

focus on REPRODUCTION



FREEZE ALL EMBRYOS?

Is the evidence there yet?

- Facing up to the 'business' of IVF
- Reproductive medicine in the Nordic countries

// MAY 2016



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MAY 2016

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CHAIRMAN'S INTRODUCTION

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Several ESHRE meetings scheduled for early April - including the Executive Committee and Scientific Committee to complete abstract selection for Helsinki - had to be cancelled following the tragic events in Brussels in March. These meetings would have involved strategy and finance, communications and publications, as well as the Annual Meeting's scientific programme. All very important for running and planning both day-to-day and future activities of the Society. So plans had to be rescheduled, and live meetings replaced by video links and shifted venues.

Running a large and complex society like ESHRE demands a huge input of human as well as financial resources. Everything that ESHRE does - annual meetings, Campus workshops, memberships, registrations, certification, data collection, guidelines and communication with members and speakers - is outstandingly handled by an 11-member team under Bruno Van den Eede at Central Office. In parallel and working closely with Central Office is the Executive Committee, who meet five times a year and, together with smaller specialist committees, manage all the Society's strategic, scientific, ethical and political developments. It is all these people, investing so much time and energy, who really keep ESHRE healthy and growing.

One of the major items on our reshuffled April agenda was of course the Annual Meeting, which, despite the problems in Brussels, will go ahead as planned in July. As reported in this issue of *Focus on Reproduction*, we received a total of 1764 abstracts from 68 different countries, which suggests yet another high number of participants and many interesting free sessions. Helsinki itself feels like a safe place, and we of course hope that our members, speakers and exhibitors will all feel free and secure enough to enjoy this wonderful city and outstanding congress.

We have 13 exciting pre-congress courses this year, and three full days of presentations. The invited programme includes many hotly debated issues, ranging from basic physiology to clinical applications, from novel research to state of the art. And of course, one of the reasons for going to a meeting like this is to meet old and new friends and colleagues, and find out what's going on. So there will be social events too, with a warm welcome from ESHRE. On the Tuesday we have a networking party, an informal event where for a small fee you will receive a couple of drinks, some fingerfood and fantastic live music. We hope this will be another memorable unrivalled congress, attractive to both our young and older members - and that we will see you all in Finland in mid-summer.

Kersti Lundin
ESHRE Chairman 2015-2017



// MAY 2016

Abstracts still sky high

- More than 1700 abstracts of new studies submitted for this year's Annual Meeting.

- Asian countries now responsible for more than one-third of all submissions

MORE THAN 230 abstracts of original studies - from a sky-high total of 1764 submissions - have been selected for oral presentation in Helsinki. A further 800 abstracts have been selected for poster presentation.

'The number of abstracts submitted for Helsinki was only 40 short of last year's record-breaking total,' said ESHRE Chairman Kersti Lundin. 'These consistently high rates of submission yet again highlight ESHRE as *the* scientific event of the year and *the* place to present the very best new work in reproduction. Few other meetings in reproductive medicine can command this sort of support.'

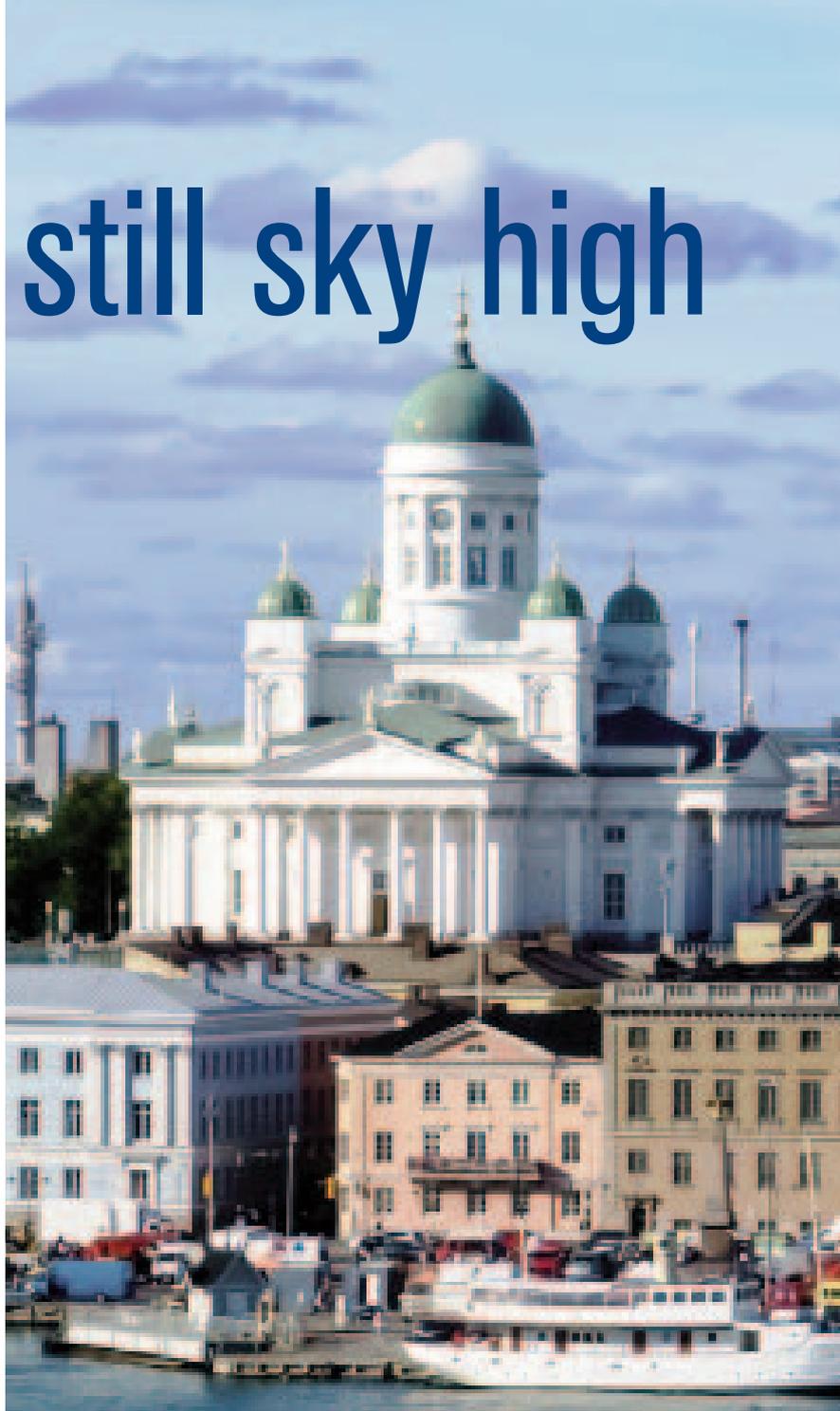
This year's abstract total not only marks a near-record entry but also reflects the very high standards now required for oral presentation selection. As ever, submissions were refereed blind by a selection committee, which included, among others, the co-ordinators of ESHRE's 12 Special Interest Groups. Selection for the oral or poster programme was dependent entirely on the committee's score, and represented an acceptance rate of around 13%.

As ever, the greatest number of abstracts were in clinical science, of which embryology (358 total abstracts) is now the most prolific. Female fertility (237 abstracts), reproductive endocrinology (230), andrology (174), endometriosis (146), and reproductive genetics (126) were also popular.

All abstracts, which were submitted in the *Human Reproduction* format, were reviewed according to ESHRE's standard procedure of screening and scoring. Screening aims to ensure that abstracts are

designated to the correct topic category, while selection for oral and poster presentation is done solely on the basis of scores awarded by reviewers. The International Scientific Committee finally selected 234 abstracts for oral presentation from the 1764 submitted.

The highest number of abstracts came from Spain (147 submissions), China (141), Italy (131), Japan (131), and UK (128). The ever-growing presence of China and Japan in the scientific programme of an ESHRE Annual Meeting continues, described as a welcome development by the ESHRE Chairman, a trend reflected too in submissions to the ESHRE



AGENDA OF 2016 GENERAL ASSEMBLY OF MEMBERS

The Annual General Assembly of Members will be held on Tuesday 5 July 2016, from 18.00 to 19.00, at the Messukeskus Expo and Convention Centre, Helsinki, venue of the 32nd Annual Meeting. The agenda will be as follows:

1. Minutes of the last meeting (held in Lisbon and published in *Focus on Reproduction*, September 2015)
2. Matters arising
3. Membership of the Society
4. Society activities
 - Annual meetings

- Campus meetings
 - Special Interest Groups and Task Forces
5. *Human Reproduction* journals
 6. Paramedical Group
 7. Financial report
 8. Composition of the Committee of National Representatives
 9. Election of the Honorary Members for 2017
 10. Any other business
 11. Date of the next General Assembly of Members

journals. Europe remains the Meeting's most prolific source of abstracts, with around 53% of all submitted, with Asia responsible for more than 30%. China is now ESHRE's second largest contributor.

Scientific programme

The main scientific programme is now in place and its high quality begins in the very opening two keynote lectures. The subject and presenter of the Human Reproduction Lecture are derived from papers with the highest number of full-text downloads during their first six months of publication in the journal between January 2014 and June 2015. You can find more details of the winning study on page 8.

This lecture is followed immediately by a report from one of Finland's most influential investigations, the longitudinal Helsinki Birth Cohort Study, which comprises lifespan data on more than 13,000 subjects born between 1934 and 1944. The main aim of the study is to assess the importance of early life factors on later health taking into account adult lifestyle, as well as socioeconomic and genetic factors. Principal investigator Professor Johan Eriksson will report on one of the study's main research objectives, the long-term effects of maternal obesity on the health of offspring.

The main programme will continue with a series of invited presentations on topics of current interest and development. Notable among these will be this year's renewal of the Fertility Society of Australia exchange award, now in its 20th year. This year's speaker, following his award last year at the FSA annual meeting in Canberra, is Peter Coleman, PGD lab director of Melbourne IVF; his presentation in Helsinki will be on the validation of next-generation sequencing for chromosome aneuploidy. Another Australian in the invited programme certain to attract a keen audience is Christos Venetis from IVF Australia in Sydney who, as an adjunct to optimising IVF outcome, will assess the relevance of progesterone levels during ovarian stimulation. A *Human Reproduction* study by Venetis and colleagues from last year found that live birth rates were significantly

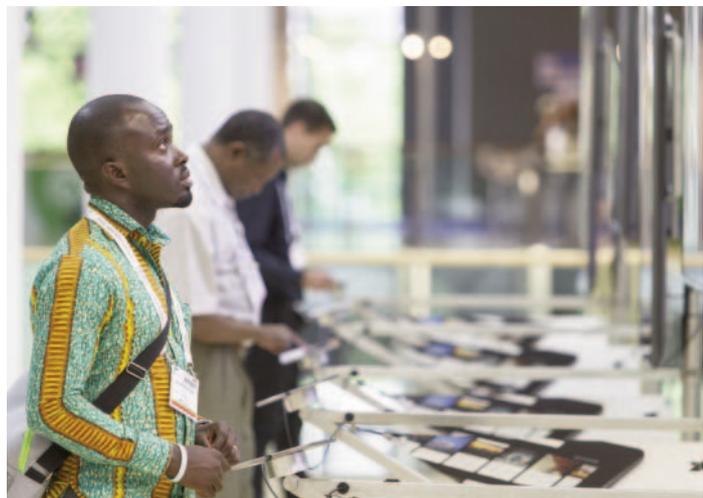
decreased in the group with elevated progesterone levels on the day of hCG.

Posters

As ever, around 600 abstracts have been selected for poster presentation. As before, all posters must be available in electronic format, but this year, in line with the congress's paper-free credentials, there will be no paper posters or poster boards. However, discussions will be arranged for those selected posters considered for the two poster awards (in basic and clinical science).

Precongress courses

Thirteen precongress courses will be staged on the Sunday preceding the Opening Ceremony. The majority are organised by ESHRE's Special Interest Groups, but there are additional courses run by the editors of the ESHRE journals on academic authorship, by the ASRM on the techniques of embryo transfer, by the Middle East Fertility Society on innovations in ART designed to improve outcome, and on epigenetics organised by the Paramedical Group.



Only electronic posters this year.

Social programme

The Opening Ceremony, to be held on Sunday 3 July at 19.00, is the first of the meeting's social events and will be followed by a welcome reception in the exhibition area. Admission to the Opening Ceremony, which will take place in the main hall of the congress centre, and welcome reception are complimentary. All registered participants are warmly invited to both events. At the Opening Ceremony ESHRE will pay tribute to this year's two Honorary Members for their outstanding contribution to reproductive medicine and science.

ESHRE's charity run will start near the congress centre on Monday 4 July at 18.30. The run, now in its fourth year, gives ESHRE members a chance to team up with Fertility Europe, ESHRE's partner patient organisation, to do a little good for their own health and help raise funds for patient groups throughout Europe. You can register for the run (and/or make a donation as an extra) online on the registration form.

An ESHRE evening networking event will take place on Tuesday 5 July at 18.30. Venue for this relaxed gathering - with fingerfood, drinks and entertainment - will be at Kaivohuone, a historic Finnish venue with views over the marina. This is an optional event but will give everyone the chance to say hello, for scientists to meet clinicians, juniors to meet their seniors, and of course for everyone to meet friends and colleagues. The entrance fee is just €30 per person, and registration details are on the ESHRE website.

Paper-free

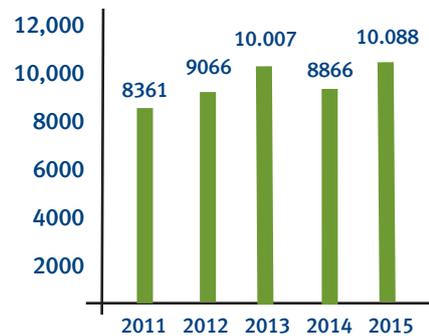
This year's congress will be another paper-free event, with congress bags only available to those who want them, and programme and abstracts available online and via the congress app. The app, downloadable to all devices, will be the easiest way to browse the programme, create an individual itinerary and read the abstracts.



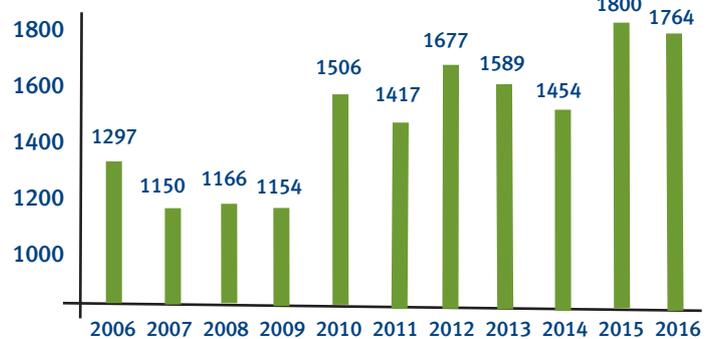
With its historic facade and traditional Finnish appeal, Kaivohuone creates a truly atmospheric venue for this year's get-together - with local foods and views over the famous marina.

Last year's Annual Meeting in Lisbon attracted a record attendance of 10,088. Such consistently high numbers make the ESHRE congress the world's stand-out event in reproductive medicine and science.

Annual Meeting attendance 2011-2015



Annual Meeting abstract submissions 2006-2016



A steady growth in the number of abstracts submitted, largely driven by submissions from Asian countries, with China now second ranked.

Awards on offer this year

There are six awards this year, each with a prize of €2000. In addition, one presentation will be selected for the Fertility Society of Australia Exchange Award. Top-scoring presentations and posters will be judged by committee, and authors of pre-selected abstracts may be asked to submit an extended abstract. This year's awards are:

- Basic Science Award for oral presentation
- Clinical Science Award for oral presentation
- Basic Science Award for poster presentation
- Clinical Science Award for poster presentation
- Nurses Award
- ART Laboratory Award for the best oral or poster presentation by a lab technician
- The Fertility Society of Australia Exchange Award by which an educational travel grant will allow the winner to present their data at the next annual meeting of the FSA

All awards will be presented at the closing ceremony on Wednesday afternoon, the final event of this year's social programme.

Two honorary members whose histories go back to the very origins of ESHRE

It is a remarkable coincidence - or perhaps just a measure of their respective esteem - that both this year's honorary members of ESHRE each figured in the very first issue of *Human Reproduction* in 1986. Henry Leese, writing with embryologist David Gardner, reviewed the measurement of nutrient uptake by mouse embryos as a marker of viability pre-transfer, while Markku Seppälä, in a report with colleagues from Helsinki and elsewhere, proposed the validity of two endometrial proteins as markers of endometrial function in early reproductive events.

Indeed, both Seppälä and Leese were early members of the editorial board of *Human Reproduction*, with Seppälä an associate editor from 1990 (and later too of *Human Reproduction Update* and *Molecular Human Reproduction*). Leese went on to become a co-founder and editor of the journal *Human Fertility*, a publication representing eight of the UK's learned societies.

Seppälä's major research interests, as reflected in that first *HR* paper, have been in embryonic, fetal and placental proteins in early development and cancer, endometrial protein secretion, growth factors and their binding proteins, carbohydrate ligands and functional glycomics in cell attachment and human reproduction.

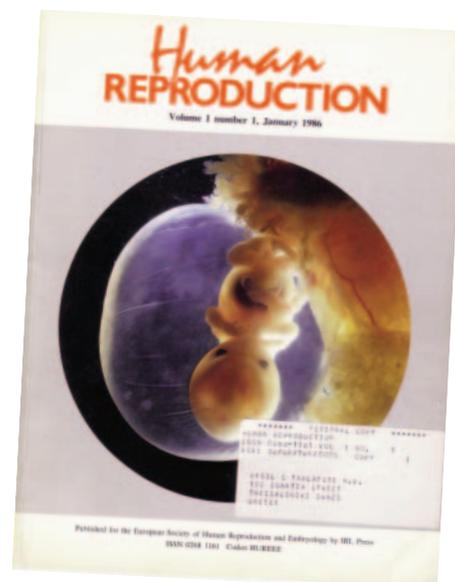
By a further coincidence, Seppälä was president of the third World Congress of IVF and Embryo Transfer, which took place in Helsinki in 1984, and it was at this congress at the Finlandia Hall that Robert Edwards and the French gynaecologist Jean Cohen gathered a few colleagues together to discuss the formation of a European society for reproductive medicine. That society, following the formation of a 'temporary committee', would later that year become ESHRE.

Today, Seppälä is Emeritus Professor and Senior Research Associate at Biomedicum Helsinki, a centre for research and training operating in collaboration with the University of Helsinki, Helsinki University Central Hospital, and Finland's National Institute of Health and Welfare. Seppälä has spent the majority of his career in Helsinki. It was at the city hospital in 1984 that Finland's first IVF baby was born in the care of Seppälä and IVF clinic director Aarne Koskimies (who is a member of the local organising committee of this year's ESHRE congress).

Seppälä with ESHRE founders Robert Edwards and Jean Cohen at the Society's first annual meeting in 1986 in Germany.



Volume 1, number 1, with papers from both this year's honorary members.



Honorary members 2016: Markku Seppälä and Henry Leese.

Henry Leese too is a basic scientist, a reproductive biologist working for many years in embryo metabolism. His work has enhanced our understanding of the nutritional requirements of the early embryo, and laid the foundations for a non-invasive assessment of embryo viability. It was Leese in 2002 who proposed the 'quiet embryo hypothesis', by which viable embryos would have a more tranquil metabolism than those which arrest. The hypothesis was based on data largely derived from Leese's own experiments on the net depletion or release of nutrients such as pyruvate, glucose and amino acids by mouse and human embryos. According to the hypothesis, 'quieter' embryos - that is those with a lower metabolism - have a higher potential for implantation, a principle somewhat confirmed recently by the finding that mitochondrial DNA levels are lower in viable blastocysts than in those failing to implant after transfer.

The now widely recognised concept of DOHaD (developmental origins of health and disease) - that the periconceptual period is critical for the healthy development of the embryo - reflects the direction of Leese's work and the importance of maternal nutrition in the early developmental stages of the embryo.

Henry Leese is now Emeritus Professor of Biology at the Hull York Medical School and was a member of the UK's regulatory authority (HFEA) from 1998 to 2002.

Little effect of lifestyle on sperm morphology

● Opening Helsinki keynote lecture on predisposing factors in male infertility

IT WAS THE LANDMARK paper of Carlsen, Giwercman, Keiding and Skakkebaek in 1992 that sparked the controversy of a 'genuine' decline in sperm quality over the preceding 50 years and an attribution of its cause to environmental factors. Since then a whole cottage industry has sprung up dedicated to the discovery of lifestyle and environmental evidence for this implosion of global sperm count and quality.

There emerged many well supported claims that the exposure of the male foetus to endocrine disrupting chemicals (notably phthalates and pesticides) could cause disturbances in the development of cells within the testis, which would in turn lead to decreased sperm concentrations and an increasing incidence of testicular cancers, cryptorchidism and hypospadias. Later studies suggested that even the eating, smoking and drinking habits might also contribute to the poorer semen qualities found in modern-day young men.

The paper which now forms the basis of this year's opening Human Reproduction keynote lecture would have frustrated many of those studies, for it was here, in a highly downloaded paper from the journal between January 2014 and June 2015, that UK andrologist Allan Pacey and colleagues reported that most common lifestyle habits have little effect on the risk of poor sperm morphology.¹ Previous papers from the same study had found a similarly neutral effect of lifestyle on motile sperm concentration, and few effects of occupational chemicals (other than glycol ethers) on motile sperm count.^{2,3}

The Human Reproduction lecture has quickly set a record-breaking precedent of bumper crowds and maximum attendance to fire the ESHRE congress into life. Last year in Lisbon around 4000 packed the auditorium for the two opening keynote lectures.

This year's lecture will be given in Helsinki by the study's principal investigator, Allan Pacey, Professor of Andrology at the University of Sheffield



UK andrologist Allan Pacey will deliver this year's opening Human Reproduction lecture.

and a recent chairman of the British Fertility Society. The paper - a fourth from the Chaps-UK (Chemicals and Pregnancy) study - was highly downloaded from the *Human Reproduction* website during the six-months assessment period.

The bottom line of the study and its three predecessors is that lifestyle makes little contribution to the risk factors for poor sperm morphology. And morphology, Pacey told *Focus on Reproduction*, is associated with DNA fragmentation and sperm aneuploidy - and is thus a reasonable marker for the overall quality of spermatogenesis. 'So on the basis of these results,' said Pacey, 'there seems little point in delaying IVF just for the male partner to make lifestyle changes.'

Although many studies have made claims that a man's lifestyle can and does affect sperm morphology, Pacey describes them as 'weak', with many underpowered and poorly controlled. This study, however, was a substantial case-referent study with 318 cases and

1652 referent controls; cases had poor sperm morphology (<4% normal forms based on 200 sperm assessed), and exposures included self-reported use of alcohol, tobacco, recreational drugs as well as occupational and other factors.

Of the risk factor variables for poor sperm morphology, only the use of cannabis in young men in the three months before sample production and sample production in the summer months proved significant. No significant association was found with body mass index, type of underwear, smoking or alcohol consumption. 'This suggests that an individual's lifestyle has very little impact on sperm morphology,' said Pacey, 'and that delaying IVF to make changes to lifestyle is unlikely to enhance the chance of conception.'

Pacey describes the findings as 'unbiased', noting that all lifestyle details were disclosed before the subjects knew the results of their semen analysis - 'a major strength of the study design'. 'If there is a risk factor, we would have found it,' he insisted, 'but the fact that

there were so few is in itself significant.

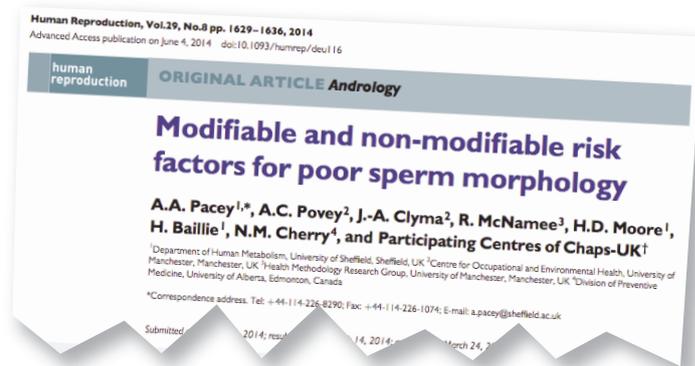
The association with cannabis prompted big headlines when the study was publicised by press release in 2014, and this, Pacey admits, may be one reason for its high level of professional interest. However, the lifestyle questionnaire (and subsequent interviews) were not able to determine any dose effect, although the association with younger men may well be a reflection of greater use. Pacey said that other studies on cannabis and male fertility have largely focused on the negative effects of the main psychoactive compound on sperm motility.

So, if lifestyle has little effect on sperm morphology, what does? Pacey believes there may be a statistical effect dependent on age-related infertility in the female partner, and inevitably genetic factors. Smoking, for example, has been shown to have a definite effect on DNA fragmentation in the sperm cell. But he

also stresses that 'morphology' and 'motility' are two distinct processes, such that an effect of, say, tight underwear on motile sperm concentration may not be evident on sperm morphology.

It is also intriguing that this study began its recruitment in 1999, when lifestyle - including mobile phone use! - was much different from today. Pacey says he'd like to do the study again, to see if life in the mid 2010s has any more pronounced effects on sperm morphology and motility than it did 25 years ago.

Meanwhile, the cottage industry of small studies and big headlines is likely to continue, with the mobile phone now elevated to risk factor status alongside tight jeans and underwear.



1. Pacey AA, Povey AC, Clyma J-A, et al. Modifiable and non-modifiable risk factors for poor sperm morphology. Hum Reprod 2014; 29: 1629-1636.
2. Povey AC, Clyma JA, McNamee R, et al. Participating Centres of CHAPS-UK. Modifiable and non-modifiable risk factors for poor semen quality: a case-referent study. Hum Reprod 2012; 17: 2799-2806.
3. Cherry N, Moore H, McNamee R, et al. Occupation and male infertility: glycol ethers and other exposures. Occup Environ Med 2008; 65: 708-714.

A fourth title added to the ESHRE Human Reproduction journals

ESHRE will introduce a fourth journal to its successful family of publications in Helsinki. *HROpen*, approved in concept by the Executive Committee late last year and likely to publish its first papers before the end of this, will be an open access journal and available only online.

'This is the future for medical journals,' said ESHRE's Chairman Elect Roy Farquharson. 'Paper journals have a finite future, and more and more funding organisations require open access.' Indeed, an analysis performed by the journal *Nature* earlier this year showed that around 17% of new manuscripts were published as open access in 2014, up from 12% in 2011.

Siladitya Bhattacharya, Professor of Reproductive Medicine at the University of Aberdeen, UK, will be the first Editor-in-Chief of *HROpen*. His appointment, which was confirmed by ESHRE's Executive Committee following interviews in February, will be for a three-year term with opportunity for extension for a further three years.

The primary aim of *HROpen* is to broaden the editorial range of the ESHRE journals and provide a publication of high quality research beyond the traditional focus of infertility - thus, a rapid and inexpensive means of publication with a wider scope than ESHRE's other titles.

Authors will incur no processing fees for the first three years of the journal's life, and thereafter the introduction of processing fees - as components of the open access publishing model - will be at the

discretion of ESHRE's Executive Committee.

Following its advertisement on the ESHRE website, there were more than 20 applications for the post of Editor-in-Chief, a number of whom were short-listed and interviewed. Bhattacharya, who has earned an international reputation in health services research, randomised trials and the epidemiology of reproductive medicine, was a welcome appointment to steer the new journal to a respected place alongside its three sister publications.

Open access is a fast growing trend in journal publishing, but has not been without its controversies, not least the rise of questionable operators with few objectives other than fees from authors. There has also been heated debate over what are now known as 'hybrid' journals - usually well established subscription titles which will also take open access papers for a fee. In one bid to crack down on the double fees of hybrid titles, a consortium of 14 institutes in the Netherlands has now negotiated several deals with major publishers to make more Dutch papers open in subscription journals - and with the reported aim of shifting the journals to an open access business model and away from the hybrid anomaly.

HROpen, however, will be a fully open access journal with papers published online immediately after peer review and acceptance. Once published, papers will contribute to the journal's eligibility for an impact factor, which ESHRE estimates will be available in around three years.



Siladitya Bhattacharya, editor of *HROpen*

Ethics committee hosts expert meeting on commercialisation in reproductive medicine

THE BIGGEST challenge likely to face ESHRE over the coming years is not membership or the progress of its journals, not e-learning or sustainability of the certification programmes, but the encroachment of business great and small into the everyday life of the Society. The commercialisation of IVF is 'everywhere', said former *Update* editor Bart Fauser at a meeting on the subject specially convened by ESHRE. 'Being a university professor has now become an exercise in money generation.'

Such trends are similarly apparent in the university institutions themselves, where technology transfer officers are vigilantly on the look out for any scientific development amenable to patent and profit a little way downstream. Short term financial gains are now the aim of much university research.

With the ART 'business' now posting an annual growth of around 7%, former ESHRE Chairman Arne Sunde forecast an \$11 billion industry by 2021, 'a safe investment with a relatively high return' for those scanning the commercial horizon. Within its 'value chain' from patient to clinic to baby lies a whole cornucopia of diagnostics, consumables and IT, few of which are free of commercial interest.

Regulation, added Sunde, was still 'immature', with little control over the science underlying most of the new introductions now popping up with frequent regularity in the IVF lab. 'The weak link in all this is us,' said Sunde. 'We accept these developments with little question and minimum evidence. Clinics are



Disclosure of interest

- ART will be an \$11 billion industry by 2021
- Facing up to the business of reproduction
- Transparency and integrity the way forward

easily seduced by these new disruptive technologies.'

His prescription for greater clinic control was more science-based regulation - which he urged ESHRE to support - although elsewhere at this meeting hopes seemed firmly based on individual integrity and a more detailed and transparent disclosure of interest, whether personal or institutional, financial or non-financial.

Moreover, in the reporting of results the incumbent editor of ESHRE's new journal *HROpen*

Siladitya Bhattacharya called for a shift in the parameters of outcome and a move away from pregnancy rates per transfer to cumulative live birth rate per started cycle. He noted in the current interpretation of results 'the opportunity for spin, a difficulty in interpreting genuine results, little emphasis on safety, and an 'airbrush effect' on outcome such that 'success' was manipulated as the attracting factor for patients.

Around 14% of manuscripts published in *Human Reproduction* are randomised trials, some but not



Speakers at this meeting included (left to right) former editor of *Human Reproduction Update* Bart Fauser and three former chairmen of ESHRE, Arne Sunde, Hans Evers, Editor-in-Chief of *Human Reproduction*, and Basil Tarlatzis, Chairman of ESHRE's Ethics Committee.

all of which will have a suspicion-raising commercial interest. However, said Editor-in-Chief Hans Evers, not every development in ART needs an RCT, nor should disclosures of interest necessarily affect a paper's scientific value or the outcome of peer review. But, with a huge decline in the number of display adverts in *Human Reproduction* (down to just two pages per issue in 2016), the reality is that journal editorial, not ads, has now become for many companies 'a part of their sales and marketing'. So one major problem for the editor in this commercial world is 'bad science', reflected in protocol deviation, endpoint switching, outcome manipulation and selective reporting. Later discussion on this subject raised the possibility that ESHRE itself could play a greater role in the facilitation of meaningful trials by identifying the knowledge gaps and bringing together the most suitable investigators.

What else about ESHRE itself? How can a Society so reliant on commercial support for its basic existence remain resistant to bias and retain its integrity? Bruno Van den Eede, managing director of ESHRE, said the Society needs about €5 million a year to conduct its everyday activities (including the Annual Meeting) and maintain its central office. This revenue is derived mainly from the Annual Meeting itself (72%), and then from publications (20%) and membership fees (5%).

One way for the Society to resolve any potential conflict of interest would be to remodel the entire organisational structure and remove satellite symposia, the commercial exhibition hall and all sponsored registrations - but such denial, of course, by concentrating only on unadulterated and unbiased educational ambitions, would be to undervalue the huge networking event that the Annual Meeting has now become. There are, as many here pointed out, other reasons than education why so many attend.

Van den Eede's more realistic position for ESHRE and its Annual Meeting lay in transparency and the clear understanding that commercial interests 'have no direct or indirect

influence on what we do'. This, he said, is ESHRE's guiding principle, that the Society has a 'clear and transparent relationship' with its supporters, and that they too are quite clear what their support implies. This, said Van den Eede, was the 'pragmatic' course through this potential minefield, a reasonable path to safeguard the integrity of the Society and its supporters.

It was this view - already implicit in the presentation of Bart Fauser - that transparency alongside individual and collective integrity would resolve many of these potential difficulties, but Basil Tarlatzis, chairman of ESHRE's newly formed Ethics Committee, insisted that a Society like ESHRE had now to ensure its actual and perceived financial autonomy, that the ever-encroaching commercial sector in ART should be 'kept at arm's length', with clear guidelines to define relationships, and that officers and editors should make full disclosure of their interests. The conflict of interest problems, he said, 'are not yet solved'.

*Simon Brown
Focus on Reproduction*



ESHRE managing director Bruno Van den Eede: A 'clear and transparent relationship' the guiding principle.

- At its meeting in February ESHRE's Executive Committee agreed that the Society's declaration of interest (DOI) form would be set-up electronically so that all members of ESHRE committees could declare their interests online and with full transparency.

Updated guidelines for IVF lab good practice

New focus on personnel, traceability and back-up

The first version of ESHRE's guidelines describing the minimal requirements for an IVF laboratory was published in 2000. The aim was to support IVF laboratories in the implementation of a quality system with adequate laboratory procedures, quality control and quality assurance, with emphasis on the responsibility for correct and justified performance of ART in the laboratory.

Now, 15 years later, the second revised version has been published (the first revision was in 2008). The guideline development group (GDG) was assembled at the request of the ESHRE Executive Committee. The group was led by the past Co-ordinator of the SIG Embryology Maria Jose de los Santos and consisted of ten embryologists representing six European countries. The GDG received huge methodological support from Nathalie Vermeulen, ESHRE's research specialist.

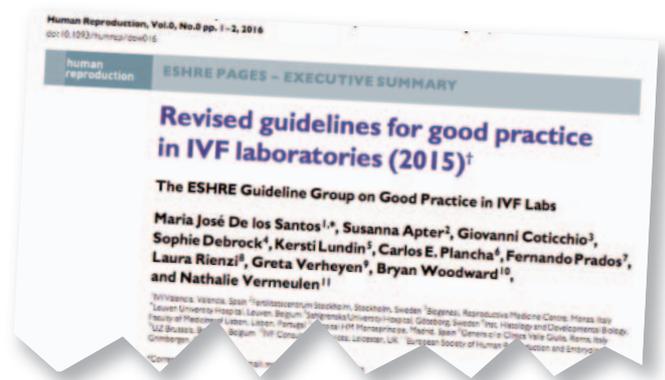
Every section of the earlier guideline was rewritten by an assigned GDG member and later commented on by all the other members of the group. The new recommendations were thoroughly discussed during two two-day meetings until consensus was reached. The draft version was published on the ESHRE website and members of the SIG Embryology were invited to comment. Opening the draft to proposals allowed members to both influence and contribute to guideline development. The final version has now been published on the ESHRE website and an executive summary in *Human Reproduction*.¹

What's new?

Many sections have been comprehensively revised. The first section on staffing is an excellent example of this. More focus has been given to personnel questions since staff (number, qualification, a proper introduction) are a key factor in any IVF laboratory.

The two sections on quality in the previous versions have been combined for clarity. Also the section on laboratory safety has been restructured to minimise unnecessary repetition and give a clearer presentation of the requirements of an IVF laboratory.

In the new version of the guidelines more focus has been placed on traceability (identification). This includes both the handling of cells and tissues in



Members of the guideline development group: from left, Giovanni Coticchio, Maria Jose de los Santos, Susanna Apter, Greta Verheyen, Sophie Debrock, Carlos Plancha, Kersti Lundin, Fernando Prados, Nathalie Vermeulen, Laura Rienzi, and Bryan Woodward.

addition to the consumables used.

Many details, as well as two whole sections (assisted hatching, preimplantation diagnosis), have been removed. Evidence on several issues is limited and readers are thus referred to other consensus documents. For example, on PGD, readers are referred to the Task Force paper published in *Human Reproduction* in 2014.² In accordance with ESHRE's instructions for publication of guidelines, references to other than consensus documents or similar have been removed.

A completely new section on emergency planning has been added to emphasise the importance of back-up systems and risk analysis in the IVF laboratory. Ensuring safety of personnel and patient material, protecting cryopreserved material, and limiting any damage of equipment and medical records are essential and require an appropriate systematic approach.

Susanna Apter
For the Guideline Development Group

1. See [https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-\(2015\).aspx](https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Revised-guidelines-for-good-practice-in-IVF-laboratories-(2015).aspx)
2. De Wert G, Dondorp W, Shenfield F, et al. ESHRE Task Force on Ethics and Law 22: Preimplantation Genetic Diagnosis. *Hum Reprod* 2014; 29: 1610-1617.

Pregnancy loss linked to uterine stem cell deficiency

Tissue sample study opens door to new therapeutic approaches

While aneuploidy in the embryo is common and now known to be a major contributor to implantation failure, the 'treatment' of recurrent miscarriage from a range of tested interventions has been largely characterised by failure and disappointment. A large randomised trial reporting in November, for example, showed that progesterone supplements given in the first trimester of pregnancy were of no help in women with a history of unexplained recurrent miscarriages.¹

With their underlying pathways still not clearly understood, a research group led by Jan Brosens at the University of Warwick, UK, has now demonstrated that recurrent pregnancy loss is strongly associated with uterine stem cell deficiency and accelerated stromal senescence.² This in turn disrupts the process of decidualisation, whose recurrence over several conception cycles leads to consecutive miscarriages. The findings emerged from a study of endometrial tissue samples taken from 183 women with recurrent implantation failure.

In a report for *Focus on Reproduction* in January last year Brosens and Nick Macklon identified the decidualised endometrium as 'an active gatekeeper' to implantation.

With the clinical implications described as 'potentially far reaching', study co-author Siobhan Quenby - who is also Co-ordinator of ESHRE's SIG Early Pregnancy - said: 'The real challenge now is to develop strategies to increase the function of stem cells in the womb lining.' This may include endometrial scratch, a procedure, said Quenby, with the potential to increase endometrial stem cell populations.

1. Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med* 2015; 373: 2141-2148.

2. Lucas ES, Dyer NP, Murakami K, et al. Loss of endometrial plasticity in recurrent pregnancy loss. *Stem Cells* 2016; 34: 3446-356.



Investigator Siobhan Quenby: Study has 'potentially far-reaching' clinical implications.

Genetic pattern to repeated IVF failure

A pattern of abnormal gene expression has been identified in endometrial biopsies taken from 43 women diagnosed with recurrent implantation failure following IVF.

'A specific gene fingerprint, when present, is always associated with failure,' said investigator Nick Macklon, working with his group in Southampton, UK, and former colleagues in the Netherlands.

The signature, which contains 303 genes, was found to predict repeated implantation failure with 100% accuracy - and with a further ability to stratify patients into distinct groups with different subsequent implantation success rates.

Koot YEM, Van Hooff SR, Boomsma CM, et al. An endometrial gene expression signature accurately predicts recurrent implantation failure after IVF. *Scientific Reports* 6, doi:10.1038/srep19411

Study finds no developmental delays in ART children up to three

Children conceived with infertility treatments are no more likely to have developmental delay than those spontaneously conceived, according to an NIH study recently reported.¹ The authors say the results 'may help to allay longstanding concerns that conception after infertility treatment could affect the embryo at a sensitive stage and result in lifelong disability'. There were no differences in developmental assessment scores in more than 1800 children born following infertility treatment (including IVF, FET, assisted hatching, ovulation induction and IUI) and more than 4000 controls.

Parents completed a questionnaire to screen children for developmental disabilities at 4-6, 8, 12, 18, 24 and 36 months. The questionnaire covered five main developmental areas, in which, overall, children conceived via fertility treatments scored similarly to the control children.

However, the study did find that the ART children were at increased risk for failing any single one of the five domains, with the greatest likelihood in personal-social and problem solving domains. Moreover, twins were more likely to fail a domain than singletons. However, after compensating for the greater percentage of twins in the ART group (34% vs. 19%), the study found no significant difference between the ART and control groups.

'Our results provide reassurance to the thousands of couples who have relied on these treatments to establish their families,' said investigator Edwina Yeung from the US National Institute of Child Health and Human Development.

1. Yeung EH, Sundaram R, Bell EM, et al. Examining infertility treatment and early childhood development in the Upstate KIDS Study. *JAMA Pediatr* 2016; 170: 251-258.

Time to 'abandon' the implantation rate?

● 'Methodological pitfalls and interpretational difficulties' the reason

The use of implantation rate as a measure of IVF outcome should be abandoned, according to Georg Griesinger, Head of Reproductive Medicine at the University Hospital of Schleswig-Holstein, Lübeck, and a member of ESHRE's Executive Committee. He gives 'methodological pitfalls and interpretational difficulties' as the reason.¹

The principal difficulty - as gleaned from an invited commentary in *Human Reproduction* - is a distortion of the implantation rate in studies in which unequal numbers of embryos are transferred between study groups, particularly when those rates are calculated on an aggregate and not individual basis. This, Griesinger notes, becomes apparent in studies in which fewer embryos are transferred in the intervention group than in the control group, and this, accordingly, is especially pertinent in studies in which embryos are positively selected for transfer - for example, by PGS or morphokinetics.

Implantation rate - usually defined as the percentage of transferred embryos which implant, or more specifically the number of gestational sacs seen on ultrasound at six weeks divided by the number of embryos transferred - will inevitably be affected by the number of embryos transferred (ie, the statistical denominator); thus, calculating the aggregate implantation rate in two groups of patients will inevitably distort the calculation towards a higher rate in the group with fewer embryos transferred. 'This phenomenon of fewer embryos transferred in the study group comes naturally with the nature of any embryo selection procedure,' Griesinger told *Focus on*



Georg Griesinger: Implantation rate 'nothing but a surrogate outcome.'

Reproduction.

In his *Human Reproduction* commentary he gives a classical example in which pregnancy rate is higher in one group, while the aggregated implantation rate is higher in the other group. In studies comparing elective single embryo transfer with double embryo transfer these two outcomes typically show divergent effects in different directions. 'It is important to understand this statistical phenomenon,'

Griesinger warns, 'so not to fall prey to the flawed idea that the embryo implantation potential would benefit from a single transfer.'

There are various other statistical and methodological problems around the implantation rate, he adds, and these have previously been highlighted by a number of authors already, yet there remains continuous use of the implantation rate in efficacy studies.

Beyond these statistical anomalies, Griesinger anyway dismisses implantation rate as 'nothing but a surrogate outcome', and irrelevant to most couples whose only aim is to have a healthy baby. With moves to make IVF outcome reporting more consistent with everyday practice (particularly in the USA), there may indeed be little room for implantation rate in future outcome measures.²

1. Griesinger G. Beware of the 'implantation rate'! Why the outcome parameter 'implantation rate' should be abandoned from infertility research. *Hum Reprod* 2016; 31: 249-251.

2. Williams RS, Doody KJ, Schattman GL, Adashi EY. Public reporting of assisted reproductive technology outcomes: past, present, and future. *Am J Obstet Gynecol* 2015; 212: 157-162.

ART and delayed childbearing explain rise in twin delivery rates

The overall rate of twin deliveries has increased dramatically over the past four decades in developed countries, according to a recent study from the French National Institute for Demographic Studies.¹ The authors provide two explanations for the increase: delayed childbearing (and the trend for older women to have twins more frequently than younger), and the expansion of ART. The effect of other factors is 'probably small'.

The twinning rate, defined as the proportion of twin deliveries in a given

year out of the total number of deliveries, increased in the USA from 9.5 twin deliveries per 1000 in 1975 to 16.9 in 2011. It roughly doubled in many other developed countries over the same period, increasing from 9.9 to 16.1 in England and Wales, 9.2 to 17.2 in Germany, 9.3 to 17.4 in France, and 9.6 to 21.2 in Denmark.

Using civil registration data, the investigators estimated that the effect of ART was about three times as important as the effect of delayed childbearing.

However, in one-quarter of the countries studied the twinning rate reached a plateau around the early 2000s and decreased thereafter. The main explanation for the partial decline appears to be the slow fall in ART multiple rates, evident in both ESHRE and ICMART data, and now in Europe apparently settled below 20%.

1. Pison G, Monden C, Smits J. Twinning rates in developed countries: trends and explanations. *Population and Development Review* 2015; 41: 629-649.

UK first to approve gene editing in embryos

● Licence granted to explore genes active in early human development

The first experiments outside China in the genetic modification of embryos are likely to take place this summer in the UK. The development follows a research license granted by the HFEA to the Francis Crick Institute in London to use the gene editing system of CRISPR to identify and understand the single genes involved in early embryo development.

CRISPR/Cas9 allows scientists to target, delete and replace specific genes, and reports suggest that the UK work will target and knock-out up to four genes thought to be active in early human development. According to *Nature*, the group's first experiment will involve blocking the activity of a 'master regulator' gene called OCT4, which is active in cells that go on to form the fetus. The HFEA licence will allow the study of these embryos for 14 days (as in all UK embryo research), and there will be no attempt to transfer them.

'Miscarriages and infertility are extremely common,' said researcher Kathy Niakan, 'but they're not very well understood. We would really like to understand the genes needed for a human embryo to develop successfully into a healthy baby.'

The techniques of genome editing have moved on at remarkable speed in recent months. Just six months ago an international summit meeting on gene editing agreed that basic and preclinical research in the specific alteration of genetic sequences should proceed, subject to appropriate legal and ethical rules and oversight.¹

In non-reproductive human cells genomic editing - using the same CRISPR technology - aims to repair or eliminate a mutation underlying a monogenic disease - in the hope that corrective changes to cells carrying the mutation could provide a once-and-for-all curative treatment for patients with some types of genetic disease. In December US scientists reported that they had used CRISPR to remove part of a defective gene in mice with Duchenne muscular dystrophy.²

More recently, scientists in the USA reported their use of CRISPR technology to repair a genetic mutation responsible for retinitis pigmentosa, an inherited condition that causes the retina to degrade and leads to blindness in at least 1.5 million cases worldwide. The study was the first in which researchers replaced a defective gene associated with a sensory disease in stem cells derived from a patient's own tissue.³

With the HFEA's OK, Britain has now become the first country to approve the use of public funding for gene editing - although it remains illegal to alter the genomes of reproductive embryos. In the USA labs must find private funding for any research that creates or destroys human embryos. In China, where the first



reported - if inefficient - editing experiments took place, any guidelines seem foggy at best.

A writing group including several members of ESHRE has evaluated the current status of genomic editing in the human germline. In a paper recently published the authors have identified numerous technical challenges and limitations associated with the CRISPR/Cas9 editing system, which will require more research.⁴ However, they conclude that these limitations should not prompt a generalised moratorium on the technique in human embryos, but rather encourage efforts to establish an international regulated framework for transparent research.

- A discussion of the risks, advantages and possible applications of gene editing will be featured in an ESHRE workshop in September this year organised in Amsterdam by several of the Society's Special Interest Groups (see page 30).

‘Limitations of the CRISPR system should not prompt a generalised moratorium’

1. See <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=12032015a>
2. See <http://www.sciencemag.org/news/2015/12/crispr-helps-heal-mice-muscular-dystrophy>
3. Bassuk AG, Zheng A, Li Y, et al. Precision medicine: Genetic repair of retinitis pigmentosa in patient-derived stem cells. *Sci Rep* 2016; doi: 10.1038/srep19969.
4. Vassena R, Heindryckx B, Peco R, et al. Genome engineering through CRISPR/Cas9 technology in the human germline and pluripotent stem cells. *Hum Reprod Update* 2016; 10.1093/humupd/dmw005.

Cautious US support for mitochondrial transfer

Another controversial technique first approved in the UK - mitochondrial replacement - has been given cautious ethical endorsement by an expert committee of the US National Academy of Sciences.¹ Research now moving forward in Newcastle (and described in a plenary lecture at ESHRE's annual meeting last year by Mary Herbert) indicates that replacement of mitochondrial DNA (mtDNA), the only source of DNA in human cells found outside the nucleus, can potentially prevent transmission of disease-causing mtDNA by transferring the intended mother's nuclear DNA into another woman's oocyte in which nuclear DNA is removed but healthy mtDNA is still present. The committee acknowledged that, from an ethical perspective, the desire of some women to reduce the risk of passing on a mitochondrial disease provides justification for proceeding with clinical investigations of replacement techniques. However, to prevent the possibility of heritable modifications being passed down within female lines, the committee advised that initial human trials should only involve male embryos (mtDNA is only passed on from mothers).

1. Claiborne AB, English RA, Kahn JP. Finding an ethical path forward for mitochondrial replacement. *Science* 2016; 10.1126/science.aaaf3091.

Guido Pennings, Co-ordinator of ESHRE's SIG Ethics & Law and Professor of Ethics and Bioethics at the Bioethics Institute Ghent, Belgium, has been a prominent contributor to many of the recent and current debates in reproductive medicine - not least cross-border reproductive care and social egg freezing. Here, he tells Focus on Reproduction what he hopes to achieve in these discussions.



FoR: How did you become a bioethicist?

GP: Partly by accident. I studied moral science, which includes human sciences, so there was always a certain link. I'd been working for several years in the private sector and then became unemployed. I looked at many jobs, including a project in gene therapy, for which I applied and got the job. That was in 1992.

Now, how would you define bioethics? What does it mean to you?

It's a combination of empirical knowledge and normative structures - meaning, you try to find out how things work in real life, and you try to combine that with normative ideas. That's the most difficult part. Take autonomy. You could say that people should decide for themselves. But in practice that doesn't work. People are limited by circumstances, by lack of time, understanding. Autonomy is a normative principle, but if you want to apply it in a medical setting you have to take into account these limitations. You can't just let people decide for themselves.

And is this only evident in medicine?

No, it's everywhere. In fact what we call empirical ethics - or bioethics - is based on one single idea, contextualisation. Meaning, look at how a principle is being used, how it works. Autonomy is still a good example. I had quite a fight in Belgium over the disposal of embryos. The law said that patients should decide for themselves in a contract at the start

Problems in everyday life

'What I'm trying to do is react to popular opinion . . . to analyse the arguments and contribute.'

of treatment. However, we know that people change their minds and don't contact the clinic. Why? Because they're not rational decision-makers. So if you know this, that people are fallible, you should at least write to them at the end of the storage period and ask them what they want. If you don't, you're not giving them real autonomy.

Ethics has always seemed an entirely academic discipline, yet - in ART especially - it's all about patients. There's an overlap between the academic and the clinical, so you're dealing with something that seems entirely cerebral, yet is really about a woman who wants to have a baby.

Yes, but there's no reason why they should be separate. Part of the reason I'm here - why I'm so active in ESHRE - is because from the very start I made a professional link with the Centre for Reproductive Medicine in Brussels. I was immediately involved in ART and they allowed me to find out how things work in the clinic through their ethics committee. How should we handle the difficult requests? What policies should we adopt? How do we balance the rights of the patient, the welfare of the child, the role of the clinic? How can we help the decision-making process?

So that's the practical objective? To help people make decisions?

Yes, broadly speaking. To see what people do in real life, combine that with a normative structure, and then try to improve it.

Is this especially relevant to infertility? That there's something almost spiritual about it because of what IVF can achieve?

Yes, but many of the issues - such as autonomy - would be just as prominent in oncology. What is different is the way people perceive the field of infertility, especially its extremities with designer babies or cloning. There are good reasons for this - to do with sex, family building, and religion. All the criticisms that Bob Edwards had to face in the early days with the embryo were really about what it means to be a person.

So what have been the biggest ethical questions you've tried to answer?

Contextualisation includes all the technological developments. Vitrification, for example, has brought about big changes. We can now do something we couldn't do before. So small steps make big changes. And that's happening all the time. They change the context of people's perception. Next it will be artificial gametes.

So are you saying that the big ethical questions are always based on small developments, not fundamental challenges?

Well, a relatively simple thing like ICSI has brought about major changes - for millions of people. From the point of view of ethics, however, it's changed our perspective on donor insemination. It's changed how we consider the manipulation of gametes. The whole process of treatment gets more and more complicated with each development. But the underlying factors in a way remain the same - the value of genetic parenthood hasn't changed, or level of risk we accept.

But what can your work do about this? Do you see a practical outcome? How do you evaluate what you do in the context of these small developments?

Well, right now I'm asked to speak a lot on social egg freezing, which has only become possible because of vitrification. But now we suddenly have women without a partner who want to postpone pregnancy. That for me is a very real consequence of vitrification. So what I'm trying to do is react to popular opinion - in this case about older women having babies. I'll look at the literature to find out about older mothers or if the children will be affected. Next come the normative structures, which you can see in the media - the idea that there's a certain time in your life when you should have children. Is there any

basis for this? So I analyse the arguments and try to contribute to it.

So you'll form some judgement which you hope will contribute to the discussion?

Yes. If someone tells me that it's very bad for a child to have a mother of 45, I can tell them to look at the literature. It's not true. So I'm really asking if these changes or opinions make sense. Is there a logic there.

Do these judgements contribute in a practical way to clinical progress, or are they just a slice of academia?

That's very difficult to measure. But what I can do is tell my clinical colleagues that there are good arguments, or no good arguments, to do something. Most of my job anyway is to do with policy considerations. Should we accept social freezing, and I'm saying that at the moment there is no sound argument to say we shouldn't.

And where else do you think we need this ethical guidance?

Donor anonymity still, where I've been fighting a battle for the past 20 years. First to accept non-anonymous donors, and now to accept anonymous donors.

And where else?

I think we should also reconsider our attitudes to regulation. For example, in the field of donor gametes people who don't like the regulations just go on the internet or go abroad. People simply make their own decisions, and the question is, how do regulators and clinics react to this.

And should ESHRE also take positions - through guidelines, position papers?

I think ESHRE should do something. We've moved from paternalism to patient rights, and now we're in the phase of commercialisation - so I'll pay and you should do what I want. It's like a pendulum, swinging between where the doctor decides and where the patient decides. But in reality this whole practice, in as far as it's framed in a societal context, is neither one nor the other, and if society is involved society should have a say on how things are being run. Society has a responsibility in reproduction. The question is, how far do you go, and where do you stop. But I think there should be a balance between the patient and society, a middle ground. ESHRE is in a position to contribute, and I think should try. We have the capacity, and people rely on expert opinion. We shouldn't be over hasty, but I think on a certain number of topics it would be a good thing if ESHRE gave an opinion.

PROUST QUESTIONNAIRE*

● **Which historical figure has inspired you the most?**

Can't think of one

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

Distractedness

● **... an in others?**

Indecision

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

Whisky

● **Who do you most admire?**

I like people, but don't admire them

● **Your greatest achievement?**

Initiating the debate on cross-border reproductive care

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

'Rather'

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

Spain

● **What book are you reading now?**

The Defense by Vladimir Nabokov

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

Czech Republic

● **What is your favorite occupation?**

Doing nothing with friends

● **The last film you saw?**

Le Tout Nouveau Testament by Jaco Van Dormael

● **Your favourite composer?**

Frank Zappa!

● **And your favourite writer?**

Hugo Claus

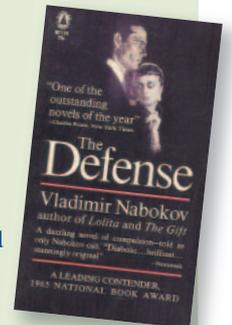
● **Champagne or beer?**

Beer, definitely

● **Do you have a personal motto?**

No

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



The freeze-all protocol

Instant gratification or low-risk investment?

While a freeze-all embryo policy is now well established in the prevention of OHSS, Christophe Blockeel says the evidence is not yet emphatically apparent in everyday practice.



Ovarian hyperstimulation syndrome (OHSS) is one of the most feared iatrogenic complications of an ART treatment. Its incidence ranges from 0.5% to 30% and varies according to the elected ovarian stimulation protocol and the baseline risk of the patient. The most devastating consequence of OHSS, affecting otherwise healthy women, is its threat to the patient's life. From the patient perspective (but also from a medico-legal point of view) the prevention of OHSS should remain the number 1 priority in reproductive medicine.

The segmentation principle for OHSS prevention

The segmentation concept has been increasingly acknowledged as a worthy strategy to minimise the risk of OHSS and is currently applied more broadly - namely in cycles with abnormal late follicular

progesterone levels and in oocyte donation programmes. The aim of this approach is to minimise the risk of OHSS at each step of IVF procedure.

1. GnRH antagonist downregulation during ovarian stimulation

The use of a GnRH antagonist protocol has been widely used in fertility clinics worldwide for many years. The pharmacological action of this analogue makes it more patient-friendly, especially because of its shorter duration of stimulation and fewer side effects. This increasing popularity of antagonists is also supported by an apparent lack of clinically significant difference in live birth rates between GnRH antagonists and agonists.¹

2. Final oocyte maturation and ovulation triggering with a GnRH agonist

Although associated with a significant

reduction in the occurrence of OHSS, the GnRH antagonist protocol has thus far been unable to eliminate it completely, especially when ovulation is triggered with hCG. For this reason, alternative trigger modalities, such as a GnRH agonist, have been the focus of much research.

However, the widespread application of these alternative trigger modalities has been limited by early corpora lutea demise and luteal phase dysfunction. Various strategies to amend the luteal phase defect have been suggested, such as intensive luteal phase support with transdermal oestradiol and intramuscular progesterone, dual triggering (with a GnRH agonist and lower doses of hCG) or luteal phase support with 1500 IU hCG following oocyte retrieval.

Others, however, have proposed that the complete disconnection of ovarian stimulation from embryo transfer (instead of attempting to counteract the luteal phase



is also proving an effective option for treating women with oligo- or amenorrhoea.

Freeze-all in everyday practice?

1. Favourable clinical outcome

The results of the first meta-analysis comparing fresh and frozen embryo transfer (FET) cycles suggested a significantly higher implantation and clinical and ongoing pregnancy rate in FET cycles.³ FETs may also be associated with a significant reduction in the rate of ectopic pregnancy, results which may be explained by the negative effect of ovarian stimulation on endometrial receptivity in a fresh cycle. Last but not least, reduced rates of low birth weight and preterm birth have been observed in some studies following FET

2. Shortcomings

Unfortunately, OHSS is yet to be completely eliminated, as the first cases of severe OHSS following a freeze-all strategy have now been reported. Moreover, while most perinatal outcomes seem to be more favourable following a frozen transfer, other studies have suggested that the latter might be associated with an increased incidence of large for gestational age singletons, even after accounting for maternal age and birth order.⁴

3. Another limitation: instant gratification!

Physicians are commonly asked by their patients whether ovarian stimulation may bear any carryover effects to a subsequent

defect) could be a more appropriate solution.

3. Elective vitrification of all embryos

The cryopreservation of all embryos after GnRH agonist trigger is a safe alternative for patients undergoing IVF and at-risk of OHSS. Furthermore, the vitrification process has made tremendous progress over the past decade and live birth rates following the replacement of thawed embryos have increased substantially by the widespread use of this embryo cryopreservation method.

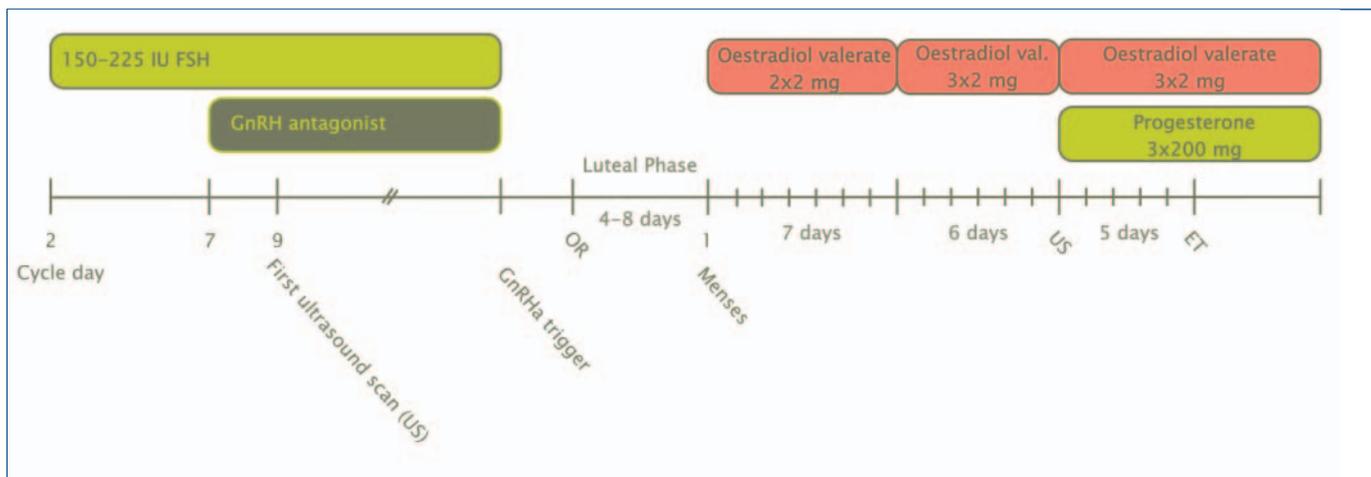
4. Transfer deferral of a single cryopreserved embryo to a subsequent natural or artificial cycle

The transfer of cryopreserved embryos can be successfully conducted in both natural and artificial cycles.² Although transfer of a cryopreserved embryo in a natural cycle

is a less expensive and more patient-friendly approach, artificial endometrial preparation has become more popular, especially for organisational reasons, and



CHRISTOPHE BLOCKEEL: 'THIS RELATIVELY NEW APPROACH IS GAINING POPULARITY AND MAY BECOME THE GOLD STANDARD FOR IVF STIMULATION IN THE FUTURE'



Freeze-all protocol for patients having IVF/ICSI at Universitair Ziekenhuis Brussel.

treatment. FETs are frequently postponed in an attempt to minimise any conceivable residual effect which ovarian stimulation may have on endometrial receptivity. However, the literature on this matter is scarce. Thus, while the empirical decision to defer transfer may be based on the best of intentions, its practice may unnecessarily frustrate couples who wish to become pregnant as soon as possible. To this extent, a recent study including data from two centres suggested that FETs performed immediately after a freeze-all protocol appear to result in higher pregnancy rates than those deferred to a later timing.⁵

4. Future perspectives

Although high-quality RCTs are still needed (and are still ongoing), this relatively new approach is gaining popularity and may become the gold-standard for IVF stimulation in the future! However, as our patients are eager to conceive as soon as possible, the delay in embryo transfer might cause distress.

If it is confirmed in larger prospective trials that an immediate FET has no detrimental effect of pregnancy outcome, time to pregnancy would only be delayed by a couple of weeks - and physicians would be one step nearer the widespread

application of the segmentation concept.

Thus, for the freeze-all strategy to thrive in the near future, specialists should not underestimate the importance of their own role as patient counsellors, to inform them of the possible disadvantages of pursuing instant gratification from a quick positive pregnancy test instead of an intervention associated with both safer and potentially better long-term outcomes.

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Past and future perceptions of an ART treatment cycle

Yesterday

GnRH agonist protocol

hCG for final oocyte maturation

Fresh embryo transfer - slow freezing of supernumerary embryos

Embryo transfer as SET, DET, TET, QET

OHSS 2-5%

Multiple pregnancies 20%

Tomorrow

GnRH antagonist protocol

GnRH agonist for final oocyte maturation

Vitrification of all embryos - 'freeze all'

SET in subsequent natural or artificial cycle

OHSS 0%

Multiple pregnancies 0%

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2. Glujovsky D, Pesce R, Fiszbajn G, et al. 2010. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2010: CD006359.
3. Roque M, Lattes K, Serra S, Sola I, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril 2013; 99: 156-162
4. Pinborg A, Henningsen AA, Loft A, et al. Large baby syndrome in singletons born after frozen embryo transfer (FET): is it due to maternal factors or the cryotechnique? Hum Reprod 2014; 29: 618-627.
5. Santos-Ribeiro S, Polyzos NP, Lan V, Siffain J, et al. The advantage of an immediate frozen embryo transfer following a freeze-all protocol: a retrospective analysis from 2 centres, Submitted for publication.

Finnish on a high note



With Finland the host of this year's 32nd Annual Meeting of ESHRE, Aila Tiitinen, one of the country's leading experts in reproductive medicine and a pioneer of single embryo transfer, reviews the benchmarks of registry studies, fertility preservation and safer IVF in the Nordic countries.

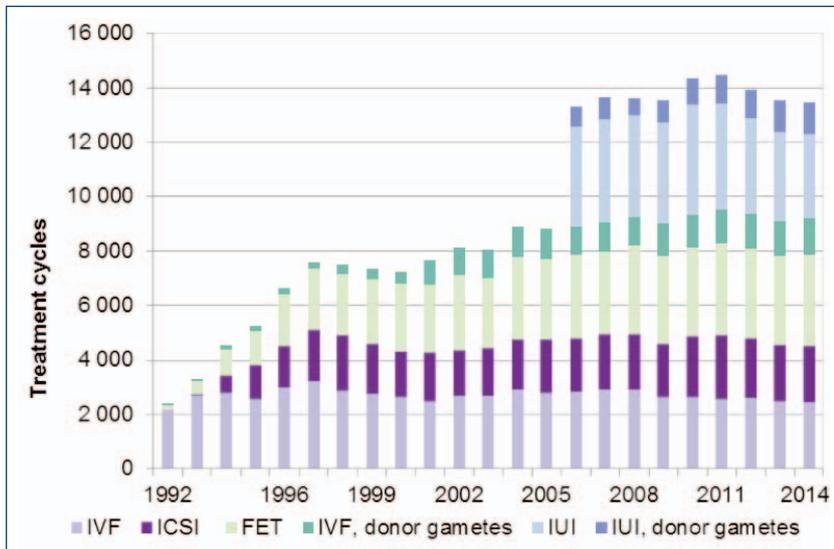
It is now beyond debate that twin pregnancies in IVF bring a higher risk to both mother and child than singleton. Preterm delivery and low birth weight mainly explain the excess neonatal morbidity.

According to the latest report from ESHRE's IVF Monitoring Consortium, the trend of transferring fewer embryos and freezing more seems to continue, although twin delivery rates ranged from 4.8% in Sweden to 41.6% in Greece.¹

More than ten years ago Finland adopted a policy of elective single embryo transfer (SET) combined with extensive use of frozen embryo transfer (FET), and

currently the proportion of frozen versus fresh embryo transfer cycles is higher than in most other countries. The ESHRE data for 2011, for example, show that the proportion of FER cycles compared with 'fresh' was 82.2% in Finland in contrast to an overall European rate of 32.3%. This SET strategy, which now dominates Nordic ART, also highlights how important the quality of cryopreservation programmes is; indeed, our policies of limiting the number of embryos transferred would not even be possible without good cryopreservation programmes.

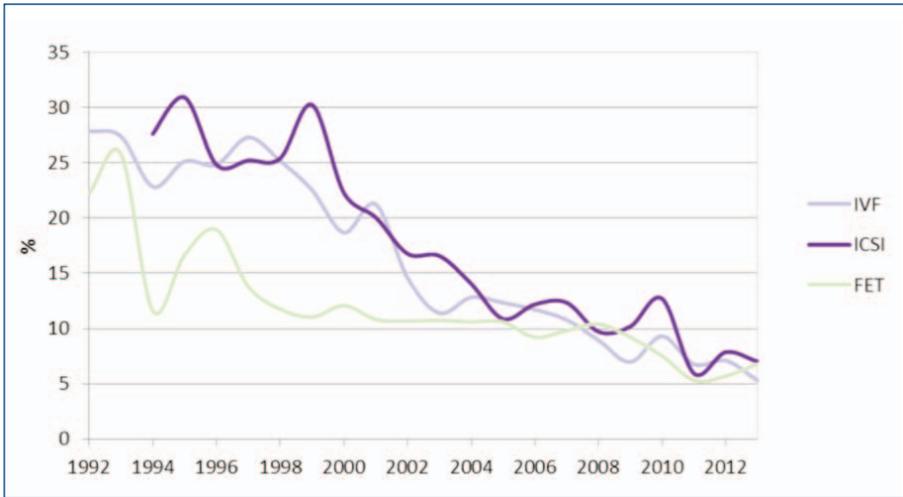
The Nordic countries were the pioneers of SET. The first randomised study from Finland was published in 2001 and demonstrated the efficacy of an SET approach.² The largest of the studies, a randomised multicentre trial performed in Scandinavia, also showed that in women under 36 years old transferring one fresh embryo followed by the transfer of one frozen embryo dramatically reduced multiple delivery rate while achieving an overall live birth rate no lower than with one two-embryo transfers (DET).³ A recent study from Finland showed that elective SET with cryopreservation is more effective and less expensive than DET, with the incidence of multiple births reduced more than twofold.⁴ Access to public funding for ART, availability of good cryopreservation facilities and legislation seem the most important reasons for the uptake of SET.



ART treatments in Finland 1992-2014.
(Source: Statistics, National institute for health and welfare, Finland)

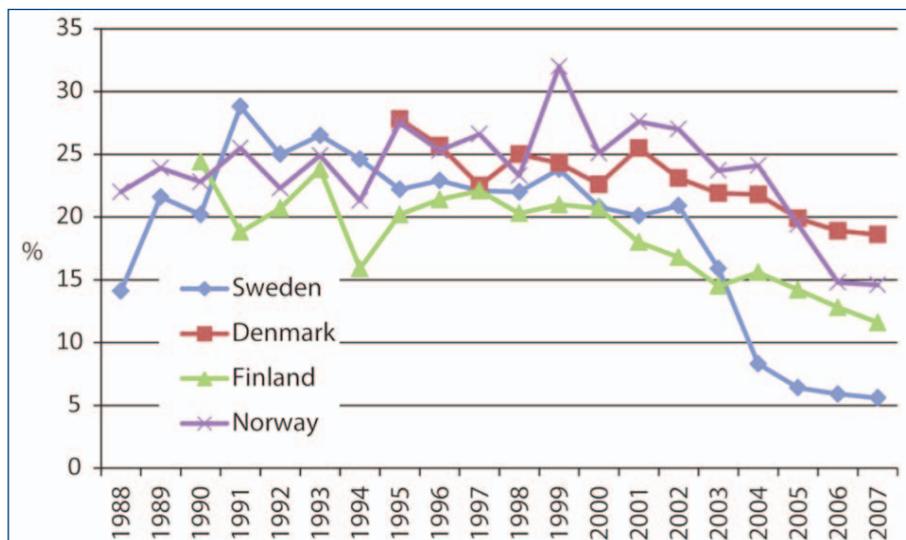
Registries

The Nordic registers, together with



*Percentage multiple births in Finland 1992-2012.
(Source: Statistics, National institute for health and welfare, Finland)*

individual identification systems, provide a unique basis for epidemiological studies, with follow-up of infant and maternal health after ART. The aim of the CoNARTaS task force is to provide a continuous Nordic monitoring system with data on all ART pregnancies, deliveries and children born in Norway, Sweden, Finland and Denmark.⁵ All singletons and twins conceived after IVF, ICSI and FET are included in this Nordic database, with ART singletons and multiples matched 1:4 with spontaneously conceived children from their own country. The perinatal outcome of 62,379 ART singletons and 29,758 ART twins born between 1988 and 2007 in the four Nordic countries has been analysed and compared, with results clearly showing that perinatal outcomes in ART have improved over the last 20 years, mainly due to the reduction in multiple births. We found a marked decrease in the rates of adverse perinatal outcomes - such as preterm birth and low birth weight - among ART singletons. The rate of twin deliveries was



Proportion of twin deliveries among ART births in four Nordic countries.⁵

reduced by one-third over the study period.

The safety of children born after FET is fundamental to an ART approach which combines SET with embryo cryopreservation. A Finnish register-based cohort study has a large sample size of 1825 FET singletons, which is still the largest controlled population-based cohort on morbidity associated with FET children. It shows that the early physical health of FET children is similar to that of children born after fresh ET until the age of three.⁶

Research on the neurocognitive development and mental health of ART children is also growing, particularly as related to early childhood. Generally, our findings show comparable socio-emotional development and well-being as found in

naturally conceived children. Some early neurocognitive and sensorimotor developmental delays and deficits have been occasionally reported, but these are partially explained by increased perinatal problems (eg, preterm birth, low birth weight and admission to neonatal intensive care) inherent in ART pregnancies. A recent cohort study from Finland compared mental health and developmental outcomes between ART and naturally conceived children, and the results confirmed the earlier view that ART is not generally associated with increased problems in child mental health or cognitive and social development.⁷ Indeed, ART boys showed even less cognitive developmental problems than control boys. Furthermore, normative gender differences in higher aggression and social and cognitive developmental problems among boys were present only in the control group, whereas ART boys and girls did not differ from each other.

Fertility preservation

The cryopreservation of ovarian tissue is likely to become integrated into the treatment of young women with cancer who face the risk of losing their fertility. More than 36 children worldwide have now been born following this procedure. A recent retrospective cohort study of 41 women who had thawed ovarian tissue transplanted 53 times over a period of 10 years describes the present situation in Denmark.⁸ The transplanted ovarian tissue seems viable for up to 10 years, with no relapses evident following the 53 transplantations, and the chance of a successful pregnancy is currently around one in three (for those with a pregnancy-wish).

Ovarian tissue cryopreservation is now considered a realistic clinical option in most centres of the Nordic countries. In Denmark



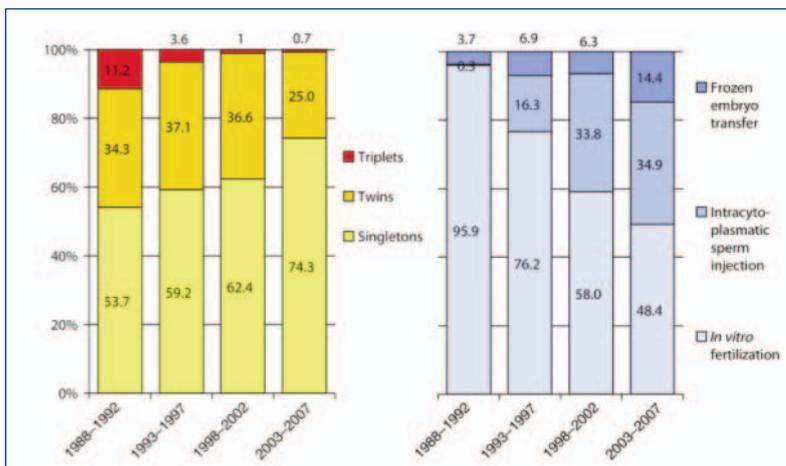
The world's first live birth from uterine transplantation. Brännström and his group in Gothenburg speaking at a press conference in December 2014.

and Norway it is available as routine treatment with centralised programmes, while in Sweden nearly all centres consider it experimental. In Finland two centres perform ovarian tissue cryopreservation. However, most centres prefer egg freezing after hormonal stimulation for fertility preservation when clinical conditions allow. The birth of a healthy baby after ovarian tissue cryopreservation and transplantation after thawing has been reported in most Nordic countries.

Pathways to parenthood

The recent first live birth in Sweden following human uterus transplantation is dramatic proof-of-concept of a treatment for women with absolute uterine factor infertility. The 15-year-long translational project, from its beginning in rodents to the first human live birth in 2014, has so far completed nine human uterine transplantation cases and achieved four healthy babies.

There have been recent discussions in many European countries, including all the Nordic countries, on surrogacy. In Iceland the Government has now prepared a law proposing the legalisation of altruistic gestational surrogacy, and the National Advisory Board on Social Welfare and Health Care Ethics in Finland and Swedish Medical Advisory Board in Ethics have



Proportion of twin deliveries among ART births in four Nordic countries.⁵

each proposed that surrogacy treatments should be allowed in restricted medical situations. While surrogacy is not officially allowed in many European countries (Austria, Bulgaria, Denmark, Finland, France, Germany, Italy, Malta, Norway, Portugal, Spain and Sweden), altruistic, but not commercial, surrogacy is allowed in Belgium, Greece, Netherlands and UK. Commercial surrogacy is legal in Georgia, Israel, Ukraine, Russia, India and California, USA.

According to a systematic review, most surrogacy arrangements are successfully implemented and most surrogate mothers are well motivated, having little difficulty separating from the babies born. Perinatal outcome is comparable to standard IVF and oocyte donation and there is no evidence of harm to the children born as a result of surrogacy.

Novel pathways to parenthood (including ART for single women) are currently a matter of wide discussion in Nordic countries. A recent opinion survey in Sweden found that 94% of women were positive about oocyte cryopreservation for medical reasons, and 70% for social reasons; 76% found it acceptable to offer ART to single women. Uterus transplantation was found to be more acceptable than surrogacy (80% vs. 47%) - and generally that Swedish women have a high acceptance of most new ART developments.

Aila Tiitinen is Professor of Reproductive Medicine at the University of Helsinki, Finland, and Chief Physician in Reproductive Endocrinology at Helsinki University Central Hospital. She is a member of the local organising committee for this year's ESHRE Annual Meeting.

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A new name and revised mission for the SIG EE

ESHRE's Executive Committee and the steering committees of the SIGs Early Pregnancy and SIGEE have agreed to restructure their composition and scope. The aim of the reorganisation is to emphasise their common areas of interest - ie, those elements of biology that are fundamental to understanding both endometrial receptivity and embryo implantation as well as the pathophysiological processes underlying endometriosis and endometrial disorders (such as abnormal menstrual bleeding and fibroids). We thus envisage that both SIGs will benefit from this change and that we will have greater synergy in organising high quality activities in basic and clinical research and training. This reorganisation is accompanied by changes in the mission statement of both SIGs, and the SIGEE has now been renamed the SIG Endometriosis and Endometrial Disorders (SIGEED).

Record-breaking Campus workshop

ESHRE's Central Office has declared that the number of participants (259!) at our ESHRE Campus meeting on **Controversies in endometriosis and adenomyosis**, which was organised jointly by ESHRE and the Turkish Society of Endometriosis & Adenomyosis in February in Istanbul, attracted more participants than any other Campus event. This workshop was hugely successful with meticulously prepared presentations and much interactive debate.

Annual Meeting Helsinki

This year's Annual Meeting is rapidly approaching and the event will be preceded by our pre-congress course on Sunday 3 July (09.00-17.00). The course will focus on medical treatments for endometriosis, with

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Andrew Horne (GB), Co-ordinator
 Carla Tomassetti (BE), Deputy
 Andrea Romano (NL), Deputy
 Antonio Simone Lagana (IT), Junior Deputy
 Gerard Dunselman (NL), Past Co-ordinator
 Krina Zondervan (GB), Basic Science Officer
 Lone Hummelshoj (GB), International Advisor



emphasis on basic and translational approaches, preclinical and clinical applications, and future directions.

Unanswered questions about endometriosis research

UK-based physicians are working with The James Lind Alliance Priority Setting Partnership for Endometriosis to identify and prioritise uncertainties, or 'unanswered research questions,'

about endometriosis. The aim is to ensure that those who fund health research are aware of what really matters to both women with endometriosis and healthcare providers. We encourage all stakeholders to participate - via <http://endometriosis.org/resources/jla/survey> - and submit your own unanswered questions (open until 31 May).

Future activities

We are working on an exciting programme for 2017. In January (27-28), we will be holding a Campus workshop entitled **Effects of ART and endometriosis on pregnancy outcome** in Sofia, Bulgaria. The course is a joint venture of the SIG Early Pregnancy and our SIGEED and will explore the effects of ART and endometriosis on pregnancy outcomes, including miscarriage, multiple pregnancies and ectopic pregnancy risk. The lectures will also consider the diagnosis of miscarriage, ectopic pregnancy (both tubal and scar) and pregnancy abnormality.

The 13th World Congress on Endometriosis will take place in Vancouver, Canada, from 17-20 May 2017. Abstract submission opens on 17 June, with a deadline of 9 October 2016.

Our pre-congress course for Geneva in 2017 will consider the highly debated topic of endometrial receptivity, its measurement and improvement of pregnancy outcomes.

Later in the year (18-19 September), we will be holding a second Campus meeting on **Methodological approaches for investigating endometrial function and endometriosis** in Edinburgh. This is a joint venture of the ASRM and the SIGEED, where experts will give an update on relevant methodological aspects of endometrial research.

To read more about us and our ongoing restructuring and activities, visit our page on the ESHRE website. Here you will find the latest information, recommended readings for a state-of-the-art knowledge on endometriosis and endometrial disorders, and additional useful links.

*Andrew Horne
 Co-ordinator SIG Endometriosis
 and Endometrial Disorders*



A record-breaking attendance of 259 at our February Campus meeting in Istanbul.

Campus events to follow the lead of members

Educational needs

In January's issue of *Focus on Reproduction* we printed a short questionnaire, followed by an e-mail with a link to the ESHRE website, on your priorities in continuing education. We had a good response, with more than 200 answering the questionnaire.

Based on your answers (which are briefly summarised in the table below), it seems that most of us consider our continuous training in the safety and quality of ART as very important. In addition, we found great interest in a potential Campus course on quality management and inspections by competent authorities. All proposed topics appear to present, more or less, the same average interest, somewhere between 'interesting' and 'very interesting'. We were pleased to learn that you rated the SIG SQART educational programmes attended so far as 'satisfactory'. As a result of this survey, we will now try to organise those Campus courses indicated by you as of most interest and we will continue to keep you updated by regular e-mails and reports in *Focus on Reproduction*.

Future events

Led by the success of our pre-congress course in Lisbon (**Quality assurance of ultrasound in medically assisted reproduction** whose webcast is available on the ESHRE website), we have another exciting course for this year titled **ART 2020: the next frontier**, which has been organised with the SIG Stem Cells. We have a very challenging programme with topical themes and

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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



answers to fundamental questions. Patients, doctors, basic scientists, embryologists and ethicists' perspectives will be presented, providing a full range of information on how to introduce new technologies in the safest way possible.

Later this year (22-23 September) the SIG SQART will be in Amsterdam for a

collaborative Campus meeting with the SIGs Ethics & Law and Stem Cells on **Novel gamete manipulation technologies in ART: SEEM (safety, ethical, efficient, moral) OK?**. This multidisciplinary course will target some of the recent breakthroughs in gamete manipulation as potentially new treatment methods for infertile patients.

Those interested in oncofertility have an important event on 17-18 November in Paris where we are organising a Campus course on **Innovative care and technologies for female fertility preservation**. The course will discuss the target populations of women and female children diagnosed with cancer who could benefit from fertility preservation. The course will have a pragmatic emphasis, exploring how to develop a multidisciplinary approach of benefit to cancer patients and the development of cryobiological platforms for urgent fertility preservation. Participants will hear about the different fertility preservation strategies appropriate to specific patient groups and oncology conditions, the risks/benefits balance and ethical considerations of these approaches. Also highlighted will be those treatments now at an experimental but promising phase of their development. The course will also raise discussion about the reaction of patients to preservation of their fertility potential and will cover many of the ethical aspects involved.

All 36 e-posters from Lisbon on the topic of Safety and Quality are available on the ESHRE website and we are expecting a similarly high number to be selected for Helsinki from the abstracts now submitted.

Finally, we invite all our SIG members to submit their ideas for the development of a new ESHRE guideline. And we are now looking forward to seeing you all in Helsinki.

Arianna D'Angelo
 Co-ordinator SIG SQART

Campus course survey results from 207 responders

1. How important do you rate continuous training in ART safety and quality (1-5)?
 Weighted average 4.58

2. Your interest in continuous training and education (1 to 5)?
 Weighted average

MART Quality Management	4.26
MART Guidelines	4.23
The management of IVF Clinics	4.19
MART Risk Management	4.24

3. How do you evaluate SIG SQART's programmes so far (1 to 5)?
 Weighted average 3.82

4. Your interest in a Campus course on quality management and inspections (1-5)?
 Yes 44.8% No 9.8% Don't know 29%, Yes depending 16.4%

5. Most effective way for SIG SQART to keep in contact
 Website 7.1% Focus on Reproduction 14.7% e-mail 78.1%

Application for ovarian stimulation guidelines

Our pregress course in Helsinki is dedicated to **Managing the difficult IVF patient: facts and fiction**. It will offer update knowledge of how the older IVF patient, the medically complicated, the overweight and underweight, and those with comorbidities such as endometriosis and uterine cavity distortion might best be managed.

Guideline development

In the context that the SIG RE supports guideline development in the field of reproductive endocrinology, we note with interest that a former SIG RE Steering Group member, Terhi Piltonen, and past ESHRE Chairman Juha Tapanainen, both from Finland, have applied for an ESHRE grant to revise and extend an Australian guideline on health aspects related to PCOS. This new international guideline, building on the Australian original, will cover such



Former SIG RE Steering Committee member Terhi Piltonen hoping to develop international PCOS guidelines with ESHRE support.

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



topics as reproduction, metabolism, psychosocial well-being and cancer. This collaborative project will be steered by Helena Teede and Robert Norman, directors of the Australian PCOS Alliance.

Meanwhile, the SIG RE has also submitted a first application to initiate development of a guideline on ovarian

stimulation for ART, addressing topics such as FSH dosage, protocol type, response monitoring and OHSS prevention. Practice variation here is tremendous, and the guideline aims to reduce this variation and thereby improve safety and patient compliance, as well as cut costs. A first meeting of the guideline development group will be held in Helsinki.

Campus events

Late this year our Campus workshop on the **Multifaceted challenge of female reproductive ageing**, which was originally planned for April, will now take place on 1-2 December, still in Istanbul. The workshop, organised on behalf of the SIG RE by Efstratios Kolibianakis and local organiser Bulent Urman, will focus on the physiology of the ageing ovary and the management of couples with age-related fertility decline, both from the assisted reproduction and the prevention point of view.

Taken together, the year is already buzzing with activities, and we are looking forward to meeting you all in Helsinki - to see how we are moving ahead and what new ideas will emerge.

*Frank Broekmans
Co-ordinator SIG Reproductive Endocrinology*

SIG PSYCHOLOGY & COUNSELLING

First steps for ESHRE accreditation for psychologists and counsellors

An initial proposal for accreditation for psychologists and counsellors working in infertility submitted by Uschi Van den Broeck (Past Co-ordinator) to the Executive Committee will now be followed by a more detailed proposal. We are keen to develop an interesting proposal which ensures an opportunity to raise and guarantee the quality of counselling and psychosocial intervention in certified members.

STEERING COMMITTEE

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

Welcome to Helsinki!

We are now looking forward to seeing you all at the next Annual Meeting in Helsinki. We are very excited about our pregress course on **Complex cases in infertility counselling: Discovering new territories, implementing new techniques and**

creating new conversations. Complicated cases are common and we are expecting an animated response from psychologists, mental health

Hot topic of morcellation for Helsinki pregress

We have already had two important workshops this year. The first, **When is surgery the answer to early pregnancy complications**, in Coventry, UK, and the second, **The impact of reproductive surgery on cross-talk between embryo and the endometrium**, in Milan. The latter was a repeat of a similar workshop held in Vienna in 2014, and because of its ongoing success we have decided to repeat it once again in 2018 (in a location still to be decided).

Upcoming events

April's workshop in Leuven under the supervision of Stephan Gordts on **Endoscopy in reproductive medicine** had a totally new programme in which live

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



demonstrations and hands-on demonstration and exercise took a large part. This same workshop which, as usual, is being run in two editions (Spring and Winter) will undoubtedly become a must for every gynaecologist wishing to be trained in reproductive surgery.

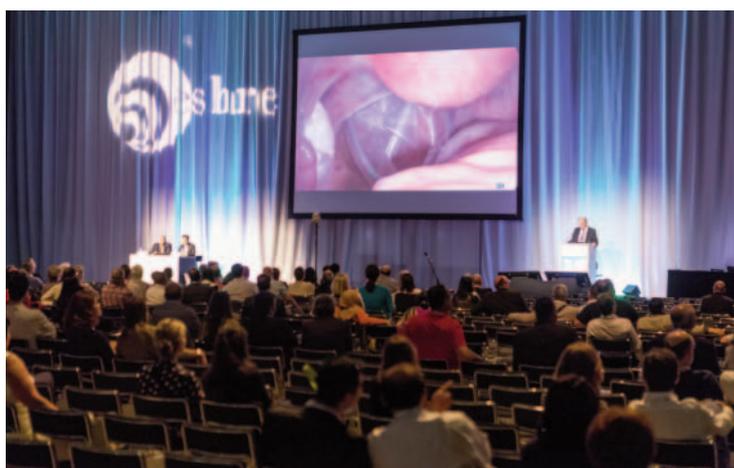
In early May we are hosting a joint meeting in Thessaloniki with the SIG Reproductive Endocrinology on **Surgery in reproductive medicine: benefits and limits**, which will develop shared themes between surgery and endocrinology

This year's pregress course in Helsinki is on myomas, a very hot topic right now because of the highly controversial question of morcellation. Leading experts in this field will help to define a sensible approach to this problem.

The live surgery session, which is always followed with great interest, will take place on 2 July with transmission from the specialist gynaecological Hôpital Natecia in Lyon. The very well known reproductive surgeons Rudy Campo from Belgium and Filipa Osorio from Portugal have already agreed to participate. This event, supported by the Karl Storz company, will cover a wide range of procedures from transvaginal endoscopy to advanced laparoscopies.

*Antoine Watrelot
Co-ordinator SIG Reproductive Surgery*

Live surgery - always of great interest at the Annual Meeting - will cover a range of procedures in Helsinki.



professionals, nurses, physician, ethicists and other professionals willing to share their experiences. We invite all members to join us for the next SIG business meeting, which will take place after the pregress courses (Sunday 3 July at 17.00). This is a good opportunity to air your views and make known your suggestions about our activities.

Upcoming events

We will be hosting a new Campus **Basic training course for infertility counselling: from theory to practice** in Vienna on 29-30 October 2016. With an aim to provide basic knowledge on the medical and counselling aspects of reproductive medicine and to develop counselling skills and techniques, this course will include basic information on counselling



issues, such as medical knowledge, psychosocial implications of treatment, use of ESHRE psychosocial care guidelines, and third-party reproduction.

In the second part, participants will have the opportunity to discuss and develop specific practice techniques. The course has been designed for counsellors, psychologists, and nurses new to the field of reproductive medicine. At the end of the course participants should have a basic understanding of fertility counselling - and we hope you can take advantage of this great opportunity.

*Juliana Pedro
Junior Deputy
SIG Psychology & Counselling*

In Olympic year, precongress on the impact of exercise, sport and doping on human fertility

One of the recent highlights of the SIG Andrology was a Campus workshop on **Donor sperm banking: medical, socio-cultural, ethical and legal considerations** held in Leuven in December last. The meeting was a co-organisation of three SIGs (Andrology, Ethics & Law, Socio-cultural aspects of (in)fertility) and the Task Force Developing countries and infertility. The course covered all the relevant considerations of sperm banking, with best practice recommendations provided. The course proved highly attractive and was sold out more than a month before the event. Most participants were very satisfied with the content of the meeting and the quality of discussions. It was suggested by many that a similar meeting on oocyte freezing should now be organised as well. A full report of the meeting was published in the January issue of *Focus on Reproduction*.

Upcoming events

The next meeting on our SIG calendar is a Campus workshop on **Future fertility for the male child and adolescent with cancer: best practice, research breakthroughs and current dilemmas**. This is the joint endeavour of five ESHRE SIGs (Andrology, Ethics & Law, Psychology & Counseling, Socio-cultural aspects of (in)fertility, and Stem cells) and will take place on 13-14 May at the Factory Hotel in Münster, Germany. The workshop will consider clinical dilemmas in the field of fertility preservation

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Willem Ombelet (BE), Co-ordinator
Jackson Kirkman-Brown (GB), Deputy
Ellen Goossens (BE), Deputy
Heloisa Lavorato (IT), Junior Deputy
Stefan Schlatt (DE), Past Co-ordinator



with a strong emphasis on pre-pubertal boys. Impressive breakthroughs have been made in the cure rate of childhood cancers but survivors face an often devastating loss of fertility as a side effect of oncological therapies. Novel fertility preservation strategies targeting the regenerative potential of stem cells may be developed, especially for boys whose testes contain spermatogonial stem cells.

This important workshop brings together clinical and biomedical specialists from oncology, paediatrics, andrology and stem cell biology to describe current and future procedures for fertility preservation in boys with practical information on cryo-banks for immature human testis tissue. The workshop will also consider the ethical, psychological and socio-cultural issues associated with the availability of new treatments in order to generate guidelines for best practice.

Just weeks before the Olympic Games in Rio, our precongress course will review the physiological aspects of sports and exercise on gonadal function and gamete quality in both sexes. Because the number of people abusing drugs or participating in intense sports continues to rise, this course aims to provide an important introduction to dealing with associated problems. Speakers will cover the influence of exercise on gonadal regulation and a possible impact on gamete quality and fertility. The effects of doping on general health and fertility will also be explained.

Willem Ombelet
Co-ordinator SIG Andrology

PARAMEDICAL GROUP

Opportunity for basic training ahead of Helsinki

Our basic training course will be held for the first time in Belgrade on 19-21 May. This is an ideal opportunity for those lab technicians, nurses and midwives looking to update their knowledge or revise for Certification exams in Helsinki in June. You'll find a short interview about the course on the ESHRE website.

Our precongress course in Helsinki is titled **Epigenetics – connecting health to lifestyle and the laboratory**, and will

take place on Sunday 3 July. It has been designed to provide basic information on the effect that lifestyle, nutrition and laboratory interventions might have on genes with resulting epigenetic impact.

We are also very pleased to collaborate with the SIG Embryology in a Campus course on **Optimising IVF success** in Gothenburg 3-5 November 2016. This comprehensive course will include basic reproductive biology, quality in the lab, handling of non-viable gametes and

hands-on training in quality control, time-lapse and cryopreservation.

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.

Helen Kendrew
Chair Paramedical Board
helen.kendrew@bathfertility.com

Survey on oocyte cryopreservation now complete

SIG to merge with Task Force Developing Countries in 2017

Collaboration with other SIGs as well as other groups such as the EIM Consortium has been an important aspect of our work, reflecting the fact that societal and cultural issues have no more boundaries in the different aspects of reproductive science than in real life.

STEERING COMMITTEE

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

options as well as the legal, familial and social questions raised in the difficult circumstances the young people face. For ESHRE 2017 in Geneva we are now planning a pre-congress course on similar themes regarding transgender people.

Oocyte cryopreservation in Europe

Cryopreservation and its uses for non-medical (otherwise known as 'social' or age-related fertility loss) and medical indications has been on our agenda for over a year and we hope to complete the report on oocyte cryopreservation in Europe in time for the next Executive Committee meeting in Helsinki. The SIG survey was carried out with members of the EIM Consortium and Committee of National Representatives, and a first draft of the report received much constructive criticism in February.

The final report will describe response to a questionnaire sent to the 34 European country members of EIM. We collected and analysed answers from 27 countries about different statutory or professional conditions for oocyte cryopreservation, and found that, while almost half the responding countries do provide oocyte cryopreservation for medical reasons with state funding, none provides funding for non-medical reasons. Indeed, this indication is actually forbidden in a couple of countries.

We also received actual recorded data from 17 countries, with data on the numbers of cycles performed and oocytes cryopreserved and used, again for both medical and non-medical reasons. In total we had data for 9078 aspirations in 2013, representing around 3% of all ART aspirations and yielding a total number of 23655 oocytes, or an average of 9.11 oocytes per aspiration. We also found that storage activity has increased in the last five years in most countries, whilst data on actual use are few apart from in oocyte donation cycles.

Upcoming events

However, we don't just concentrate on the female side, and indeed before the next Annual Meeting in Helsinki we are taking an active part in a large Campus meeting in Munster, Germany, in May. We are collaborating with the SIGs Andrology, Ethics & Law and Psychology & Counselling to address the issues faced by those male children and adolescents who need and are able to cryopreserve their reproductive future with either sperm or testicular tissue. We will consider the scientific and clinical



A broader scope

This will be another year of transition for the SIG with our merger with the Task Force Developing Countries, as approved by the Executive Committee in February. This is a very natural progression following completion of the Task Force's remit, and our new chosen name will be the 'SIG Global and socio-cultural aspects of infertility'. In such new circumstances and because of the relatively small size of both groups, it has been agreed that Willem Ombelet will become the next Co-ordinator when the official change takes place at the Annual Meeting in 2017 in Geneva. We will of course arrange elections for new deputies after Helsinki in order to be ready with a new team for 2017.

Much will need to be done in the next 12 months, and it is therefore opportune for our members to reflect on the role they wish to play when we go global. We invite all ESHRE members who feel strongly about international issues in infertility, such as access and reproductive rights, to think of joining this new SIG.

Last but not least Anna Pia Ferraretti has expressed a wish to relinquish her Deputy role from the 2016 Annual Meeting for personal reasons. I wish to express here my personal thanks for her unfailing support in planning all our activities and her very active role in the oocyte cryopreservation study.

Françoise Shenfield

Co-ordinator SIG Socio-cultural aspects of (in)fertility



Oocyte cryopreservation: SIG's European survey report later this year.

Full differentiation of mouse embryonic stem cells

Gamete formation in a dish?

A recent major breakthrough in the field of stem cells attracted the attention of both the popular and scientific media - with headlines such as 'Making sperm in the lab', 'Chinese scientists turn mouse stem cells into working sperm cells', and 'Lab-grown sperm makes healthy offspring'. The origin of the headlines was a paper from Zhou et al. published in *Cell Stem Cell* which, for the first time, reported the complete differentiation of mouse embryonic stem cells towards functional sperm-like cells in vitro.¹

This success had only previously been achieved after an in vivo transplantation to mature primordial germ cells to functional sperm cells.² The key to success of the Chinese researchers was their starting population of mouse embryonic stem cells in a naive state of pluripotency, and in vitro co-culture with neonatal testicular somatic cells and sequential exposure to supplemented culture media (sex hormones, morphogens) to obtain functional sperm-like cells.

It has to be noted that only late stage spermatids were obtained, and not the fully mature sperm cell; however, these sperm-like cells were able to produce healthy and fertile offspring. For human translation, questions remain whether neonatal testicular tissue is really necessary for success, and whether the procedure also works with induced pluripotent stem cells.

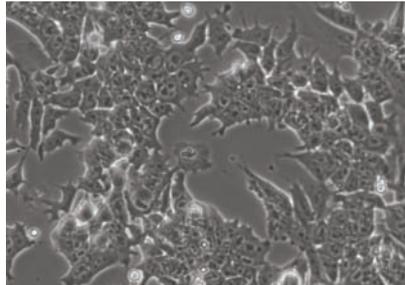
Nevertheless, this landmark paper is particularly fascinating for the field of human ART, as it opens doors to the production of stem cell-derived gametes for patients who lack their own functional gametes. Alternatively, if reproducible in the human, more insight into the process of human spermatogenesis and infertility may be obtained, because the precursor cells of gametes, primordial germ cells, are difficult to harvest in human.

Along with this success, the technology of CRISPR/CAS enabling genomic editing in cells is also now very much debated in human ART, with the technology recently applied in human embryos and the UK giving the green light for use in human embryos for research purposes.³ Some members of the SIG Stem Cells, together with other ESHRE members, have recently reviewed the state of the art of this technology in *Human Reproduction Update*.⁴

Another controversial technology, the transfer of mitochondria harvested from egg precursor stem cells to ameliorate the quality of human oocytes, has been highlighted by the SIG Stem Cells in a recent opinion published on the ESHRE website (see SIG Stem Cells).

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



SIG SC activities

Our pregress course ahead of the scientific sessions in Helsinki this year has been organised with the SIG Safety & Quality in ART on **ART in 2020: the next frontier**. New research technologies are becoming clinically available for patients, but what is the value of these new developments in daily

practice? Can they be considered safe? These fundamental questions will be discussed from the perspective of patients, doctors, basic scientists, embryologists and ethicists.

In the main ESHRE programme there will be one invited session dedicated to stem cells, with Jacob Hanna of the Weizmann Institute in Israel discussing the importance of the naive state of pluripotency of

human stem cells for germ cell differentiation. With the recent findings of the Chinese researchers described above, we all looking forward to this presentation. Next, another pioneer in the stem cell field, Myriam Hemberger, will report on the use of trophoblast stem cells as a model for the early steps of placental development.

The SIG SC has co-organised an ESHRE Campus symposium on **Novel gamete manipulation technologies in ART:**

SEEM (safety, ethical, efficient, moral) okay? to be held in Amsterdam on 22-23 September 2016 with the SIGs Ethics & Law and Safety & Quality in ART. This ambitious Campus course will consider all the current hot research topics in ART, namely (i) mitochondrial disorders and how to overcome transmission, (ii) the use of mitochondrial replacement to improve oocyte quality, (iii) the possibility of stem cell-derived gametes and last but not least (iv) the possibility and possible applications of gene editing in gametes and embryos. All these topics will be considered from a scientific, ethical and safety perspective.

Björn Heindryckx
Co-ordinator SIG Stem Cells

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Outstanding Campus meeting on oocyte maturation

The SIG Embryology is very pleased to note publication of its *Revised guidelines for good practice in IVF laboratories (2015)*. The full guidelines are freely accessible on the ESHRE website and are summarised in the March issue of *Human Reproduction*. A commentary written by Susanna Apter – SIG Embryology Deputy and a co-author of the guidelines – may be found on page 12 of this issue of *Focus*.

I would here like to highlight the importance of this document, the most comprehensive and by far the most up-to-date of its kind. I would also wish to thank all those who made this achievement possible, in particular Maria José De Los Santos – project co-ordinator – and our ESHRE Chairman Kersti Lundin for her continued support.

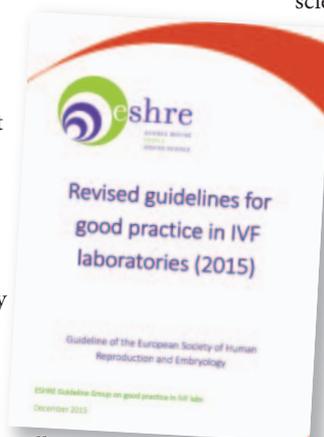
In vitro maturation

Our recent Campus meeting on **Oocyte maturation: from basics to clinic**, held in Brussels in March, proved to be one of our most significant activities ever. The meeting, which grew from an initiative of Johan Smits and was fully supported by the SIG Embryology, took its inspiration from previous Campus courses on mammalian oogenesis. Interest raised by the course was reflected in numbers registered (fully booked, with 137 participants), 35 represented countries, and 14 abstracts presented as posters or selected oral communications. The range of interest was extraordinary: energy metabolism, cytoskeletal remodelling, DNA damage, cumulus cell transcription regulation, biomarkers of developmental competence, mitochondrial transfer, clinical in vitro maturation, to mention but a few.

Some speakers were ‘veterans’ of ESHRE meetings, while others (Marie-Helene Verlhac, Alberto Luciano or Petro Marangos) were speaking at an ESHRE Campus for the first time.

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



The meeting's success was summarised by scientist and speaker David Albertini: ‘Rarely does an opportunity arise at a time when the confluence of basic science and clinical advance energise ART to the level of practicality. This ESHRE workshop took participants from the basic mechanisms of oocyte

maturation to promising clinical findings which reflect the safety and suitability of IVM for understanding the mechanisms of developmental competence. While much remains to be refined before large scale clinical application, this meeting synergised the available evidence into a workable paradigm that will in the near future translate into clinically valuable dividends.’

The opinion of Valentina Lodde, a postdoctoral scientist working at the University of Milan, is also indicative of the importance of these events for new networks. ‘This was my first ESHRE Campus ever, and I was very pleased to attend. There was a very good match between basic science and the clinic, very well balanced with some of the most renowned scientist in the field of reproductive biology. The programme and the atmosphere were great and allowed me to talk to many other participants.’ Undoubtedly, this sort of response encourages us to plan similar events in the future.

Status of clinical embryology

Another project that has raised much interest in the international ART community, growing from a collaboration between the Embryologist Certification Committee (EmCC) and the SIG Embryology, is their survey on *The educational and professional status of clinical embryology and clinical embryologists in Europe*. The survey collected data from 27 European countries, and we have now learned that its publication was the fifth most downloaded paper from *Human Reproduction* in 2015.

Helsinki

Finally, we invite you to participate in our pre-congress course at the next Annual Meeting in Helsinki. The course will focus on alternative approaches in the IVF lab - for example, oocyte cryopreservation vs. embryo cryopreservation, or embryo selection by morphology vs. genetic testing) - within the framework of greater versatility in the lab and a growing demand for personalised treatment.

Other projects are taking shape and we hope to have more information in the coming months.

Giovanni Coticchio
Co-ordinator SIG Embryology



Full house.
Participants at the
March Campus
meeting in
Brussels on in
vitro maturation.

New IT system aims to speed up EIM publications

● Technological developments in ART will also mean changes to data collection

According to its bylaws, the main objective of the European IVF Monitoring (EIM) Consortium is to collect national data on availability, efficacy and safety of IVF treatments initiated each year, including cohort data for corresponding deliveries and infants.

To this end it gathers data from European countries through the contribution of local members either representing national registries or doing their best to collect data on a voluntary basis. At present over 90% of European countries where ART is available provide data to EIM, representing 82% of all European clinics in the field.

These joint efforts have resulted in 15 annual reports (the 16th coming out soon) giving detailed information on ART activity in Europe. Despite the heterogeneity of registries in some countries, EIM reports are of great importance because they reveal real trends in practice and outcomes in Europe and provide a clear picture of the differences existing between countries. And it must be stressed that, according to the latest published ICMART report (referring to 2007 data), almost 50% of world ART treatments are now performed in Europe.

Now, maintaining this main focus on data collection, the new Steering Committee elected during last year's

STEERING COMMITTEE

Carlos Calhaz-Jorge (PT), Chairman
Christian de Geyter (CH), Chairman Elect
Markus Kupka (DE), Past Chairman
Jacques De Mouzon (FR), Special Advisor
Karin Erb (DK), Member
Edgar Mocanu (IR), Member
Giulia Scaravelli (IT), Member
Christine Wyns (BE), Member
Tatjana Motrenko Simic (ME), ExCo representative
Veerle Goossens (BE), ESHRE Science Manager

Annual Meeting intends to develop and improve on some previous initiatives of the Consortium.

In house, the consolidation of a new IT system able to perform automatic calculations on the data received and table construction is expected to speed up analysis and hopefully allow a significantly shorter delay of annual publications.

Full coverage, reliability and validity of data may be an issue in many countries. EIM has planned

to take some steps in this direction in the near future, defining a minimum core-data set, and contacting key people in the official institutions of those countries with practical difficulties in understanding the relevance of contributing to the EIM effort.

Other practical changes are planned in the collection of ART data dependent on technical and strategic modifications in the field. So, the data required will be slightly updated from 2014 on. Unfortunately, however, the vast majority of countries are at present unable to gather reliable information on cumulative rates in IVF/ICSI.

In addition to pursuing its main objective, we feel that there is room to extend EIM performance through new initiatives. Thus, in accordance with

secondary objectives fixed in the EIM bylaws, we plan to start several projects in the coming year - such as firstly an updated and further detailed European survey on the legal, funding and cultural frame for ART in Europe, secondly, a comparative study among European countries with cycle-by-cycle registries, and thirdly, reflections on new trans-European data collection system. Also envisaged are collaborations with some of ESHRE's SIGs to co-organise future workshops and/or pre-congress courses. The use of data coming from national registries as a means to a better understanding of the real ART world is of unquestionable relevance.

Carlos Calhaz-Jorge
Chairman
EIM Steering Committee



National EIM representatives at last year's Annual Meeting in Lisbon, with Chairman Carlos Calhaz-Jorge and Past Chairman Markus Kupka standing in the foreground.

French ART protest

● Four banned treatments highlighted in open letter signed by 130 specialists

Popular protest, from the storming of the Bastille in 1789 to attack on pension reform in 2010, is exercised as a right in France. The latest demos - for and against gay marriage in 2013 - saw France once again take to the streets in an emotive confrontation which, despite protests, culminated in France being the 14th and most highly populated country in the world to legalise gay marriage.

Another protest of sorts - though not yet of Bastille proportions - is taking place in France right now, this time sparked not by popular demonstration but by an open

letter from 130 of the country's leading IVF specialists to the newspaper *Le Monde*.¹ The letter, published in March, calls for a relaxation in France's IVF legislation and the creation of a national 'plan contre l'infertilité' - as already exists in formal strategies against Alzheimer's disease or cancer. The plan, say the authors, would not only allow clinics to treat the infertile with the same complement of treatments as available elsewhere, but would also develop a preventive strategy - targeting obesity, addictions, air pollution - which is now 'cruelly' lacking in France.

The letter highlights four treatments which are currently outlawed in France: egg donation, for which patients who travel abroad may presently and 'incoherently' be reimbursed by French Social Security; genetic analysis of embryos, now routine in most European countries and 'a mark of good practice'; autologous oocyte cryopreservation, whether for medical or non-medical fertility preservation; and sperm donation for all women irrespective of their relationship status.

Each of these treatments, say the letter's signatories, reflects legal anomalies and inconsistencies within the French system - that PGS is disallowed for the detection of chromosomal defects while antenatal testing is encouraged in high risk cases, that single women can't have treatment with donor sperm but can legally adopt a child, that men can preserve their fertility with semen banking but women are denied the same opportunity.

As studies by ESHRE have made clear,



René Frydman, led the letter to *Le Monde*.

the simple route around such restrictive legislation is travel - egg donation in Spain, sperm donation in Belgium, egg banking in Britain. Their proposals, say the 130 specialists, would create a 'non-commercial' framework for egg donation in France and avoid the risks of cross-border care.

The snapshot of ART regulation in Europe published in *Focus on Reproduction* last year showed just how out of step France is with its neighbours, despite generous state-funding for IVF. Indeed, France was the only major country to outlaw PGD, and one of only a few with limitations in PGS. Only in Italy following the implementation of Law 40 in 2004 have such restrictions been evident, and even they have now been dismantled, not by open letter or street protest but by legal challenge in the constitutional courts. Even Poland, which has long agonised over ART in both its public and political arenas, extended its legislation and introduced



Street protests against gay marriage in 2013.

reimbursement three years ago (though that now may again be under threat following a change of government).

However, what gave the French campaigners weight in their letter to *Le Monde* was the admission that they had regularly helped couples and single women access the fertility treatment they needed when it was not legally available in France. According to a follow-up of the letter in *Le Monde*, the signatories' admission to this breach exposes them 'theoretically' to judicial process.²

The one item of complaint which seems most publicly sensitive is the denial of fertility treatment to single women and lesbians - what *Le Monde* says has most 'crystalised' debate in France since François Hollande came to power. Indeed, the newspaper adds, if the proposition of the 130 signatories is ever validated it would according to their leader René Frydman mark a 'decisive step' in the freedom of women to decide for themselves about their bodies.

No-one in France is holding their breath for a quick change in ART legislation. Indeed, even Frydman's fellow IVF pioneer in France, Jacques Testart, took to a long and detailed blog to denounce the open letter as a call for 'societal intervention', and not change in medical care.³

Simon Brown
Focus on Reproduction

1. http://www.lemonde.fr/idees/article/2016/03/17/pour-la-creation-d-un-veritable-plan-contre-l-infertilite_4884871_3232.html

2. http://www.lemonde.fr/idees/article/2016/03/17/un-manifeste-transgressif-pour-accompagner-le-desir-d-enfant_488487_3232.html

3. <https://blogs.mediapart.fr/jacques-testart/blog/010416/reponse-au-manifeste-des-130-protecteurs-des-femmes-0>

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