcelona between 2000 and 2012 - in 4195 women having 5841 cycles of IVF. Cumulative LBRs (fresh and frozen) declined significantly with increasing age - from 23.6% in women 38-39 years, to 15.6% in 40-41 years, to 6.6% in 42-43 years, to 1.3% in 44 years and older. Presenter Marta Devesa described the study as the largest ever to analyse cumulative live birth rates in women over 38, and, based on its results, said that women aged 44 and over should be advised against IVF with their own eggs, as the chances of success are so slim. For the others under 44, age and the number of eggs retrieved provide the best guide to outcome.

The congress's scientific highlight was deemed by many to be the invited presentation of Mary Herbert on techniques to prevent the transmission of mitochondrial disease. Her centre in Newcastle, UK, will be the first in Britain to develop the techniques in a clinical programme following their approval by Parliament earlier this year. Herbert said the UK regulations will come into force in October. While the prevalence of mitochondrial diseases is relatively low (around one per 5000 population), their effects are debilitating and fatal, she said. Their severity, however, depends on the mutation load, which may be evident in only some copies of mitochondrial DNA (heteroplasmy) or in all copies (homoplasmy). The favoured technique being presently explored to



As ever, the press programme was keenly followed, making front page news in several UK papers.

'uncouple' the inheritance of nuclear DNA from mitochondrial is by pronuclear transfer, whose proof of principle has already been demonstrated by the Newcastle group in abnormally fertilised zygotes.

On the question of embryo research, Dutch bioethicist Guido de Wert proposed that arguments in favour of the 14-day window were 'pragmatic' and 'unconvincing' - and that the time limit was now 'open for further debate'. Extending the limit, however, will still be difficult

'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

High-resolution imaging of meiosis in live human oocytes - *Zuzana Holubcova (UK)*

Clinical Science Award for oral presentation

The Neurokinin B receptor antagonist AZD4901 decreases LH and testosterone secretion in women with PCOS: a randomised, double-blind, placebo-controlled clinical trial - *Jyothis George (UK)*

Basic Science Award for poster presentation

Crucial role of hypoxia inducible factor 2 alpha in the pregnant uterus - *Leona Matsumoto (Japan)*

Clinical Science Award for poster presentation

Reliability of the ESHRE/ESGE and ASRM classification systems of uterine congenital malformations - *Artur Ludwin (Poland)*

The Fertility Society of Australia Exchange Award

Balancing between totipotency and differentiation in the human embryo - *Marie Krivega (Belgium)*

The Nurses Award

Fertility awareness in the Flemish population: optimism can be disadvantageous - *Ilse Delbaere (Belgium)*

The ART Laboratory Award

Frozen-thawed in-vitro matured oocytes collected at the time of ovarian tissue processing, for the purpose of fertility preservation for transsexual persons, show normal spindle formations - *Sylvie Lierman (Belgium)*



Prizewinners receive their awards from incoming ESHRE Chairman Kersti Lundin.

Annual Assembly of Members

Membership at a record high, finances in good order

ESHRE's Annual Assembly of Members took place at the FIL, International Lisbon Fair, Portugal, on 16 June 2015 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 Helsinki.

1. Minutes of the last meeting held in Munich

- The minutes of the 2014 Annual Assembly of Members (AAM), having been circulated to all members in *Focus on Reproduction* (September 2014), were approved.

2. There were no matters arising.

3. Membership of the Society

- Membership of the Society now stands at 6685, an increase on last year's figure of 6495 (December) and an all-time record membership; 68% of members coming from Europe. The top European membership countries are UK (483 members), Italy (365), Germany (316), Spain (299), Netherlands (291), and Belgium (276). The USA is represented by 314 members, India 267 and China 106.

- The Chairman reported that 77.4% of members hold 'ordinary membership', and 13% paramedical membership.

- Disciplines with greatest representation (according to SIG membership) are embryology (30%) and reproductive endocrinology (26%), but there is strong presence in andrology, early pregnancy, safety & quality, and reproductive surgery.

4. Society activities

Annual meetings

- Last year's Annual Meeting in Munich attracted 8866 participants, somewhat fewer than in London the year previously. Feedback, said the Chairman, was generally positive about both the organisation and scientific programme.
- Attendance in Lisbon was already at a record high, with a total of 10,088 registered (including 1840 exhibitors and 35 press).
- From a record total of 1800 abstracts submitted, 225 had been selected for oral presentation and 800 for poster. The greatest number were from embryology (360) and reproductive endocrinology (317). The majority (56%) were from Europe, with high representations from Asia (29%) and Americas (11%).
- Next year's event will be at the Messukeskus Expo and Convention Centre, Helsinki, from 3-6 July, with 13 pre-congress courses organised by the Special Interest Groups, and the invited programme already available online.
- The 2017 Annual Meeting will be held in Geneva from 2-5 July, and 2018 in Barcelona from 1-4 July.

Training

- The Chairman reported that 11 Campus courses had been held in 2014 and six in 2015. Three further events were scheduled for 2015, and five formally planned for 2016.

- The Chairman encouraged all members to check the Campus programme on the recently updated ESHRE website for previews of all Campus events.

Data collection

- The Chairman praised the work of the European IVF Monitoring Consortium (EIM) and PGD Consortium. The EIM group, under the chairmanship of Markus Kupka, 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 in 1997.
- Data collected for 2011 has now been published in *Human Reproduction*; preliminary data for 2012 were presented in Lisbon, and data for 2013, which will be the first to use a new online data collection system, has a deadline of 31 October 2015. Online data collection 'will probably speed up the process by six months,' said the Chairman.
- Data reported for 2011 (from 1034 reporting clinics) indicate that the number of frozen cycles is slowly reaching that of fresh cycles (120,032 FER vs 137,621 fresh), with pregnancy rates from FER rising from 14.1% in 1997 to 21.4% in 2011. The majority of transfers are with two embryos, while SET continues to rise (to now almost 30% of all cycles). Multiple delivery rates continue to decline, while pregnancy rates increase (now at 32.1%, from 26% in 1997).
- Data XIII (for 2010) from the PGD Consortium has now been published in *Human Reproduction*, and data collections XV and XVI (for 2011 and 2012) are ready in preliminary form. Data XVI (2013) will be the first to use an online collection system introduced in Lisbon and planned to go live in autumn 2015.

ESTEEM trial

- The ESHRE Study into The Evaluation of oocyte 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, and presently some 244 patients have been randomised (171 patients randomised at June 2014). The target, said the Chairman, is 560 cycles. Professor Karen Sermon (UZ Brussels) has been appointed as a new chairman of the steering group, and the estimated completion date has now been extended to the end of 2016.

Other studies

- The TROPHY study, part funded by ESHRE, is a multicentre

ESHRE's new Executive Committee for 2015-2017: 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).



randomised study of pre-IVF outpatient hysteroscopy in women with recurrent IVF failure, and in its final stages of preparation (for submission to the *New England Journal of Medicine*).

- A consensus on the diagnosis of female genital tract anomalies, supported by ESHRE and the European Society for Gynaecological Endoscopy, is in its final steps before publication in the ESHRE pages of *Human Reproduction* and *Gynaecological Surgery*.

ESHRE research grant

- The Chairman described response to ESHRE's research grant scheme as 'remarkable', with 259 applications. The first grant was awarded to a joint UK/Italy project to prevent ovarian damage from chemotherapy. The winning co-ordinator was Professor Norah Spears from Edinburgh. The next award will be made in 2016, with a call for proposals on the ESHRE website in February 2016. High ranking proposals will be assessed over two rounds.

Guidelines

- Guidelines on the *Management of women with endometriosis* were published in 2013, and on *Routine psychosocial care and medically assisted reproduction* in April 2014 (with full text available on the ESHRE website). A summary of the endometriosis guidelines has been submitted to *Human Reproduction* for publication, while a patient information booklet is in preparation.

- Three other guidelines are in development: on premature ovarian insufficiency; recurrent miscarriage; and as revised guidelines for good practice in IVF laboratories.

ESHRE accreditation and certification

- Certification is now available to ESHRE members in embryology, reproductive endoscopy, and fertility nursing.
 - By the end of 2014 the cumulative total of certified clinical embryologists was 1100 (with 643 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 2014 five candidates applied and four passed at level 1; eight candidates from 11 applicants were successful in the level 2 exam.

- 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

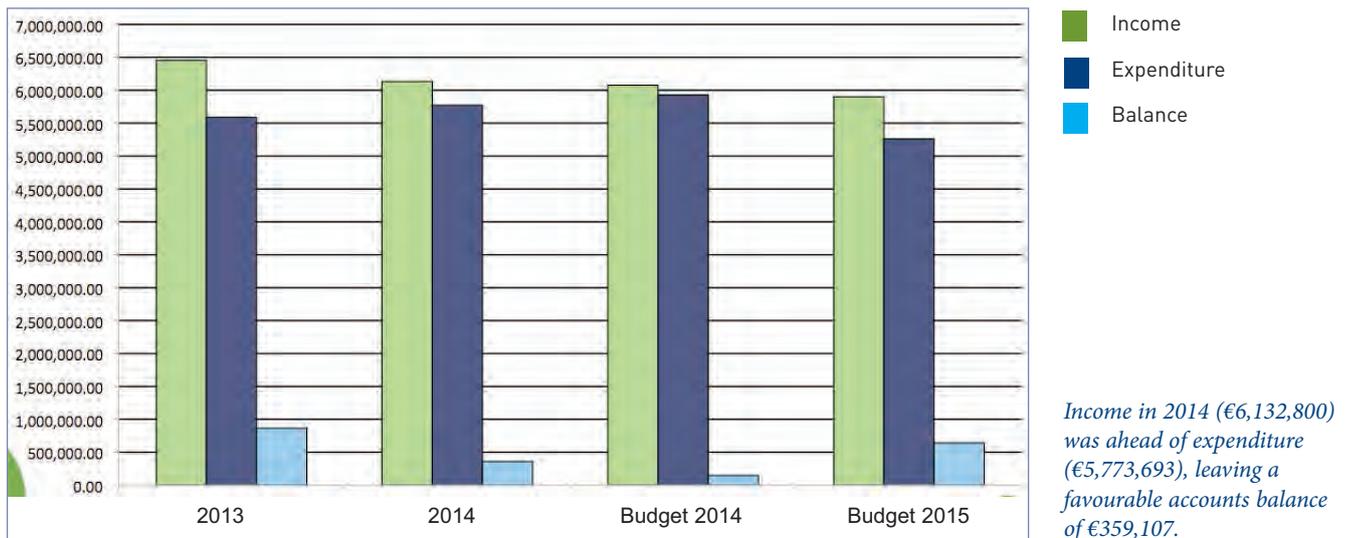
- Elections for co-ordinators and deputies have been held, and new steering committees are now in place. The Chairman advised that updates and information are available on the ESHRE website.

5. ESHRE journals

- Speaking on behalf of the Publications Sub-committee, Hans Evers, Editor-in-Chief of *Human Reproduction*, reported that 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.

- Evers reported that print subscriptions to all OUP journals were on the decline, from 20% in 2013 to an estimated 15% in 2015. Declines in print subscriptions are most apparent in UK, USA, Germany and Japan. This shift, said Evers, has implications: that the online version is now the version of record, and that the main perspective is now 'web, mobile, tablet and iPhone'. Amid considerations of open access, Evers reminded the meeting that Oxford Open (including the ESHRE journals) can provide immediate full open access if required, and free access to all after 12 months.

- Evers, who paid tribute to his fellow editors Chris Barratt and Felice Petraglia, emphasised that 'peer review is at the core of our business', and pointed out that, from 2000+ papers submitted to *Human Reproduction* each year, the average paper had five authors, and required the expertise of five reviewers and editors.



6. Paramedical group

- Helen Kendrew, Chair of the Paramedical Board, reminded the AAM that paramedical members comprise nurses, midwives, lab technicians (the largest group), counsellors and psychologists, and clinical embryologists up to BSc level.
- Helen paid tribute to Jolienke Schoonenberg-Pomper, who has now stepped down from the Board, and welcomed Valerie de Blanchet as a new member. Jolienke will continue as Chair of the certification steering committee.
- The first exam in ESHRE's nurse/midwife certification programme took place in Lisbon, with 63 sitting was described as a 'tough but fair' test.

7. Financial report

- The Chairman presented the balance sheet (income and expenditure) for 2013/14 and the budget for 2014/15. Income in 2014 (6,132,800 euro) was ahead of expenditure (5,773,693 euro), leaving a favourable balance of 359,107 euro. Expenditure in 2014 was slightly higher than forecast in the budget, which, said the Chairman, was explained by downpayments for the Annual Meeting in Munich. A budget similarly constructed to 2014 - to provide a positive balance - has been set for 2015.
- The Annual Meeting continues by far to provide the Society's greatest source of income (69%) and expenditure (53%). Educational activities are the major source of SIG expenditure.
- The 2014 value of ESHRE's assets in capital and reserves was put at 12,452,737 euro.
- The financial report for the year ending 31 December 2014 and the budget for 2015 were approved by the members.

8. Executive Committee

- Nominal changes to the membership of the Executive Committee were unanimously approved by the membership. They were:
- Juha Tapanainen (FI) stepped down as Chairman to become immediate Past Chairman, Kersti Lundin (SE) became the new Chairman of ESHRE, and Roy Farquharson (GB) the new Chairman Elect.



Anna Veiga stepped down as Past Chairman and was thanked for ten years of tireless work for ESHRE.

- Stepping down from the Executive Committee after two two-year terms in office were Carlos Calhaz-Jorge (PT), Jacques de Mouzon (FR), Anis Feki (CH), Nils Lambalk (NL), and Cristina Magli (IT). Stepping down as ex-officio members were Timur Gurgan (TR) and Anna Veiga (ES, as Past Chairman). All were thanked for their tireless work and commitment, and Anna Veiga for a 'very active' period in office of ten years.
- Continuing for a second two-year term as members of the Executive Committee were Petra De Sutter (BE), Grigoris Grimbizis (GR), Tatjana Motrenko (ME), Andres Salumets (EE), and Georg Griesinger (DE).
- New members, whose nominations were ratified by the AAM, were Basak Balaban (TR), Mariette Goddijn (NL), Borut Kovacic (SI), Nicholas Macklon (GB) and Rita Vassena (ES). Cristina Magli (IT) joins the Executive Committee as an ex-officio member (as Chair of the SIG and TF Committee).

9. Election of honorary members for 2016

- The two nominees proposed by the Executive Committee for honorary membership in 2016 were Professor Henry Leese, from York Medical School, UK, and Markku Seppälä, Emeritus Professor at the University of Helsinki Both nominations were ratified by the AAM.

10. Any other business

- Two matters were raised from the floor. The first, with a view towards developing countries, urged ESHRE to provide more basic hands-on training.
- The second, from the Editor-in-Chief of *Human Reproduction*, sought confirmation that ESHRE-sponsored studies should be published in ESHRE journals. The Chairman confirmed that this is indeed ESHRE's position, but noted that in the case of the TROPHY study ESHRE was not the sole sponsor. This matter, said the Chairman, had been discussed by the Executive Committee, with concession to the wishes of other sponsors.
- The next Annual Assembly will be on 5 July 2016 in Helsinki at 18.00.

ESHRE's role in speciality training rests on three pillars

● ESHRE's responsibilities for subspecialty training set out in new F&S review

ESHRE's place in subspecialty training in Europe has been summarised and clarified in an invited report recently published in *Fertility and Sterility*.¹ The report brings together the three cornerstones of ESHRE's role: accreditation of training centres; development of a subspecialty syllabus for reproductive medicine; and, with an eye to the future, accreditation of individual specialists through its own certification schemes.

These responsibilities are met independently by ESHRE (as in the embryology or nursing certification programmes) or in collaborations (as in training centre accreditation with European Board and College of Obstetrics and Gynaecology (EBCOG)).

The report makes clear that, while ESHRE has been the responsible agency for accreditation of subspecialty training alongside EBCOG, both organisations are ultimately responsible to the Union of Medical Specialties (UEMS), which represents the EU governing body for medical education. ESHRE is registered



ESHRE's Chairman Elect Roy Farquharson, instrumental in developing ESHRE's partnership with EBCOG.

with UEMS as the specialist education provider for training in reproductive medicine via EBCOG.

ESHRE's Chairman Elect Roy Farquharson, who has recently been ESHRE's liaison with EBCOG, hopes that

two ESHRE proposals (on basic training in infertility and on advances in reproductive surgery) will prove attractive to EBCOG's 2016 congress programme in Istanbul.

At the end of their F&S report, the ESHRE authors speculate that 'encouraging centres to apply for training accreditation may well prove to be an increasingly attractive option as educational needs across Europe become integrated and formalized through UEMS. ESHRE holds the view that accredited centers for training are beacons of excellence that often go hand in hand with high-quality research.'

This year, accreditation requests for specialist training have been approved for Milan Humanitas centre, Thessaloniki, VUB Brussels and Leuven, with future enquiries anticipated from Barcelona and Brno.

1. Calhaz-Jorge C, Feki A, Farquharson R. European view of subspecialty training on behalf of the European Society of Human Reproduction and Embryology (ESHRE). *Fertil Steril* 2015; 104: 8-11

IVF bill finally becomes law in Poland

After years of agonising and in the face of persistent opposition from the Catholic church, the Polish Parliament has finally approved a bill which will provide statutory regulation of IVF. Although IVF has been privately available in Poland for 25 years, it has so far remained largely unregulated, with Poland the only EU country without some form of legislation.

In 2013, in anticipation of moves towards legislation, the government announced measures by which 15,000 couples in a three-year programme would receive state funding for IVF. Now, however, in a vote convincingly won in Parliament all couples will be eligible for state-funded IVF if other treatments have proved unsuccessful in the previous 12 months.

The bill, which was signed into law by Poland's outgoing President in July after the required approval of the Senate, will allow fertilisation of up to six oocytes per couple, and any unused embryos may be used by other women after 20 years, but cannot be destroyed. The bill will also make reproductive cloning and manipulation of DNA illegal, as well as any technique of gender selection.

Despite the President and Parliament's approvals, opposition from the Catholic church remained strong, with local bishops saying in a statement they were 'deeply disappointed and pained' by the new law. However, in a survey run by Warsaw's government-run Public Opinion Research Centre more than three-quarters of Poles said they were in favour of IVF, with 17% against, a position said to be unchanged for more than 20 years.

One, two or three kids?

Among the highlight papers published online by *Human Reproduction* this summer is the 'first' mathematical model of when to start a family. Crunching 300 years of fertility data, Rotterdam researchers have calculated the most likely female age at which couples should start a one, two or three-child family with or without IVF.

The model incorporates studies on natural fertility collected over 300 years up to the 1970s, which includes data on 58,000 women.

A family of three children would mean getting started at 23 years for a 90% chance of success without IVF, and at 28 years with IVF. For a 90% chance of having a one-child family, make a start at 32 years without IVF, and 35 years with IVF.

'We have tried to fill a missing link in the decision-making process,' said investigator Dick Habbema.

Habbema JD, Eijkemans MJ, Leridon H, Te Velde ER. Realizing a desired family size: when should couples start? *Hum Reprod* 2015 Jul 15. pii: dev148.

Updates to regulation and reimbursement in Europe

There have been one or two updates to our regulation and reimbursement chart published in the May issue of *Focus on Reproduction*. Details were supplied by members of the Committee of National Representatives.

Switzerland

A referendum held in Switzerland in June resulted in an overwhelming vote in favour of PGD and PGS. The referendum vote - with 62% in support - would thus amend the existing constitution to include the two previously outlawed procedures. The referendum would also remove restrictions on the number of embryos generated in an IVF cycle, which have so far been limited to those that 'can be immediately implanted'. The vote, if confirmed and incorporated into the constitution, would thus make embryo freezing legal and encourage single embryo transfer.

'So we should be allowed to culture more than three 2PN zygotes, to freeze

embryos and perform PGD and PGS,' says Felix Roth, CNR member for Switzerland. 'However, according to Swiss law one has the right to challenge such a vote - within a period of 100 days and with 50,000 signatures of those who didn't accept the referendum result. This deadline is 22nd September.' If such a challenge is accepted by the government, a second popular vote would be required in Spring 2016.

In this case, says Roth, the earliest date for any modified Swiss legislation would be 2017. However, if the challenge fails (through insufficient signatures, for example), legislation allowing embryo freezing, PGD and PGS could be effective by Spring 2016.

France

CNR member Pierre Boyer has clarified the legal position of PGD and PGS in France, which in our table in May was listed as 'not allowed'. PGS is indeed not allowed, but PGD - as for the same

indications as prenatal diagnosis - is allowed in a small number of specialist centres (Paris-Clamart, Montpellier, Strasbourg and recently Nantes, all of them university-based public centres). Boyer also notes that full social reimbursement for IVF and ICSI is only available to women under 43 years.

Hungary

There was also some confusion over our listing that PGS is not allowed in Hungary. As far as we can tell from information supplied by CNR member Peter Kovacs, 'PGS is still considered experimental by the Human Reproduction Committee and could only be practised if the clinic received an approval for it [from] the Human Reproduction Committee . . . PGS is not allowed for routine, everyday use.' This position was confirmed as correct by Professor György Kosztolanyi, President of the Hungarian National Human Reproduction Committee.

Howard Jones, 1910-2015

The death of Howard Jones at the age of 104 marked the close of a remarkable chapter in the history of IVF, for Howard was a pioneer of IVF in the USA in much the same way as was his friend and colleague Robert Edwards in Britain. Yet Howard had only come into IVF following his official retirement at the age of 65, setting up the USA's first IVF programme with his wife Georgeanna in 1980.

Leaving Johns Hopkins in Baltimore in 1978, they were moving to a new division of reproductive endocrinology at the Eastern Virginia Medical School in Norfolk, Virginia, on the very day of Louise Brown's birth in England. Invited to comment on the news by a local journalist, and asked what it would take to have a test-tube baby in the USA, Howard replied in his characteristic laconic way, 'Just a little money'. That proved enough to set the Norfolk programme in motion and, after a frustrating year pursuing pregnancies in a natural cycle, Norfolk finally achieved its first success in its 13th patient to receive gonadotrophins. Delivery by Caesarean section followed on 28th December 1981.

Howard and Georgeanna were frequent and welcome visitors to ESHRE's annual meetings, and in 1998 in Gothenburg were jointly awarded honorary membership of ESHRE. Like Bob Edwards, Howard was ever sensitive to the ethical issues raised by assisted reproduction, and their initial work in Norfolk had also been delayed by public protest. Howard was a founding father of the ASRM's ethics



Receiving joint honorary membership of ESHRE at the 1998 Annual Meeting in Gothenburg.

committee and, even at the age of 102, self-published a book on the religious, legal and bioethical implications of ART for defining 'personhood'. His last book appeared just a few months ago, a memoir of the early days of IVF in the USA.

Today, the eponymous Jones Institute for Reproductive Medicine in Norfolk is named in honour of Howard and Georgeanna. Together, they demonstrated the validity of ovarian stimulation with hMG in what would become the forerunner of today's universal low dose protocols.

The Joneses published, either individually or together, more than 400 peer-reviewed papers and received nine honorary degrees. Georgeanna Jones died in 2005.

Frozen embryo transfer and egg donation both heading upwards

- European twin delivery rate falls to 17.3%
- Egg donation pregnancy rate at 52%

The number of frozen embryo transfers continues to rise in European clinics, with preliminary data collected by ESHRE's European IVF Monitoring (EIM) Consortium for 2012 and reported in Lisbon by EIM Chairman Markus Kupka recording almost 140,000 FER cycles, an increase of around 20,000 cycles from 2011. The rise in numbers, Kupka added, has been accompanied by a notable rise in success rates over the past 16 years of data collection: pregnancy rate per thawing was just 14.1% in 1997, the first year of EIM activity, which by 2012 had almost doubled to 23.5%.

Also seeing a remarkable rise in pregnancy rate was egg donation, which, said Kupka, 'is doing really well'.



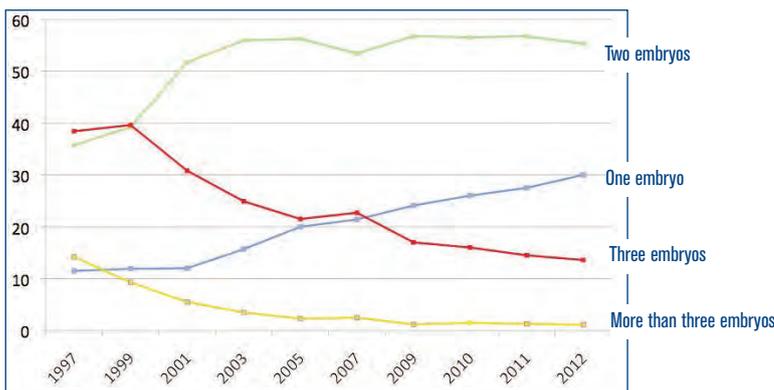
EIM Chairman Markus Kupka: success rates 'generally stable since 2008'.

Pregnancy rate with fresh donations was already 31% in 2001, yet had reached 52% in the latest 2012 analysis. 'I can't really explain the results,' said Kupka, but they certainly begin to reflect trends now evident in the USA - that more older patients are being treated with egg donation (and not IVF) and that success rates reflect more the age of the egg than the age of the patient. European delivery rates - from 21,000 fresh and 9500 egg donation cycles monitored - were 22% frozen and 31% fresh. Donation cycles from frozen oocytes achieved a 26% delivery rate.

Overall pregnancy rates in 2012 continued to show marked variation between countries, with high usage countries such as France, Spain, UK and Italy all recording rates between 24 and 34%. But generally, said Kupka, 'rates have been stable since 2008.' Also stable appear the rates of distribution between IVF and ICSI. Uptake of ICSI took off at the turn of the century and overtook IVF usage in 2002. Between then and 2008 ICSI use was in a steep upward curve, but thereafter usage appears to have levelled off, with ICSI use stable at around two-thirds of all cycles, and IVF at one-third. This rate too, however, also varies markedly between countries, with low utility countries (for example, Denmark, Finland, Sweden, Norway and Ireland) using ICSI far less than high utility countries (Belgium, Germany, Czech Republic, Greece, Italy, Poland and Spain).

The 2012 EIM figures continue to show a difference in outcome between IVF and ICSI and, despite the

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



ALMOST 80% OF EUROPEAN CYCLES MONITORED

ESHRE's EIM Consortium has now been active for over 16 years and has reached the remarkable data milestone of more than 1.16 million babies recorded. The Consortium is presently evaluating around 640,000 cycles a year in an ever escalating total of European ART activity, which, Kupka said, now represents almost 80% of total activity. In 1997, the first year of EIM analysis, just 482 clinics in 18 countries were represented in 203,225 cycles of IVF and ICSI; in 2012, the year described provisionally in Lisbon, 1093 clinics in 34 countries were represented in the data collection.

	1997	2001	2008	2009	2011	2012
IVF	21.9%	25.1%	28.5%	28.8%	29.1%	29.4%
ICSI	24.3%	26.2%	28.7%	28.7%	26.8%	27.7%
FER	14.1%	14.3%	19.3%	21.0%	21.4%	23.5%
ED	-	30.8%	38.3%	42.2%	47.6%	51.7%

Pregnancy rates per aspiration 1997-2012.

TOTAL OF WORLD'S IVF BABIES NOW SOARS BEYOND 6 MILLION

Hold those abstracts. Easy on the front pages. For in just three years the total of IVF babies throughout the world has risen from a remarkable 5 million to well over 6 million, according to the USA's David Adamson presenting global results for 2011 on behalf of ICMART. His figures were based on an estimated 1.6 million cycles now being performed each year and the delivery of around 430,000 babies.

Of course, Adamson reported 'huge differences' in availability, practice and results, but was confident ('almost certain')

that China is performing more cycles than any other country - including Japan, which, with 268,255 cycles recorded in 2011, ranked by far as the world's most prolific reported IVF nation. Adamson said that even the number of clinics in China ran into thousands and it was likely that they now represent the major portion of global activity. 'Asia,' added Adamson, 'has caught up and passed all other regions.' The USA recorded 142,000 cycles in 2011, with Europe's biggest nations, France and Spain, on 72,000 and 88,000 respectively.



uptake trends, favouring IVF in the past three years.

However, Kupka's remarks of greatest emphasis were concentrated on the numbers of embryos transferred, which yet again showed an increase in single embryo transfers. SET has now reached an overall uptake of 30%, while DET remains stable at around 55%. Three embryo transfer also continues its decline, and is now just 14% of all transfers. A few countries in eastern Europe (Lithuania, Moldova, Serbia and Montenegro) still have the highest rates of three embryo transfer.

Nevertheless, the rate of triplet deliveries remains below 1%, and the overall twin delivery rate

throughout Europe fell to a record low of 17.3, with singletons at an all-time high of 81.9%. 'This is good news,' said Kupka, 'and I'm very happy to report it.'

Europe's twin rate, added Kupka, remains much lower than that recorded by the CDC in the USA. There, twins account for 26% of all ART pregnancies and deliveries, with singleton live births at 72%.

Kupka was also upbeat about the introduction of online data collection this year which should provide a digital data connection between the clinic, national ART registries, and the EIM hub. The EIM's next data collection - for 2013 - will be gathered electronically.

CARLOS CALHAZ-JORGE SELECTED AS NEW CHAIRMAN OF THE EIM CONSORTIUM

The term of office of Markus Kupka as Chairman of the EIM Steering Committee came to an end in Lisbon. He will be replaced by the Portuguese gynaecologist Carlos Calhaz-Jorge, a long-standing member of the Steering Committee. He is pictured here standing in the foreground with the outgoing Chairman.

Other members of the EIM Consortium pictured are, front row from left, Tanya Milachich (BU), Janos Urbancsek (HU), Nebojsa Radunovic (SW), Markus Kupka (DE), Carlos Calhaz-Jorge (PT), Jacques De Mouzon (FR), Vladislav



Korsak (RU); second row, Roberto De Luca (IT), Ladislav Marsik (SK), Giulia Scaravelli (It), Tatjana Motrenko (MO), Valeria Godunova (LV), Giedre Belo Lopez (LT), Jean Calleja-Agius (MT), Veerle Goossens (ESHRE); third row, Dejan Ljiljak (CR), Vyacheslav Lokshin (KZ), Karin Erb (DK), Anna Pia Ferraretti (IT), Christine Wyns (BE), Elena Petrovskaya (BY), Ioana Rugescu (RO); fourth row, Deniss Soritsa (EE), Bogdan Doroftei (RO), Mykola Gryshchenko (UK), Fernando Prados (ES), Michael Pelekanos (CY), Irma Virant-Klum (SI); and back row, Sandra Zamora (ES), Christian De Geyter (CH), José Antonio Castilla (ES), Dominique Royere (FR), Jesper Smeenk (NL).

The first double-digit impact factor in O&G

- *Human Reproduction Update* impact factor leaps from 8.657 to 10.165
- All three ESHRE titles set their mark of quality in latest impact factor scores

For the first time ever a journal from the fields of Reproductive Biology and Obstetrics & Gynaecology has passed into the exalted realm of double-digit impact factor to join a catalogue of leading journals in the mainstreams of science and medicine. *Human Reproduction Update* has long held its place at the head of both categories, but now, with an impact factor of 10.165, its influence and status have taken a monumental leap forward. As a review journal, *Update* is now in a league of its own.

‘The new impact factor fulfils the dream of any journal in the field of O&G,’ said *Update*’s Editor-in-Chief Felice Petraglia. ‘A truly historical achievement. But it’s a team effort, and all my thanks must go to the Deputy and Associate Editors, to the previous Editors-in-Chief Bart Fauser and John Collins, and to OUP for their great editorial management. We won’t stop here, and will continue to work for further growth of the journal. But right now ESHRE and OUP can be very proud - and we must think back to Robert Edwards for his vision in founding the journal.’

Another of ESHRE’s three titles also increased its impact factor from last year. *Molecular Human Reproduction* rose from 3.483 to 3.747, which included for the first time listing in the category of O&G. *Human Reproduction* itself at 4.569 was very similar to 2014, but just fell back in the category ranking behind *Fertility and Sterility* in Reproductive Biology and behind the ‘green journal’ *Obstetrics and Gynecology* and the *American Journal of Obstetrics & Gynecology* in the O&G category.

‘HR is no longer number 2 and that hurts,’ said Editor-in-Chief Hans Evers, ‘even though the impact factor range between 4.5 and 5.2 seems very volatile. I have congratulated the editors of *F&S*. *Update*’s 10+ impact factor is fantastic, however, under any circumstances. The jewel in our crown!’

‘Now, we’ll continue our efforts to get *Human Reproduction*’s impact factor over 5. What we need is less research, better research, and research performed for the right reasons. I’m convinced that we are on the right track given our five-year impact factor (4.729) and other indices, but the time-lag for impact factor improvement is annoyingly long. These latest figures reflect our attempts at improvement in 2012 and 2013. Weeding out more poor submissions and ruling in good ones will remain our target for 2015 and beyond - as well as clarifying the distinction between our scope (reproductive medicine) and that of *MHR* (reproductive biology).’



Editors Felice Petraglia (*Update*) and Hans Evers (*Human Reproduction*), committed to further improvements.

Reproductive biology			
Title	Total cites	5-yr Imp Factor	Impact Factor
Human Reproduction Update	6625	10.818	10.165
Fertil Steril	31236	4.255	4.59
Human Reproduction	28113	4.729	4.569
Molecular Human Reprod	5078	3.956	3.747
Biol Reprod	21382	3.784	3.318
Reprod Toxicol	4980	3.383	3.227
Reproduction	7394	3.707	3.174
Reprod Biomed Online	5335	2.709	3.015
J Reprod Immunol	2512	3.012	2.815
Placenta	6754	3.141	2.71

Obstetrics and gynaecology			
Title	Total cites	5-yr Imp Factor	Impact Factor
Human Reproduction Update	6625	10.818	10.165
Obstet Gynecol	26836	5.098	5.175
Am J Obstet Gynecol	33839	4.142	4.704
Fertil Steril	31236	4.255	4.59
Human Reproduction	28113	4.729	4.569
Ultrasound Obstet Gynecol	9248	3.584	3.853
Gynecol Oncol	19159	3.843	3.774
Molecular Human Reprod	5078	3.956	3.747
BJOG	13139	3.726	3.448
Menopause	4260	3.159	3.361

Embryologist Cristina Magli, whose lab in Bologna was among the first to test the potential of PGS, will be the next chair of ESHRE's SIG and Task Force Committee. Here, she talks to Focus on Reproduction about PGS and the impact on embryology of legislation in Italy . . . and about plans for ESHRE's SIGs and Task Forces.



Carrying on regardless

PGS? I'm still a believer But not every technique is good for everyone. Not every approach suits every patient.

FoR: You have been lab director with Gianaroli's group in Bologna for many years, and one of the first to provide some proof of principle for embryo selection by PGS. In 2004 your programme was brought to an abrupt halt when the Italian parliament passed its infamous Law 40. What effect did that have on you?

Magli: It was dramatic. Everything changed. The restrictions were so many, it was as if everything you'd studied for so many years, everything you'd gained in experience counted

for nothing. Our hands were tied and we were now being told what to do. It was extremely stressful, very depressing.

And have those feelings persisted?

It all happened so quickly, and our reactions were very intense to begin with. We were left wondering what to do and how to react. So we had to really concentrate our thoughts and think how to redirect our efforts. Our first thought was to concentrate on the oocyte - oocyte physiology, morphology and chromosome analysis of the first polar body.

So it was a heavy blow?

Yes, at the time PGS was a kind of mission for us. I always believed it would work, even when we began in 1993, when no-one really knew what it was. And to be honest I still believe it works, provided it's done in the proper way. But then all those opportunities were taken away from us. We couldn't work on the embryo, so we concentrated on the first polar body as an alternative. We couldn't work on the second polar body because it's extruded after fertilisation. Don't forget that Law 40 also affected our PGD for single gene disorders, and that was very difficult too, having to tell our patients, sorry, we cannot help you. We were also not allowed to grow more than three embryos, so we had to look at oocyte freezing as well.

So to continue your PGS and PGD work, you had to go abroad. How did that work?

We got most help from Stephan Gordts and Rudi Campo in Leuven and that's where we treated most of our PGS and PGD patients. We did a lot of cycles there and Leuven really collaborated with us. I passed on to them all I knew about PGS and PGD, so it was a real exchange. We also set up a centre in Lugano, in the Italian quarter of Switzerland. PGD and PGS on embryos were still not allowed in Switzerland, but it

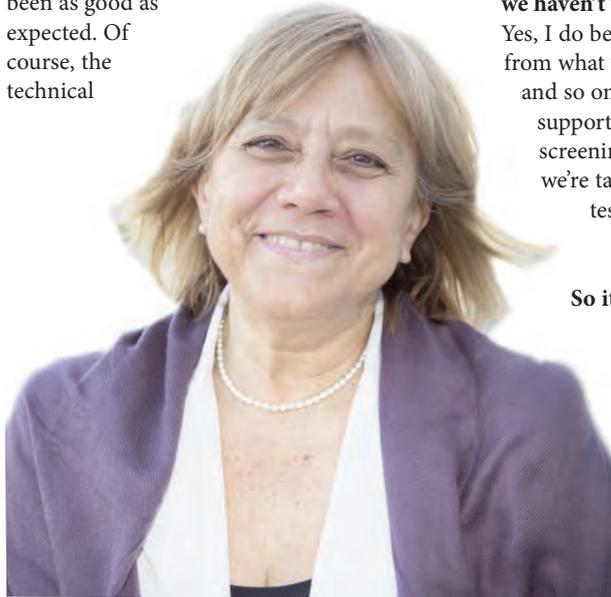
was possible to inseminate every oocyte and to analyse the polar bodies. In Italy we couldn't generate more than three embryos, and all had to be transferred. At least in Lugano we could bypass that restriction.

And what's the situation in Italy today?

We are just about back to where we were before Law 40, although we are still struggling with some points - for example, no compensation or reimbursement whatsoever can be given to gamete donors. And research on embryos is still forbidden. Considering how many embryos are declared 'abandoned', it seems strange that our politicians and legislators care so much about embryos when the legitimate owners - the couple - seem to care less once their purpose in one way or another has been fulfilled. If properly used, they could represent an unbelievable source of scientific information.

You were one of the first groups to work on PGS. Do you believe there's been much genuine progress in the past 20 years, or just a lot of work and not much progress? A lot of people have been disappointed in PGS - do you share that disappointment?

I think there has been a lot of progress and this has provided much knowledge on meiotic and mitotic processes. Even when we began, the techniques were difficult. We studied a lot, tried to gain experience. But it wasn't even easy to do the chromosome and genetic analysis. I think the problems began to occur when everything became available off the shelf. Using a laser for the biopsy was very easy, but it was also easy to cause damage. And I think this is one reason why results in PGS have not been as good as expected. Of course, the technical



developments have been huge - we can now analyse all the chromosomes, for example.

So no problems in PGS?

The biggest limitation I see is the difficulty of arranging properly done studies. This is for several reasons. One is the cost of procedures, another the difficulty of recruiting patients. The more we advance our techniques, the less people want to be randomised.

Yes, it's an interesting paradox - that the more we need to test these new developments, the less patients want to be in a control group. Do you think we will ever have randomised trials big enough to provide a strong answer?

From what I see it's going to be really difficult. We have problems recruiting patients for the ESTEEM trial of polar body analysis, so that's not a promising example.

So those recent PGS studies we've seen in the USA, do you think they're as good as we're going to get?

Those studies are not perfect, because they're in young good prognosis patients. But even in these patients, if there is a difference then there is a difference. So I don't think this is a real drawback. Studies with a limited number of cycles are a problem, and I know that from the randomisation perspective we can be critical here. But all of these studies, however small, do provide valuable information. Could we do them better? Yes, we could, but even the best planned study will have some weak points.

So basically, Cristina, you're still a believer? You believe in the concept of PGS, even if we haven't yet perfected the technology?

Yes, I do believe - biologically speaking and from what we know about meiosis, mitosis and so on. I think there is very big rational support for embryo screening. Maybe screening is not the right word when we're talking about embryo selection - testing would be more suitable. Perhaps PGT instead of PGS?

So it's reasonable for clinics to offer PGS to their patients on the assumption that it may well improve birth rates or provide a better opportunity of single embryo transfer?

Yes, if presented with honesty I think it is fair enough. We know what evidence is available, but unfortunately we also know there are some groups who tend

to over-emphasise the advantages. Money is involved, of course, and this disturbs me a lot. I work in a private centre and I don't like to hear that we are over-treating patients. PGS in our centre doesn't even cover its costs. The fact is that not every technique is good for everybody, not every approach suits every patient, so we need to customise a bit more and a bit better.

Now, your new role with ESHRE. You're about to take on responsibility for ESHRE's Special Interest Groups and Task Forces.

Yes, I find it very exciting - although my own excitement with ESHRE began when I got involved with the SIG Embryology in the late 1990s, when the SIG had been revitalised by Luca Gianaroli. Looking back, I'm not sure if I liked the idea of a special group for embryologists being run by a clinician, but that was the situation and I have to say that he is a very special 'clinician'. Now, I am very proud to say that, because, as I tried to help Luca with his responsibilities, so I learned a lot from him and actually became more and more interested - and I ended up as Co-ordinator in 2009. It was very exciting for me when the SIG Embryology became ESHRE's largest specialty group. I couldn't avoid thinking of the legacy of Bob Edwards and how strongly he had fought to have the word 'embryology' included in the name of the Society.

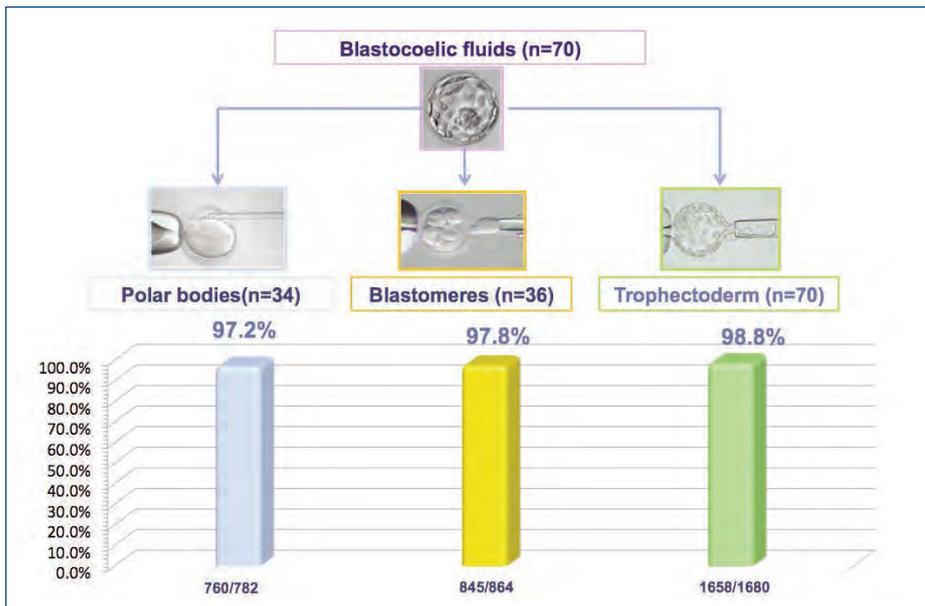
So why do you think embryology became so important in ESHRE?

Many reasons, but recently the certification programme has had a big impact. It is unbelievable that such an important profession does not have an official recognition in the great majority of states. But the *Atlas* and good practice guidelines have also been very important. The good laboratory practice guidelines were the first guidelines ever produced by ESHRE.

But hasn't there also been a big shift of interest to the lab because of the demands of single embryo transfer? Embryo selection has become more and more important.

Yes, without doubt. There have been so many advances in the past few years - much more in the lab than in the clinic. Every time I leave an ESHRE annual meeting I think of how exciting it has been. We don't have big stories every year - ICSI, vitrification, blastocysts - but we have so many advances, exchanges of opinion, new data.

Do you think the mix of pre-congress courses, Campus events, training for



A new PGS technique of 'blastocentesis' has been developed and tested by Magli's lab in Bologna, which, she says, could offer an alternative to conventional biopsy for all PGS procedures. The technique is simple and less invasive than current biopsy methods, and, because no single cell is removed from the embryo, more ethically acceptable. Data presented in Lisbon showed that blastocoelic fluid aspirated from preimplantation embryos demonstrated very high levels of chromosome and ploidy concordance when confirmed by trophoctoderm analysis, suggesting that blastocentesis is a highly reliable source of DNA for PGS. This same accuracy was also evident in the detection of segmental abnormalities, which was confirmed in every case analysed. Represented above are results from initial studies to measure the concordance of blastocoelic fluid with chromosomal status as measured by polar body, blastomere and trophoctoderm biolpsy.

certification is the right educational approach for ESHRE? Any changes you might wish to make?

This for sure is the right way to go. But we hope to organise the SIGs and Task Forces not with a single chairman but with a small board. So I will be the chair of the SIG Committee but alongside there will be the past chair and the chair elect. The educational activities of ESHRE are so important that one person is not really enough. So there should be more ideas, and better judgement when difficult situations arise. This is the starting-point. Next, we want each of the SIG co-ordinators to take a very active role that goes beyond organising just one course per year. It's a way of keeping ESHRE alive - we need new ideas and initiatives.

And the Task Forces? Have they been a disappointment?

Well, I think they have been neglected somewhat, left to get on with their jobs by themselves. But remember that the Task

Forces are quite different from the SIGs. They have a mission, and a question to answer. So there's a limit to their duration. They have a task to fulfil, and now we need to check if that task has been fulfilled or not. We need to consider the time a Task Force has been active and what it can still achieve.

And ESHRE overall . . . the journals, the Annual Meeting . . . it seems that there is a huge momentum behind the Society now. Do you sense that too?

Absolutely, that for sure. I think the Society is at a really booming time in its history, and I've no clear idea if that upward movement will continue or level off. And this is one reason why I'm trying to encourage new inspiration in the SIGs and Task Forces. ESHRE can't rely on one or a few people as happened in the past. There has to be an exchange between the membership as represented by the SIGs and the executive of the Society, and that's what I'll be trying to encourage.

PROUST QUESTIONNAIRE*

● **Your greatest personal strength?**
I'm an easy-going person, and very persistent

● **And your greatest weakness?**
Sometimes I put off doing things which I know should be done right away

● **What's your greatest extravagance?**
Going to football games



● **Which ability would you most like to have?**
Quick reactions

● **What trait do you most dislike in others?**
Insincerity - and social climbing

● **Which phrases do you most overuse?**
'I think' . . . 'No problem' . . .

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

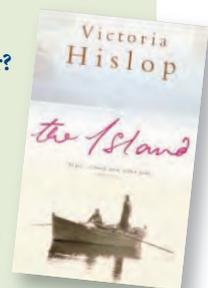
● **Where did you spend your latest vacation?**
Puerto Morelo, Cancun, Mexico

● **What is your favorite pastime?**
Anything to do with the sea - swimming, sailing . . .

● **What was the last book you read?**
The Island by Victoria Hislop

● **And your favourite writer?**
Nicholas Evans

● **The last film you saw?**
Maleficent



● **San Pellegrino or chianti?**
Chianti

● **Tea or coffee??**
Coffee

● **Do you have a personal motto?**
Never give up

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



The maturity of reproductive medicine ... as seen through the medical journals

The continuing rise in impact factor for our major journals in reproductive medicine reflects a new growth and maturity. High-class research, a new study suggests, requires high-impact journals.

A remarkable analysis of publications in reproductive medicine over the past ten years detects a maturity of clinical development which now renders its 'sub-specialty' status outdated and redundant.¹ Indeed, with the leading O&G journal now for the first time passing into the hallowed realm of double-digit impact factors, reproductive medicine can surely stand shoulder-to-shoulder alongside such established specialties as psychiatry, rheumatology and - dare we say it - cardiology. It was only four years ago that Europe's leading cardiology journal, the *European Heart Journal*, finally hauled its impact factor beyond the psychological barrier of 10.

Two of the three authors of this 'bibliometric' analysis are leading and much cited investigators themselves, and one of them, Bart Fauser, was identified as the most cited in a total of 4010 papers analysed. Fauser, a former editor-in-chief of *Human Reproduction Update* and soon-to-be editor of *Reproductive BioMedicine Online*, was followed in the citation pecking order (in all scientific areas) by Ricardo Azziz (with work in PCOS) and Paul Devroey, recently awarded honorary membership of ESHRE.

The number of published articles also spotlighted Devroey (n = 221), Wim Mol (184), and Antonio Pellicer (164), currently one of the two editors-in-chief of *Fertility and Sterility*. Fauser also led the citations in reproductive biology (5457), followed by Devroey (5263).

Markers of maturity

As a further marker of maturity, the analysis showed that the two Web of Science categories of O&G and Reproductive Biology were each dominated by journals in reproductive medicine, both in terms of impact factor and articles published. *Human Reproduction* ran the most articles in the ten years of analysis (980), followed by *Fertility and Sterility* (891). The first non-reproductive medicine journal, the *Journal of Clinical Endocrinology and Metabolism*, languished way behind with 288 articles, and the second, the *British Journal of Obstetrics and Gynaecology*, was even further back with just 77.

However, not every paper in the field was necessarily reserved for its most applicable journals. Around one-third of all high-ranking citations were in journals belonging to categories outside reproduction, such as

endocrinology or metabolism, genetics or immunology, and some of the best cited papers were to be found in such general titles as *The Lancet*, *New England Journal of Medicine* and *JAMA*. Let's not forget that the landmark paper from Fauser's own group on mild IVF turned up in *The Lancet*, and the much cited PGS trial of Mastenbroek et al in the *NEJM*. Even Devroey and Van Steirteghem sent their first announcement of an ICSI live birth to *The Lancet*, before reporting their subsequent studies in *Human Reproduction*. Can it be that the leading groups in reproductive medicine continue to save their best papers for those journals without affiliation but with high impact factors?

The evolution of keywords

The study also measured progress in the field with an analysis of keywords, and this marked a real shift of research interest in just a few years. The most important keywords with an upward trajectory - reflecting how the field in research continues to grow - involve areas such as ART (mainly IVF), pregnancy outcomes, and the future health of IVF children and mothers. 'It is laudable,' say the authors, 'that interest is shifting from merely developing novel infertility interventions toward more detailed analyses of the health implications for women and their offspring.'

Indeed, just a few years before, the recurring keywords had included infertility, pregnancy, and follicle stimulating hormone, yet those FSH battles seem now consigned to history, along with their big number trials in search of marginal gains. No wonder a press release from Merck issued just before the latest Annual Meeting of ESHRE said the company was 'going beyond drugs' to support improvements in ART! Joining FSH (and LH) on a downward keyword spiral was ICSI, no doubt, the authors propose, explained by its upgrade to 'accepted treatment'. PGD, they add, which might have been expected among the high rankers, has 'suffered from insufficient randomized studies, which has diminished interest'.

Judged on keywords, the most studied illness in reproduction is PCOS, a heterogeneous condition said to affect up to 10% of all women. No doubt it is the very heterogeneity of PCOS which explains its high citation scores and reflects an increasing awareness of its associations with many other health risks beyond

reproduction. The 2003 consensus report derived from the Rotterdam ESHRE/ASRM-sponsored PCOS workshop (the 'Rotterdam criteria') remains to this day the most cited article ever in *Human Reproduction*.

Who's been doing it?

The most cited groups working in reproductive medicine are to be found in the Netherlands (where IVF is universally available as a fully reimbursed treatment), Belgium (also largely reimbursed), Spain, USA and UK. However, a marked and emerging trend is an increase in collaborations, both nationally and internationally, which surely reflects the difficulty of staging single-centre trials today. The number one cited country (the Netherlands) mainly featured just four major centres with strong collaborations among them; in other countries, such as Belgium and Spain, one or two centres were mainly responsible for overall national performance. Elsewhere, as in the USA or UK, many different medium-sized centres were jointly responsible for their collective impact. The number of articles published as international collaborations doubled from 2003 to 2007, while domestic collaboration grew to a lesser extent - and thus decreased the articles signed without collaboration.

The most cited institutions in reproductive medicine were found to be Erasmus University Medical Center in Rotterdam (9006 citations), followed by the University Medical Center Utrecht (7108) and the Vrije Universiteit Brussels (6846). Other centres with highly cited collaborations were the Cleveland Clinic in Ohio, the Rigshospitalet in Copenhagen, and the Saint-Luc University clinic in Brussels.

The theme of this paper is the maturity of reproductive medicine and its elevated status as reflected in the medical journals. The authors acknowledge that the roots of this scientific maturity lay in the introductions of ICSI, PGD and cryopreservation, but that such landmark developments require 'high quality research and key publications'. The one, they suggest, cannot progress without the other. Now, in a catalogue of journals dedicated to reproductive science and medicine and dominating the fields of O&G and reproductive biology, those requirements seem at last to be fulfilled. Indeed, even the number of journals seems to be increasing, as surely is the number of studies performed and articles submitted. Fauser himself told *Focus on Reproduction*: 'We no longer have to be shy.' Moreover, with an impact factor passing for the first time into double-digits, the reproductive medicine journals can no longer be judged as merely sub-specialty journals. For they, like the discipline itself, seem now to have reached a new level of stature and of self-confidence.

Simon Brown
Focus on Reproduction

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BART FAUSER: 'WE NO LONGER HAVE TO BE SHY.'



What is artificial? Most of us would define conception through sexual intercourse as 'natural'. Conception with techniques such as IVF has long been described as 'assisted' . . . but 'artificial'? The idea has rarely been considered.

At the regulatory level, however, the latest European directives on advanced therapy medicinal products do distinguish between natural and artificial.¹ They make a distinction between simple or minimal manipulations in vitro (including centrifugation and cryopreservation) and 'substantial' manipulations, which include among many other items cell culture. According to this definition, a great number of our assisted reproductive techniques, including IVF, may well be considered 'artificial'.

Indeed, many laboratories are currently developing novel techniques of assisted conception which are largely 'artificial' - and these include the creation of sperm cells and oocytes through substantial manipulation of stem cells.² Our own group in Amsterdam has developed a method to proliferate both adult and prepubertal spermatogonial stem cells (SSCs) and is working towards bringing autotransplantation of SSCs into clinical practice.^{3,4,5}

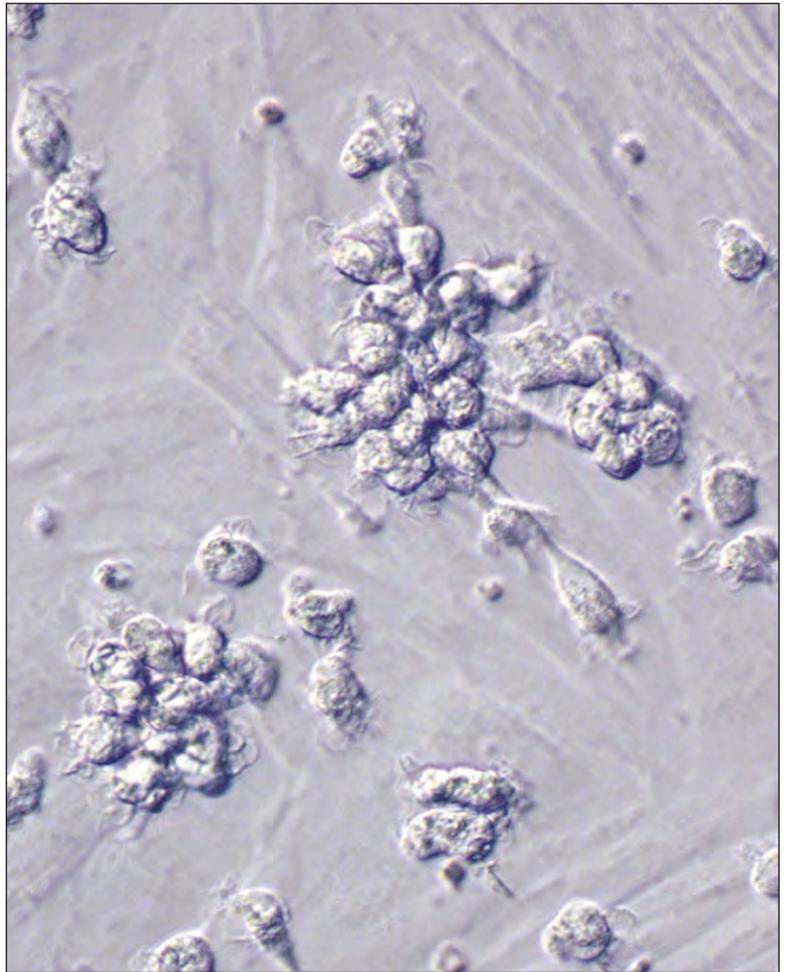
Clinical application of such 'artificial gametes' could substantially change the field of reproductive medicine. First, artificial gametes could offer genetic parenthood to all couples, including those who do not have functional gametes, or those in whom both partners have the same type of gametes (gay or lesbian couples). Second, while current treatments aim to bypass infertility by establishing a single pregnancy, some approaches with artificial gametes may even cure infertility altogether.

Biology

The creation of artificial gametes would occur in two phases, as illustrated in the the two figures opposite. In phase I, male or female stem cells would be obtained which contain the patient's own DNA. In phase II, these stem cells would be differentiated in vitro or in vivo into sperm cells or oocytes and these cells would then be used for (assisted) conception.

There are three potential routes for phase I.

- First, a biopsy from the testis or ovaries could retrieve germline stem cells directly, and their proliferation in vitro would ensure a sufficient number for phase II. However, the required adult germline stem cells might not be present in all infertile men. For example, in men with Sertoli cell only syndrome no germline stem cells are ever present. In women, the



From assisted reproduction to artificial reproduction

How feasible is the creation of sperm cells and gametes from manipulated stem cells? Saskia Hendriks, Eline Dancet and Sjoerd Repping review progress so far.

mere existence of adult germline stem cells is still disputed.

- Second, induced pluripotent stem cells (iPSCs) could be created by reprogramming somatic cells from the infertile patient - for example, from skin fibroblasts.

- Third, the nucleus of the patient's own somatic cell could be transplanted into an enucleated embryonic stem cell (ESC), to obtain ESCs with the patient's own DNA.

For phase II, there are two potential routes which might lead to conception. First, an in vitro route in

which the obtained stem cells are differentiated in the laboratory into sperm cells or oocytes, with fertilisation achieved through ICSI. The second route is in vivo. The stem cells are transplanted into the infertile patients' testes or ovaries where they would initiate and maintain gametogenesis. The formerly infertile patient would thus be able to produce sperm cells or oocytes, and theoretically be able to conceive through natural conception. While the in vitro route leading to ICSI could be considered an extension of current ART procedures (as it aims to achieve a single pregnancy), the in vivo route is quite different because it presents a cure for infertility, not its circumvention.

Further, it might even be possible to create an artificial gamete 'from the opposite sex' using, for example, iPSCs - an artificial oocyte from a male, or an artificial sperm cell (a gamete capable of fertilizing an oocyte) from a female.

Previous studies in animal models and humans

Just pie in the sky? Maybe yes, but maybe not as much as you'd think. So far, 57 papers using the techniques described above have reported the creation of artificial gametes in animal models and in the human. The birth of baby mice, hamsters, rats and zebra fish through the use of artificial gametes has been reported in 30 studies. Nine studies have reported the creation of human artificial sperm or oocytes. In humans, however, no children have thus far been born from artificial gametes.

As for the creation of artificial gametes from the opposite sex of the intended parent, seven animal studies have reported the creation of artificial sperm from a female or artificial oocytes from a male. Three

State-of-the-art of biological research into artificial gametes

Effectiveness

Proven

- ✓ birth of animal offspring
- ✓ creation of human artificial gametes
- ✓ creation of artificial gametes from the opposite sex

Not proven

- x birth of human children
- x validation of presented results

Safety

Proven

- ✓ viable animal offspring
- x genetic and epigenetic normality

Not proven

- x viable human offspring
- x long-term health of offspring

(Cost) efficiency

Proven

- ✓ feasible for study-setting

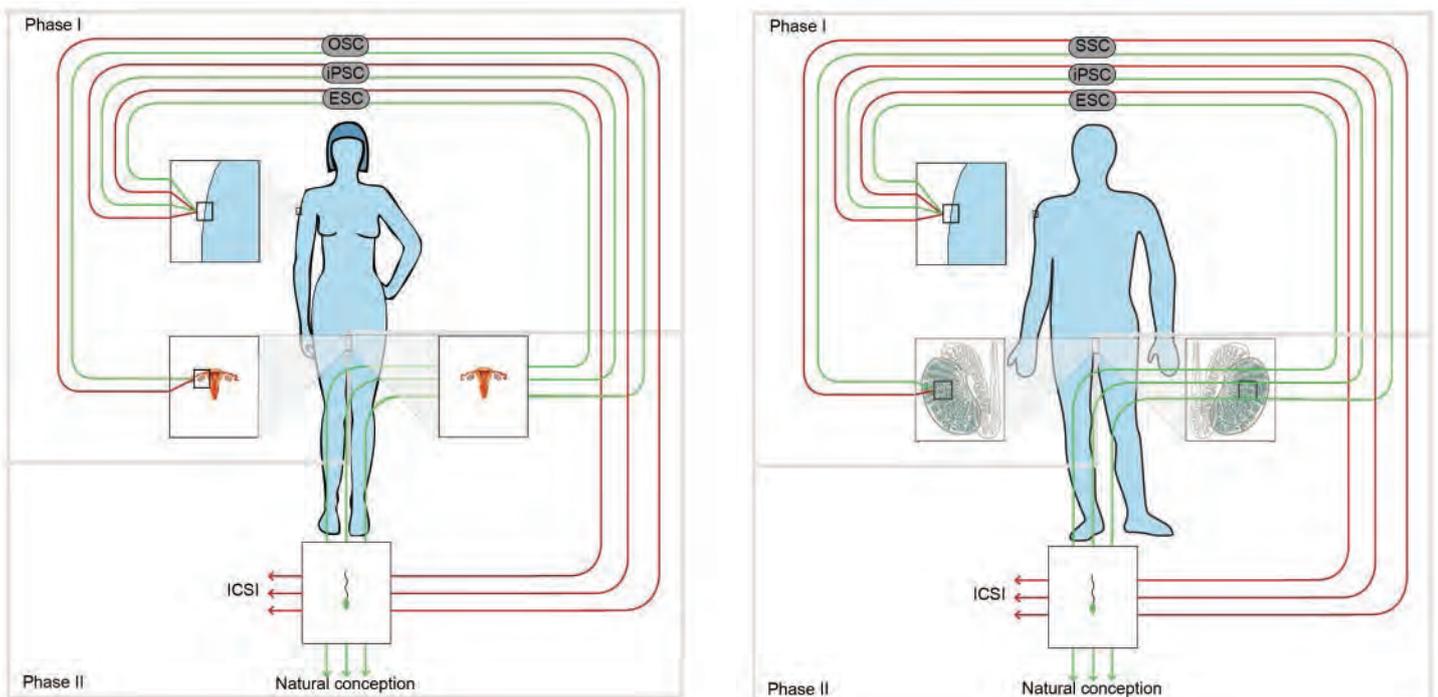
Not proven

- x feasible for clinical application

of these studies reported animal offspring originating from two mothers through the creation of artificial sperm from female mice. One study described the creation of human artificial sperm from a woman.

Although the birth of animal offspring does provide a proof of principle, several big hurdles still need to be crossed before clinical application (see table above). As for efficiency, the birth of a human child has yet to prove the functionality of these methods in humans.

Moreover, some routes have only been described in one or a few studies, and validation of the presented results by a multitude of studies remains. The long-term health of any offspring created with artificial



The six routes to artificial gamete formation in women (left) and men. Adjusted from Hendriks S, Dancet EA, van Pelt AM, et al.²

Saskia Hendriks, Eline Dancet and Sjoerd Repping: 'While current treatments aim to bypass infertility by establishing a single pregnancy, some approaches with artificial gametes may even cure infertility altogether.'



gametes also needs rigorous investigation, and the (cost) efficiency of the methods must increase for clinical application to be acceptable.

Potential clinical applications

The potential clinical applications of artificial gametes are numerous.

Artificial gametes could offer genetic parenthood to patients who lack functional gametes and can currently be treated only with donor gametes. This could include those who lost their fertility as a result of treatment for (childhood) cancer, patients with non-obstructive azoospermia or premature ovarian failure, and women who are infertile because of a naturally occurring menopause. Additionally, the creation of artificial gametes from the opposite sex as the donor could give lesbian or gay couples a child genetically related to both parents.

It is also theoretically possible that artificial gametes derived from the opposite sex as the donor could be used to fertilise the donor's own gamete, and thereby conceive a child who only has one genetic parent. It should be noted that this represents the ultimate form of incest; when compared with cloning, the individual's genetic material will have reshuffled.

Ethical implications

The implications of artificial gametes are a cause of both excitement and unease, even to healthcare professionals. So far, 84 articles have considered the potential implications of the clinical application of artificial gametes, some specified by biomedical experts (57/84 articles) and some by (science) journalists (17/84 articles).⁶ In total, no fewer than 51 different positive and negative implications have been described. For example, on the positive side, the possibility of a 'cure' for infertility is applauded, as is the potential for more couples to achieve genetic parenthood and thereby reduce the need for donor gametes, which remains troubled by issues of anonymity, scarcity and the exploitation of donors.

On the other hand, concerns have been expressed about the health of resulting children, inequality of

access to artificial gametes, and a possible slippery slope towards more controversial treatments. Some of these ethical concerns might be overcome by not using a specific method of artificial gamete formation - for example, not using ESCs would remove some concerns about the status of the embryo. Nevertheless, it seems certain that the benefits likely to be derived from the positive implications of artificial gametes will not be possible without having to risk the negative implications. Since our field has already been criticised for implementing new technologies prematurely, a professional and societal debate on the acceptability of artificial gametes and their clinical application would be timely.⁷

Saskia Hendriks is a PhD student, Eline Dancet a post-doctoral researcher, and Professor Sjoerd Repping Head of the Centre for Reproductive Medicine at the Academic Medical Center, University of Amsterdam, the Netherlands

This article is based on a presentation made by Saskia Hendriks at ESHRE's 2015 Annual Meeting in Lisbon.

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Online data collection system introduced in Lisbon

- Chairman calls for all centres to submit their PGD data to the Consortium
- Latest data show PGS just maintaining a revival in use following decline in 2007

The PGD Consortium's new system of online data collection was introduced in Lisbon and will be used for data collection XVI (2013) onwards. The system will bring greater efficiency and flexibility to the process and will maintain the Consortium's aim of providing accurate prospective and retrospective data on the reliability, efficacy and safety of PGD. Edith Coonen, Chair of the Consortium, pictured right, reported that the key parameter of the data from now on will be the genetic analysis and not the ART cycle. This, she added, will also allow a more efficient means of measuring trends in uptake and evaluating the efficiency of developments in both the reproductive and genetic field.

Thus, bringing a curtain down on the Consortium's first 15 years of data collection (and a system which was becoming increasingly unfit for purpose) is collection XV from 2012, which is now complete and ready for assembly. Data collection XIV, for 2011, is being prepared for publication. Data collection XIII, for 2010, was published in *Human Reproduction* in June this year.

Entering the data into the old system was a tedious and laborious job for the participating centres. Similarly, the task of preparing them for publication each year was a 'massive undertaking', said Coonen, but one which provides 'an extremely valuable resource' in monitoring the many new technologies in



this fast-moving field. Trends over time, she suggested, should also be more easily detected with the new system.

'The design of the new database will allow centres to input and analyse their own data in real time,' explained Coonen. 'And many of the tables needed for final manuscripts will be generated automatically. Once the database is active, we hope to encourage all our present members to submit data - and hope too to produce our reports quickly.'

Presently, said Coonen, the Consortium has 124 members, the majority (86) in Europe, but a number of large centres still do not or no

longer supply any data. She appealed to these centres, with the new system up and running, to (re)consider joining the ESHRE PGD Consortium. A total of 63 centres had supplied data for collection XV (2012), with information on 6782 cycles. These figures have been fairly steady over the past four years.

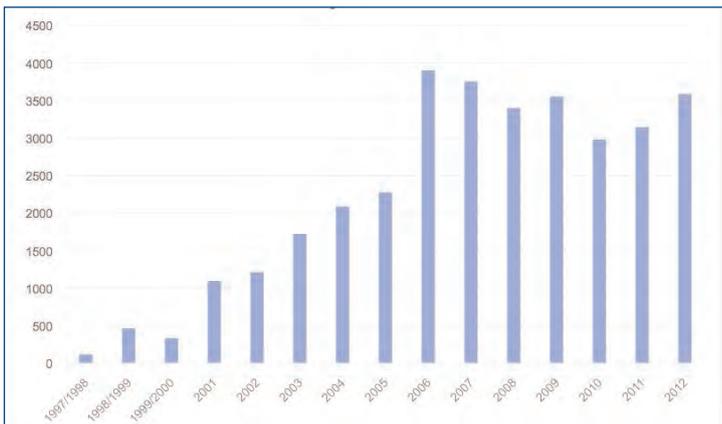
Time trend analysis presented by Coonen in Lisbon went no further than 2010, which failed to offer any clear picture of the uptake of 'version 2' methods of analysis. There has been a clear increase in the use of PGS between data I in 1997 and data XV in 2012 (32% vs 56%). However, the number of PGS cycles over time peaked in 2006 and began to decline moderately thereafter - what former Consortium Chair Joyce Harper has described as 'the Mastenbroek effect'. With around 3500 cycles per year, PGS in 2012 was just maintaining a revival in use.

Fifteen years of data collection also shed light on what a 'typical' PGD cycle might look like: that is, 12-13 oocytes retrieved at collection; 6-7 oocytes fertilised by ICSI; 5-6 embryos biopsied and analysed; 1-2 embryos transferrable; and 1-2 embryos transferred. Pregnancy rates from data 1-XV were around 30% per transfer.

In 2013, said Coonen, STR-based PCR was still the preferred analysis technique in PGD for monogenic disorders (85%), while the majority of PGD cycles for chromosomal disorders were analysed by FISH (71%). In PGS, however, FISH had been replaced by array CGH (76%).

STEERING COMMITTEE

Edith Coonen (NL), Chair
 Siobhan SenGupta (GB), Chair Elect
 Martine De Rycke (BE), Member
 Céline Moutou (FR), Member
 Georgia Kokkali (GR), Member
 Joanne Traeger-Synodinos (GR), Past Co-ordinator
 Veerle Goossens (BE), Science manager



Evolution of PGS cycles over time.

Standardisation of endometriosis data collection

Steering committee

The Annual Meeting in Lisbon brought a change in the constitution of the SIG. Gerard Dunselman stepped down as Co-ordinator to be replaced by Andrew Horne from the University of Edinburgh. Gerard was a very active member of the SIG – in particular leading development of the new ESHRE *Guideline on the management of women with endometriosis*. One of our SIG deputies, Michelle Nisolle, moved laterally to become Deputy for the SIG Reproductive Surgery. Carla Tomassetti from University Hospital Leuven and Andrea Romano from Maastricht University took over as Deputy Co-ordinators, and Antonio Simone Laganà from the University of Messina took over as Junior Deputy.

STEERING COMMITTEE

Andrew Horne (GB), Co-ordinator
 Carla Tomassetti (BE), Deputy
 Andrea Romano (NL), Deputy
 Antonio Simone Laganà (IT), Junior Deputy
 Gerard Dunselman (NL), Past Co-ordinator

A Scottish study presented in Lisbon linking endometriosis to miscarriage and ectopic pregnancy drew considerable press attention. Pictured are investigators Lucky Saraswat from the University of Aberdeen and Andrew Horne, Co-ordinator of the SIG EE.



Annual Meeting Lisbon

Our pre-congress course in Lisbon was titled **Endometriosis and infertility** and included lectures on the natural history of endometriosis, the role of the embryo and the endometrium in endometriosis-associated infertility, and discussion on the benefits of diagnosing and treating minimal/mild endometriosis before ART. There was also a lecture on the Endometriosis Fertility Index (used to predict fecundity after endometriosis surgery) and it was generally felt that this tool could provide reassurance for those patients with good prognoses - and avoid wasted time and accelerate treatment for those with poor prognoses.¹

Highlights within the main programme included a session on 'endometrial scratch', which generated a healthy discussion. One of our abstracts was also selected for press release by ESHRE and drew considerable media attention.² This Scottish study reported data from 14,655 women, with their medical records followed-up for a maximum of 30 years between 1981 and 2010. It demonstrated that women with endometriosis are at an increased risk of miscarriage and ectopic pregnancy, and that those with a history of endometriosis whose pregnancies progress beyond 24 weeks are at a higher than average risk of haemorrhage (ante- and postpartum) and preterm birth.

World Endometriosis Research Foundation (WERF)

The World Endometriosis Research Foundation (WERF), Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) – a collaboration



among 34 academic institutions as well as three medical/diagnostic companies – has agreed on the standardisation of

- collection of detailed surgical and clinical data from women with endometriosis and controls to allow collaborative sub-phenotype discovery and validation analyses
- standard operating procedures (SOPs) for collection, processing and long-term storage of biological samples from women with endometriosis and controls to facilitate current and future collaborative laboratory-based etiologic discovery and treatment development.

This unprecedented initiative for a single disease, supported by the SIG EE, will enable identification of distinct sub-types of endometriosis as they are defined by symptom presentation, treatment response and long-term health outcomes. Confirmation of these sub-types will enhance development of targeted diagnosis and treatments for different manifestations of the disease no matter how prevalent or rare.

Global commitment to the standardised collection of 'big data' – and consequent cross-country multicentre collaborations in the sharing of these detailed data – is necessary if we are truly to make progress in developing viable, long-term, solutions for the millions of women whose lives are affected daily by the impact of endometriosis.

The WERF EPHect tools are freely available from



WERF ePHect
 Endometriosis Phenome
 and Biobanking Harmonisation Project

<http://endometriosisfoundation.org/ephect/> where it is also possible to register your centre as one that utilises these global standards for the collection of data and biospecimens in endometriosis. This registry is intended to enhance the ability of all endometriosis investigators to identify potential collaborators whose data and biospecimens can easily and seamlessly be combined to ensure sufficient power and patient diversity to validly address scientific hypotheses.

Future activities: mark your agenda

We have a Campus meeting in Leuven on **Sexual functioning in women dealing with infertility and/or endometriosis** on 24-25 September. This course aims to provide in-depth information on the

interrelationship between sexual functioning, infertility and endometriosis. In addition, we have a further Campus meeting on 26-28 February 2016, co-organised with the Turkish Society of Endometriosis and Adenomyosis, in Istanbul, which will again focus on **Controversies in endometriosis and adenomyosis**.

Andrew Horne

Co-ordinator SIG Endometriosis and endometrium

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SIG SOCIOCULTURAL ASPECTS OF (IN)FERTILITY

First report imminent on oocyte cryopreservation in Europe

We have now gained momentum and our first year of real activity has been very busy. I have been asked to continue co-ordinating the SIG until the 2017 Annual Meeting, in view of our start outside the normal time frame linked to the meeting.

We have had a very good year, with an excellent pre-congress course in Lisbon organised jointly with the SIG Ethics & Law on the role of social media in our interaction with the public and patients, a necessary update for my generation and an essential tool for all of us today.

Our European oocyte cryopreservation project has progressed, and data collection was double-checked during the summer so that a preliminary report could be ready for the autumn.

This will also be a busy time as our SIG proposal was chosen for the ESHRE pre-congress course at the ASRM's 2015 meeting in Baltimore. The subject of the course will be the pros and cons of oocyte cryopreservation versus embryo freezing, from the scientific, clinical and sociocultural points of view. We hope to propose a collaboration with the ASRM on data collection, and to promote oocyte cryopreservation data collection worldwide. This proposal is to be considered by ESHRE's Executive Committee at its meeting in September.

STEERING COMMITTEE

Françoise Shenfield (GB), Co-ordinator
Paul Devroey (BE), Deputy
Anna Pia Ferraretti (IT), Deputy
Virginie Rozée (FR), Junior Deputy



Training events

Further activities include a joint workshop in Leuven in December with SIGs Andrology and Ethics & Law and Task Force Developing Countries and Infertility on **Donor sperm banking: medical, socio-cultural, ethical and legal**

considerations, participation in Milan in the workshop on **The impact of reproductive surgery on cross-talk between the embryo and the endometrium**, and a further Campus meeting in May 2016 in Munster, Germany, on the cryopreservation of gametes for adolescents with cancer.

Our pre-congress course for the 2016 Annual Meeting, organised with the SIGs Early Pregnancy and Ethics & Law, is titled **What happens in utero lasts a lifetime: A multi-disciplinary approach to improving preconception and early pregnancy care**.

At the international level we are pursuing our interest in the minefield of surrogacy with participation in a Brochet Foundation meeting on next January.

Françoise Shenfield
Co-ordinator SIG Sociocultural aspects of (in)fertility

Endometrial mesenchymal stem cells

The potential to revolutionise many aspects of reproduction

Caroline Gargett's group from Monash, Australia, first presented evidence of endometrial mesenchymal stem cells (eMSC) to the Annual Meeting of ESHRE in Denmark in 2007. Since then eMSC have been investigated by many groups and there is now accumulating evidence to suggest that these cells could lead to exciting new developments in the management of reproductive disorders.

While sessions in Lisbon on endometrial injury attracted the highest number of delegates, presentations on eMSC raised the exciting prospect of MSC manipulation as a new treatment approach, with the potential to revolutionise many aspects of reproductive medicine.

eMSC in Lisbon

The excellent preconference course developed by the SIGs Early Pregnancy and Stem Cells once again raised the importance of stem cells and in particular eMSC. Hugh Taylor explained the trafficking of eMSC from bone marrow to the endometrium with convincing evidence from animal models. He also provided data suggesting that MSC trafficking from bone marrow to the endometrium occurs on a monthly basis in humans. eMSC are attracted to the endometrium by inflammation and ectopic endometrium acts as a 'stem cell sponge', thereby absorbing MSCs that should have gone to the uterus. Thus, a potential explanation for endometriosis-associated infertility was suggested.

Jan Brosens then showed data implying that a lack of eMSC was important in recurrent miscarriage. He explained that an optimal endometrium was a balance of eMSC and stromal cell senescence to maximise regenerative capacity. He then explained that a lack of this regenerative capacity leads to pregnancy failure. This in turn raises the prospect of preconceptual interventions to prevent reproductive failure.

Later in the main programme two presentations found a strong association between endometriosis and miscarriage. First, an epidemiological study of 14,500 women by Saraswat and colleagues in Scotland found an association between endometriosis and miscarriage (see page 28). Next, in an observational study from France on outcomes after IVF, Maignien et al quoted a 50% miscarriage rate with superficial endometriosis, thereby adding clinical evidence to the concepts explained in the preconference course.

Further evidence of the importance of MSC trafficking from bone marrow to the endometrium

STEERING COMMITTEE

Siobhan Quenby (GB), Co-ordinator
Emma Kirk (GB), Deputy
Petya Chaveeva (BG), Deputy
Astrid Marie Kolte (DE), Junior Deputy
Mariëtte Goddijn (NL), Past Co-ordinator



was given in two other presentations. Xu from Hong Kong showed that monthly regeneration of the endometrium occurs due to eMSC stimulation in humans. Khatun from Finland described the characteristics of eMSC and bone marrow MSC, showing them to be different from stromal cells, particularly having

increased migratory properties and high regenerative potential. This was further evidence to suggest the physiological and pathological importance of MSC trafficking to the endometrium and then regenerating. There was thus good evidence that these eMSCs are fundamental to normal endometrial development and function - and logical too that eMSC are important in recurring miscarriage, endometriosis and sub-fertility.

It was also in our preconference course that Carlos Simon presented his pioneering data on transfusing eMSC into the uterine artery of women with Asherman's syndrome. He reported that there were currently only two ongoing pregnancies as result of this novel treatment, but he presented convincing evidence that it was possible to increase endometrial eMSC by this method.

However, Dr Emaul initiated a stimulating debate by showing data supporting the concept that surgical division of intrauterine adhesions is the optimal treatment for Asherman's syndrome. Further controversy was generated by Meng from China who showed a reduction in miscarriage from the insertion of MSC into the uterine horn of mice who recurrently miscarry.

Thus, while MSC are not yet available as a new treatment in reproductive medicine, Lisbon 2015 demonstrated their clear prospect on the horizon.

*Siobhan Quenby, Co-ordinator
SIG Early Pregnancy*

Conference abstracts:

O-122 Saraswat L, et al. Reproductive and pregnancy outcomes in women with endometriosis: a Scottish national record linkage study

O-124 Maignien C, et al. Prognostic factors of ART outcomes in a continuous series of 359 endometriosis patients

O-238 Khatun M, et al. Endometrial mesenchymal stem cells present with high regeneration and migration potential suggesting their involvement in endometrial monthly regeneration and development of endometrial disorders

O-240 Xu S, et al. Regulatory mechanism of endometrial mesenchymal-like stem cells during menstruation

O-074 Meng Y, et al. The effect of bone marrow mesenchymal stem cells (MSCs) on recurrent spontaneous abortion (RSA).

The safety and reproducibility of ultrasound in ART

Lisbon precongress course raises timely need for guidance

It was time that some attention was given to imaging and ultrasound in medically assisted reproduction to guarantee safety and reproducibility. Ultrasound plays a very important part in the daily activities in every assisted conception centre, both diagnostically and operatively.

However, only in the last few years has more interest been shown in the way ultrasound is delivered and regulated. Many aspects of ultrasound and other imaging techniques such as MRI or PET still need to be regulated and standardised.

These were the reasons for our precongress course in Lisbon, **Quality assurance of ultrasound in medically assisted reproduction**, which was organised by the SIGs SQART and Andrology. Its aim was to review what is already available, standardised, regulated, and to identify what is still needed to ensure that ultrasound is safe and reproducible in current practice.

The course was well attended by trainees, consultants, clinical assistants, andrologists, radiographers, sonographers, nurses, midwives and quality managers.

Specifically, this advanced course aimed:

- To investigate the level of evidence of quality assurance in ultrasound by exploring guidelines available in current practice
- To highlight infection control in ultrasound
- To review different approaches to interventional ultrasound and their results
- To promote training and education in ultrasound and assess how sonographers/doctors/nurses acquire and maintain skills through time
- To review different education programmes and standardisation
- To assess the quality and safety of ultrasound in ART

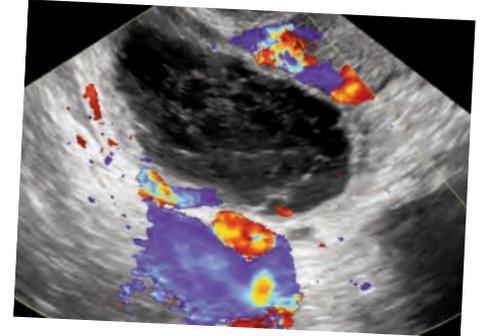
There were animated debates at the end of presentations with many reflecting a need for clear guidance on the appropriateness of ultrasound use, the reproducibility of the technique, standardisation of image acquisition, its interpretation and analysis, range of what can be considered acceptable normal values, ultrasound-guided surgical procedures, health and safety, training and accreditation. As a result of these discussions we are now considering the possibility of a position paper on these needs.

Future events

Our precongress course next year will be in collaboration with the SIGs Ethics & Law and Stem

STEERING COMMITTEE

Arianna D'Angelo (GB), Co-ordinator
Kelly Tilleman (BE), Deputy
Ioana Rugescu (RO), Deputy
Zdravka Veleva (FI), Junior Deputy
Willianne Nelen (NL), Past Co-ordinator



Cells. **ART in 2020: the next frontier** will focus on the many new developments now taking place in the fertility field. The programme is very attractive with more details coming soon. We are anticipating more collaborations with the other SIGs for Campus courses in 2016. Watch this space!

Steering committee changes

There were substantial changes made to the steering committee in Lisbon. Willianne Nelen completed her term as Co-ordinator, to become Past Co-ordinator. Arianna D'Angelo is the new Co-ordinator, with Kelly Tilleman starting her second term as Deputy. We welcome as the newly elected Deputy Ioana Rugescu, who has a background in biology and was one of the founders of the Romanian Embryologists Association. Ioana has more than 10 years experience in safety and quality assurance. 'It's important for us to engage more actively in ESHRE initiatives to influence and grow the services for members,' says Ioana. 'The SIG SQART is one of many such initiatives which has been successful for many years. It shows that collaboration, personal involvement and personal example can pay dividends for the benefit of the Society, patients and professionals.'

We had to say goodbye to our Junior Deputy Daniela Nogueira, who ended her term and was replaced by Zdravka Veleva, a clinician and researcher. Her major scientific interests are the safety and quality aspects of ART, such as single embryo transfer and cost-effectiveness of treatment. During her term, Zdravka

hopes to focus on identifying interdisciplinary hot topics, and increasing dialogue between members and ESHRE's different SIGs. We warmly welcome these newly elected members to the committee.

Arianna D'Angelo
Co-ordinator SIG SQART
dangelo@cardiff.ac.uk



Possibilities of further guideline development

A very successful pregress course was organised in Lisbon by the SIG RE on the difficult topic of recurrent implantation failure. Currently, no consensus exists on the definition, its clinical significance and the possible causes of this condition. However, from the various presentations, it became increasingly clear that low embryo quality is the most likely causal explanation. Still, many speakers emphasised a need to re-evaluate several factors that may interfere with the chance of implementation, such as the technique of embryo transfer, the optimal choices in luteal support, the normalisation of the uterine cavity in case of fibroids or uterine septa, and the possible upgrading of endometrial quality by scratching. The course was the best attended pregress course of this or any other year, and the 551 participants shared much discussion in this difficult research area.

Steering committee changes

Our business meeting welcomed many participants and members, reviewed activities of the past two years, and announced a change in crew. Terhi Piltonen and the Past Co-ordinator Georg Griesinger have now left the SIG and were offered sincere thanks for their huge contributions. New members are now Peter Humaidan as Deputy and George Lainas as Junior Deputy. As the new SIG Co-ordinator, I addressed the meeting with my personal commitments, which may go a little beyond the traditional strong educational activities.

Future activities

Nevertheless, near future activities in 2016 will comprise a Campus workshop to be organised in

STEERING COMMITTEE

Frank J. Broekmans (NL), Co-ordinator
 Daniela Romualdi (IT), Deputy
 Peter Humaidan (DK), Deputy
 George Lainas (GB), Junior Deputy
 Efstratios Kolibianakis (GR), Past Coordinator



Istanbul on the **Multifaceted challenge of female reproductive ageing**, updating knowledge on the physiology of the ageing process and the management of couples in whom the female age-related decline in oocyte quality necessitates new avenues for treatment. Notably,

specific attention will be given to the new ESHRE guideline on premature ovarian insufficiency.

A joint workshop with the SIG Reproductive Surgery has also been developed, taking place in Thessaloniki and titled **Surgery in reproductive medicine: benefits and limits**. Topics include PCOS, endometriosis, tubal disease and fibroids.

Finally, at the next Annual Meeting in Helsinki our pregress course will be dedicated to **Managing the difficult IVF patient: facts and fiction**. Our focus here will be on the older IVF patient, the medically complicated, the fat and the thin, and those with comorbidities such as endometriosis and fibroids.

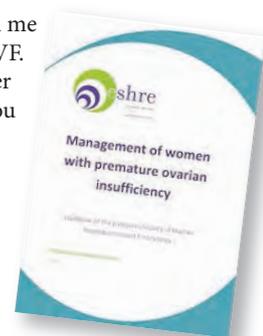
Future events for 2017 and 2018 were already discussed at our business meeting in Lisbon, with proposals from Andrea Weghofer on the impact of adjuvant treatments on pregnancy potential in IVF, from Cornelius Lambalk on reproductive hormones and higher brain functions, from Georg Griesinger on the luteal phase, and from me on progress in ovarian stimulation for IVF. The steering committee will work further on those four proposals and will keep you informed on progress.

Guidelines

In the year to come the SIG RE aims to maintain its high level of activity in the field of education, but also wishes to undertake more guideline development and research co-operation. The ESHRE guideline on premature ovarian insufficiency, which was open for comment during the summer from SIG RE members and the ESHRE community, was a perfect first example. Our next focus could be on ovarian stimulation protocols for IVF or ovulation induction in PCOS. Research co-operation may be sought in

building international networks to initiate projects on patient data analysis from published studies, which could evolve into the challenge of obtaining European Union research grants.

Frank Broekmans
 Co-ordinator SIG
 Reproductive Endocrinology



Record attendance. A total of 551 took part in the SIG RE's pregress course in Lisbon on recurrent implantation failure.



Digital 'Atlas of Embryology' near to completion

Steering committee

I wish to open this short report on SIG Embryology activity by introducing myself as the new SIG Co-ordinator. Serving ESHRE and the group will be an honour and a responsibility. Matching the performance of our Past Co-ordinator, Maria José De los Santos, will be challenging. Having led the group with passion and determination, Maria gave a major impulse to the group. Other recent changes in the SIG Embryology steering committee have seen the elections of Susanna Apter (a former Junior Deputy) to Deputy and Debbie Montjean to Junior Deputy, respectively. I wish to warmly welcome Debbie and I trust she will bring fresh energy to the group. The new appointments were ratified at the Annual Meeting in Lisbon.

As a SIG, we gave our usual significant contribution to the meeting's scientific programme and in the organisation of the pre-congress course **What a clinical embryologist should know in daily practice**. The course was the second best attended among all pre-congress courses, confirming the central role of embryology in ESHRE and ART more generally. The course incorporated a very much appreciated blend of practical needs in the IVF lab and basic science pertaining to gamete and embryo development.

Future activities

After long gestation, two major SIG Embryology projects are now close to accomplishment. Our previously announced aim to develop a web-based digital *Atlas of Embryology* is now being actively pursued. Once finalised and accessible to users (within a few months, according to the developers), the *Atlas* will have an adaptable HTML5 format suitable for computers, tablets and smartphones. This will allow much easier search modalities and access to content, with obvious and major advantages over the current PDF format. Initially, the new digital version will include the material already present in the PDF source, but it is intended to be a versatile tool amenable to continued expansion with novel contents. Many ongoing thanks in this project are due to Cristina Magli, a former co-ordinator of the SIG

STEERING COMMITTEE

Giovanni Coticchio (IT), Co-ordinator
 Sophie Debrock (BE), Deputy
 Susanna Apter (SE), Deputy
 Debbie Montjean (FR), Junior Deputy
 Maria José De los Santos (ES), Past Co-ordinator



Embryology, who was a significant contributor not just to the text but also to the platform itself.

The other project very close to completion is the second revision of the *Guidelines for good practice in IVF laboratories*. Initially published in 2000 and updated in 2008, the latest version has now been further revised.

This has required the time and dedication of several people whom I would like to thank: Susanna Apter, Sophie Debrock, Maria José De los Santos, Kersti Lundin (our ESHRE Chairman), Carlos Plancha, Fernando Prados, Laura Rienzi, Bryan Woodward and Greta Verheyen. Also, very special thanks to Nathalie Vermeulen, our ESHRE research specialist, for her technical support and determination.

I would also like to note publication in *Human Reproduction* of a paper on 'The educational and professional status of clinical embryology and clinical embryologists in Europe'. The data were obtained via a survey and prepared by ESHRE's Committee for Embryologist Certification and the SIG Embryology, with much of the organisational work performed by Borut Kovacic. The survey was answered by ESHRE national representatives (embryologists/basic scientists only) of individual countries. This is the first article to describe in detail an overview of the current situation in the field of clinical embryology in European countries. It is hoped it will act as a foundation for further ESHRE activities in the long-term process of improving the status of clinical embryology in the European healthcare system.

Finally, I wish to highlight a forthcoming SIG Embryology event, our Campus course on **Oocyte maturation - from basics to clinics**, which will be organised in Brussels from 3 to 5 March 2016.



Inspired by an initiative of Johan Smits, the event will gather many world leading specialists in a field which represents a useful treatment alternative and, at the same time, an invaluable research tool for the study of folliculogenesis and oogenesis.

Giovanni Coticchio
 Co-ordinator SIG Embryology

Stem cell research continues its rapid advance

Look back at Lisbon

The Annual Meeting is over and it's time to take stock - as ESHRE members and especially as SIG members. We very much enjoyed Lisbon, the food and the wonderful people. And as SIG Stem Cells members we were very happy with participation in our sponsored activities: an appealing pre-congress course presenting the latest updates on research in implantation and pregnancy (placentation, trophoblast formation, ectopic pregnancies), co-organised with our energetic colleagues of the SIG Early Pregnancy. Despite the differences between the two fields, we were interested to learn how stem cells can be seen both as a model to study early implantation processes (for example using trophoblast stem cells), but also how they can be involved in some processes related to endometriosis and ectopic pregnancies, establishing very nice links between these two fields.

In reproduction, stem cells are often seen merely as a possible source for the de novo generation of gametes; however, this pre-congress course highlighted the huge diversity of possible applications for stem cells. The more we can co-operate with other SIGs, the more we will show that stem cell research is involved in so many different aspects of reproductive medicine, from developmental biology to regenerative therapies.

We can proudly say that this year we were also host to two world renowned stem cell scientists: Professor Shoukhrat Mitalipov, 'father' of somatic cell nuclear transfer in the human and an expert in mitochondrial research, and Professor Jennifer Nichols, highly specialised in the different states of stem cell pluripotency. These excellent speakers presented wonderful lectures on their latest research, not just describing what they had discovered but also 'how' and 'why' they got there - things that can't be found in scientific papers. Their lectures clearly showed that stem cell research is moving forward at amazing speed.

Steering committee

There was also a substantial change in the Steering

STEERING COMMITTEE

Björn Heindryckx (BE), Co-ordinator
Cristina Eguizabal (ES), Deputy
Susana de Sousa Lopes (NL), Deputy
Mieke Geens (BE), Junior Deputy
Rita Vassena (ES), Past Coordinator



Committee in Lisbon: Rita Vassena stepped down as Co-ordinator to become Past Co-ordinator and Björn Heindryckx took over as the new Co-ordinator. Susana M. Chuva de Sousa Lopes from the Netherlands won the members election round for new Deputy, while Mieke Geens from Belgium was appointed as the new Junior

Deputy. The elections were very successful in terms of number of candidates applying and people voting, another tick for our developing SIG. Filippo Zambelli, former Junior Deputy of the SIG Stem Cells will be leaving the Steering Committee, and we would very much like to thank him for all his valuable contributions over recent years, not least his reports for *FoR*!

Future activities

The coming year will be busy for stem cells, as we are already planning several activities. First, in collaboration with the SIGs Andrology, Socio-cultural aspect of (in)fertility, Ethics & Law, and Psychology & Counselling, we are organising a Campus meeting on **Future fertility for the male child and adolescent with cancer: best practice, research breakthroughs and current dilemmas** to be held in Munster, Germany, on 13-14 May 2016.

Further ahead, in September 2016, we will organise a Campus event on novel gamete manipulation technologies, to be held in Amsterdam on 22-23 September along with the SIGs Ethics & Law and Quality & Safety in ART. This ambitious course will handle top-of-the-bill research topics in ART:

mitochondrial diseases and how to overcome vertical transmission by embryo manipulation, the possibility of stem cell-derived gametes, and last but not least the feasibility and possible applications of gene editing in gametes and embryos. All these topics will be discussed from a scientific, ethical and safety angle, a programme you cannot miss!



*Björn Heindryckx
Co-ordinator SIG Stem Cells*

Another active educational programme planned

Steering committee

After elections in May, a new Steering Committee was formed in Lisbon. The new Co-ordinator is now Claudia Spits, and Ursula Eichenlaub-Ritter becomes Past Co-ordinator. Tania Milachich remains Deputy, and Georgia Kakourou, our previous Junior Deputy, was elected to join us



as Deputy. We also have a new Junior Deputy in Signe Altmäe (pictured), who started her career at Tartu University, Estonia, followed her research at the Karolinska Institute in Sweden and is currently working in the Centre for Health Technologies in Tartu, and as Marie Curie post-doctoral fellow at the University of Granada in Spain.

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



March next year on **Oocyte maturation, from basics to clinic** organised by the SIGs RG and Embryology. The programme will cover the basics of oocyte maturation, translational science, in vitro oocyte maturation in the clinic, and the clinical outcomes of these cycles.

We are also involved in a combined practical course-Campus workshop titled **All about preconception, preimplantation and prenatal testing**. This is being run with the PGD Consortium and European Society for Human Genetics (ESHG) and will take place in April next year in Maastricht under the local chairmanship of Edith Coonen, Chair of the PGD Consortium. The programme aims to update a broad audience of both beginners and experts on current issues, controversies and latest developments in the field of preconception, preimplantation and prenatal testing.

Finally, as reported earlier, the SIG continues to work on its e-learning programme. The PGD Consortium recently ran its fourth interactive webinar, which was well received and well attended. The presentations given by members of the SIG RG and PGD Consortium are available on the website for ESHRE members and include an update of the PGD Consortium (Jan Traeger-Synodinos), accreditation of a PGD centre (Sioban SenGupta and Mike Morris), an introduction to genetics (Joep Geraedts) and embryo biopsy (Georgia Kokkali).

*Ursula Eichenlaub-Ritter
Past Co-ordinator SIG Reproductive Genetics*

Education

The topic of this year's well attended pre-congress course in Lisbon was **Genetic and genomic mechanisms and markers associated with gamete and embryo quality**, a meeting jointly organised with the PGD Consortium. The programme, which included talks ranging from molecular biology to 'three-parental' inheritance, raised fruitful discussions among participants and speakers.

Our most recent Campus workshops were held in Lisbon (**Epigenetics in reproduction**) and Rome (**An update on PGS**), as already reported in the May issue of *Focus on Reproduction*.

An advanced workshop will be held in Brussels in

ESHRE to continue funding of ESTEEM aneuploidy screening trial



Following slower-than-anticipated recruitment of patients to the ESHRE-supported ESTEEM trial, the one and only study currently able to establish the credentials of polar body biopsy for aneuploidy screening, the Executive Committee of ESHRE agreed at its Lisbon meeting to continue its financial support for the trial. The meeting was told that a further 380 patients are needed to meet study objectives, and a revised recruitment plan for the seven centres was agreed. Hopes are that the study will now be completed by the end of 2016. With retirement of Joep Geraedts from his post in Maastricht, Karen Sermon, Professor of Genetics and Embryology at the Vrije Universiteit Brussel (pictured left), and former Chair of the PGD Consortium, will take over as chairman of the ESTEEM steering committee. At the SIG RG's Campus meeting in Rome in March this year, Geraedts reported that the study's seven centres had thus far performed 212 transfers, somewhat behind schedule.

Huge attendance for live surgery in Lisbon, while certification programme continues progress

Steering committee

Changes to the SIG RS steering committee were made during the Annual Meeting Lisbon. TC Li from the Chinese University of Hong Kong stepped down from his position as SIG Co-ordinator, and, as the new Co-ordinator and with his help, I will do my best to continue his work. I would here like to express my deep gratitude for all he has accomplished during his term of office.

I would also like to thank Gregory Grimbizis (Deputy) and Sotirios Saravelos (Junior Deputy), who too are stepping down and were so efficient for our SIG. We will of course continue to work together in the future, friendship being the best cement of SIG activities. Michelle Nisolle from Belgium and Razvan Socolov from Romania have been appointed as new Deputies, and Filipa Besorio from Portugal the new Junior Deputy. I am very confident that this team will continue to steer the SIG RS with great efficiency.

Recent activities

Our pregress course in Lisbon on **Challenging reproductive surgery** was very well attended. Similarly, the live surgery held during the main programme reached a huge audience of around 1000 delegates. Procedures during the live transmission were performed by Professors Michelle Nisolle, Rudi Campo and Filipa Besorio, and included cases of endometriosis, dermoid cyst, transvaginal ovarian drilling and a special mention for the amazing demonstration of Asherman syndrome's treatment by Rudi Campo.

Future activities

2016 will be a rather busy year for the SIG RS with two Campus meetings in January, the first in Coventry, UK, on 21-22 January on **When is surgery the answer**

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



to early pregnancy complications? The second, which takes place in Milan on 29-30 January, is titled **The impact of reproductive surgery on cross-talk between the embryo and the endometrium** and is a repeat of the successful event held in Vienna in April last year. That meeting was fully booked, with many members keen for an opportunity to attend a replicate meeting.

We will also be staging a joint Campus meeting with the SIG Reproductive Endocrinology in Thessaloniki on the benefits and aims of surgery in reproductive medicine. In addition we will also be hosting our now 'traditional' course in endoscopy in in Leuven under the supervision of Stephan Gordts and Rudi Campo.

Lastly, our pregress course for the next Annual Meeting in Helsinki will be on **The management of myoma in women wishing to preserve reproductive function**.

This will be a very active time for the SIG RS and we hope to welcome many participants at these important events.

Training and education

The ESHRE Certification for Reproductive Endoscopic Surgery (ECRES) continues to run smoothly, with the latest exams in Lisbon. Despite the certification programme being only recently introduced, we have seen a steady increase in interest, with ten candidates in Lisbon taking the practical 5-hour exams. Certifications are available for the Bachelor in Endoscopy (Level 1) and for the ECRES Reproductive Surgeon accreditation (Level 2). The new ECRES Co-ordinator Vasilis Tanos provides more details on the next page.

*Antoine Watrelot
Co-ordinator SIG Reproductive Surgery*



Live surgery transmitted direct to the congress hall Lisbon. Meanwhile ten candidates for ECRES accreditation took their practical exams each under the supervision of their own personal trainer.

Certification for reproductive endoscopic surgeons into year 2

ESHRE's Certification in Reproductive Endoscopic Surgery (ECRES) successfully completed its second year during the Annual Meeting in Lisbon. Registration, experience log-book, the theoretical and practical scores can all be completed and followed online via the ESHRE website. In addition, the candidates for the ECRES Master level can also add their operation reports and videos online in real time.

Eighteen colleagues applied this year for the ECRES primary level having successfully completed the ECRES WebSurg modules. Their psychomotor skills examination was in two sessions in Lisbon, one in the morning for laparoscopic camera navigation, bi-manual dexterity and laparoscopic suturing, and a second in the afternoon for hysteroscopic camera handling - endometrial cavity navigation tested diagnostic skills while hand-eye co-ordination and dexterity tested the operative skills.

The theoretical examinations consisted of 100 MCQs of five options each, with only one correct answer. An effort was made to cover the broad spectrum of reproductive surgery and to include questions from reproductive medicine, embryology, imaging and genetics. The ECRES committee strongly believes that the knowledge of surgeons dealing with human reproduction should be broad and able to contribute

Steps	ECRES the ESHRE Certification of Reproductive Endoscopic Surgery
Step 1	Obtain ECRES websurg www.winnersproject.com (free of charge)
Step 2	Registration on ESHRE website for Basic Certification Psychomotor Skills Evaluation LASTT, HYSTT II, SUTT II + TESTT 1 & 2
Step 3	Submission to ESHRE Central Office of Logbook surgical practice curriculum (Electronic)
Step 4	Release of the Certification Primary level in Reproductive Endoscopic Surgery
Step 5	Once Primary level in RES successfully completed you can continue and register online to the Master Level in Reproductive Endoscopic Surgery
Step 6	Submission to ESHRE Central Office via Electronic Logbook - real time surgical practice according to the curriculum
Step 7	Evaluation of Surgical Experience Submission to the Central Office and blind evaluation of unedited videos
Step 8	Final theoretical exam
Step 9	Release of the Certification Master level in Reproductive Endoscopic Surgery
Step 10	CME every 5 years MCQs + List of Operations performed

The ten steps for certification in reproductive endoscopic surgery.

substantially to precision, safety and efficiency in surgical treatments of infertility cases. By following these principles it is expected that RES can improve the outcomes for spontaneous as well as assisted conception in subfertile and infertile patients.

*Vasilis Tanos
Co-ordinator ECRES*

PARAMEDICAL GROUP

Results from first certification exam: a pass rate of 81%

The Paramedical Board's pre-congress course, **From standardisation to individualisation**, was a huge success in Lisbon and very well attended. On behalf of the Board, I would like to thank all contributors and speakers for their hard work in preparing for and participating in this successful course.

Lisbon was also the venue of the first nurses and midwives certification examination; 68 nurses and midwives were eligible for the examination and on the day 63 signed in and out. One person cancelled and four did not arrive on the day. We are very pleased to tell you that 51 people passed the exam - 36 nurses and 15 midwives which is a pass rate of 81%. Congratulations to all those who were successful. We are delighted for you.

The main meeting yet again proved to be very stimulating and we were so pleased to see the Paramedical sessions well attended. Prizes were awarded in the following categories:

- Nurse award for the best oral presentation by a nurse went to **Fertility awareness in the Flemish population can be disadvantageous** from Ilse Delbaere and colleagues in Belgium,
- The ART laboratory award for the best oral or poster presentation by a laboratory technician went to **Frozen-thawed in-vitro matured oocytes collected at the time of**

ovarian tissue processing, for the purpose of fertility preservation for transsexual persons, show normal spindle formations from Sylvie Lierman also from Belgium)

The steering group for the nurse and midwives certification course will meet in October in Brussels to review the reading list and to make preparations for the next examination, which will be held for in Helsinki just before the Annual Meeting in 2016.

The Paramedical Board meet in Brussels also in October when we will be planning our Campus courses for 2016 - 2017 and our pre-congress course for 2017 in Geneva. We will also formally welcome our newest board member Valerie Blanchet, a nurse from Paris.

We would be delighted to hear from ESHRE Paramedical



Group members if there are any burning issues or topics which you would like us to address or courses that you feel would be valuable. Please feel free to contact me directly. My contact details are helen.kendrew@bathfertility.com

*Helen Kendrew
Chair Paramedical Board*

The one-in-a-million baby

● History of first IVF births unearthed in detail

According to the latest provisional calculations of ICMART, global reproductive medicine is now producing around 430,000 IVF babies a year and at some point in recent months must have topped a cumulative total of 6 million. And that's not including the huge numbers now being born in China and India.

That's a lot of babies since the first, Louise Brown, was born in a cloud of secrecy - and recorded only by Britain's 'Central Office of Information' - at the small local hospital at Oldham in the north of England.¹

'On the day I was born, my mum had to be taken to the operating theatre for her Caesarean section in pitch darkness,' Louise now explains, 'with just a torchlight showing the way.'

Her admission comes in a new book written by Louise in which, recalling the words of Patrick Steptoe, she describes her birth as a 'one in a million' chance. It now transpires, from papers and notebooks recording the work of Edwards, Steptoe and their lab manager Jean Purdy, that such odds were not far from the truth.

A 'symposium' which makes up the first issue of a new journal in reproduction, *Reproductive Biomedicine & Society Online*, describes in painstaking detail the development of IVF in the hands of Edwards, Steptoe and Purdy between January 1969 (their first laparoscopic oocyte retrieval) and 1978 (the first live birth).² Along the way this remarkable work of scholarly detection unearthed the details of 495 potential oocyte retrievals in 'a minimum of 282 women'. Most of these cycles (457/495) did proceed to egg collection, with an outcome recorded in 436. Eggs were recovered in 388 of these 436 attempts, insemination recorded in 331 and embryos identified in 'at least 167'. There were 112 embryo transfer attempts from which 11 possible preclinical and five clinical pregnancies were observed. Two healthy live births resulted, one of which was Louise Brown.

This catalogue of detail, researched and reported by Kay Elder and Martin Johnson in a series of six papers, was derived from an analysis of 21 'Oldham notebooks' and 571 pages of loose sheets and scraps of paper ('in a variety



of authors' hands') found over a period of five years at Edwards's home and in storage at Bourn Hall near Cambridge, the clinic set up by Edwards and Steptoe in 1980. The papers are now held in the archives of Churchill College, Cambridge.

In an introduction to the symposium Jacques Cohen and colleagues note that such detail is 'testimony to the Oldham team's integrity and commitment' but in total represents 'a larger than expected number of unsuccessful cycles' (457



involving 282 patients). History now shows that Louise's odds estimate of a million to one was about right.

As a young(er) journalist 20 or so years ago I interviewed Louise and her parents, and what struck me then was how normal they were as a family. The couple had joined Steptoe's laparoscopy programme because they were desperate to have a baby and would try anything, though John Brown said he thought they were volunteering for something like insemination. Following the birth of Louise in August 1978, they returned to their home near Bristol and were truly amazed to find the world's press camped on the doorstep.

Today, of course, the legacy of Louise's birth is the very ordinariness of its conception, as witnessed now in more than 6 million babies, and in a procedure which even the most reactionary must surely consider routine.

*Simon Brown
Focus on Reproduction*

1. See <https://www.youtube.com/watch?v=pqu8Y4XGFK4>

2. Symposium: The history of the first IVF births. *Reprod Biomed & Society Online* 2015; doi.org/10.1016/j.rbms.2015.05.001-6



The Brown family speaking at a press conference in 1995. From left, Lesley Brown, younger daughter Natalie (also an IVF baby), John Brown and Louise.



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