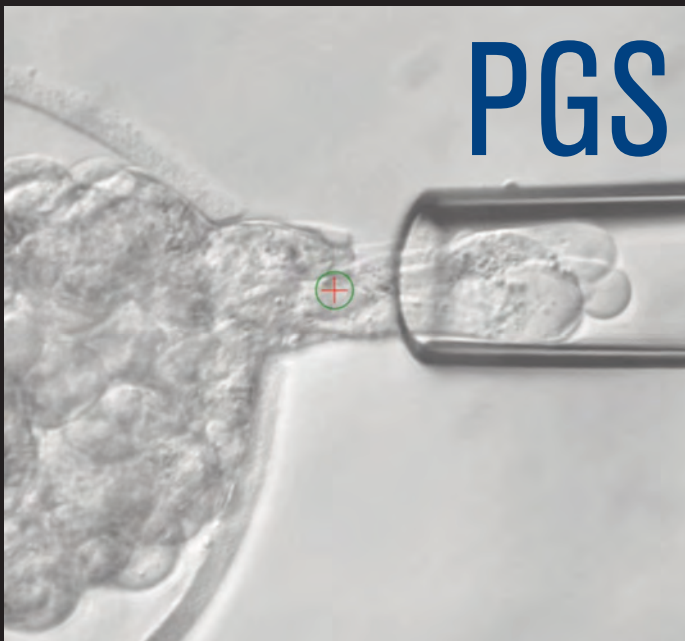
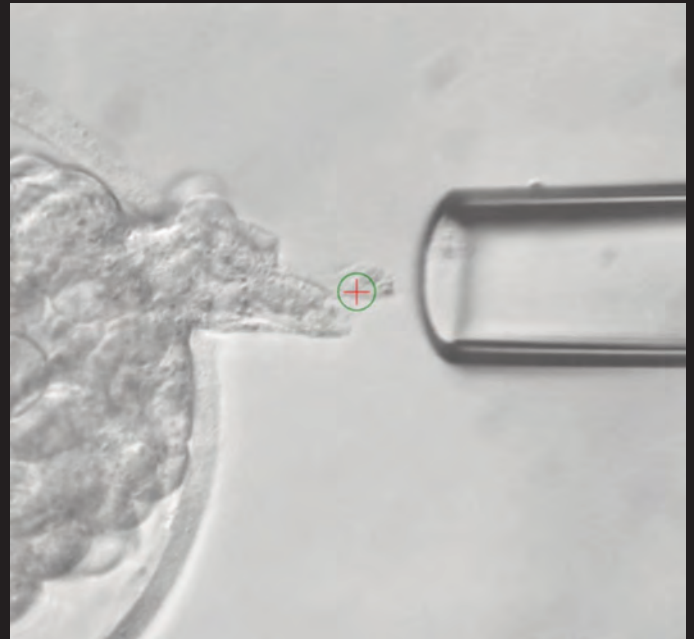
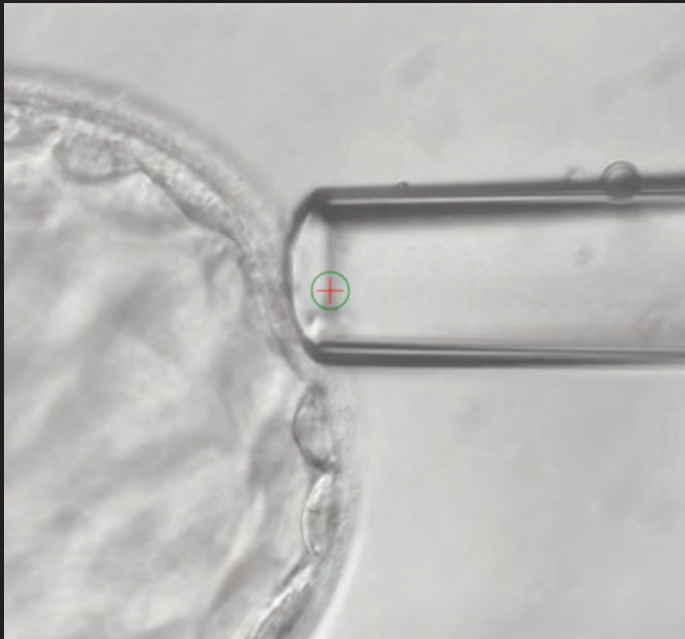


focus on REPRODUCTION



PGS in the clinic

- Gamete modification
- Fertility preservation in females

// JANUARY
2017



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JANUARY 2017

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

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CHAIRMAN'S INTRODUCTION

'As defined by WHO, infertility is a complex pathology that requires appropriate investigation and treatment. One of the most effective treatments is IVF and its related technologies; these techniques cannot be replaced by other procedures and have resulted in the birth of more than 6 million babies throughout the world. Denying the efficacy and accessibility of these treatments to infertile couples is not only unethical, but is also contrary to the principles of evidence-based medicine and good medical practice. All treatments known to be safe and effective should be available to all infertile patients, who should be given the opportunity to make informed reproductive choices on the basis of sound scientific evidence.'

These are the words of ESHRE, expressed recently in support of IVF in Lithuania, where political opinion is yet again seeking to suppress IVF in the treatment of infertility. Lithuania is not alone, and the conservative winds now blowing through parts of Europe and the rest of the world may equally be felt in the field of reproductive medicine, where other countries too are now trying to impose stricter laws and limited access in assisted reproduction treatments.

As the largest society in reproductive medicine and science ESHRE has a responsibility to make its voice heard, not only to individual members of the Society, but also to our patients and to those countries now being threatened with restricted – or even no – access to reproductive care.

It is a priority for us to express the importance that we all have equal and fair access to care. Anomalous national differences in the rules regulating IVF may also increase 'reproductive tourism' and cross-border care by which patients travel to another country to receive a treatment which is outlawed in their own country or down-prioritised with long waiting-lists as a result.

Cross-border care can thus be an acceptable option for some patient groups, but it may also jeopardise safety and quality - for example, in more aggressive stimulation regimes, or a higher number of embryos for transfer, or the use of non-proven adjunctive therapies. It's for these reasons that we aim for as much harmonisation in treatment and care as possible - and to ensure that legislation in medical care is based on sound judgement and evidence-based science, safety and efficiency.

For this end ESHRE is working on several levels. We are increasing our networking, both on a global and European level, working with all important stakeholders. We work by trying to influence global, national and international legislation and directives, research funding and guidelines in order to increase accessibility, harmonisation and knowledge. We work with patient organisations to acquire information on legislation and accessibility in different countries. And we try to educate and spread real knowledge, to diminish the influence of non-scientific arguments through our workshops, our journals, our website and our guidelines.

Kersti Lundin

ESHRE Chairman 2015-2017



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2017

Ready for Geneva

- Invited scientific programme in place
- All abstract submissions to be with ESHRE by 1 February 2017



ESHRE's next Annual Meeting - from 3 to 6 July - will be held for the first time in Geneva and for the second time in Switzerland. Deadlines for abstracts and registrations are at their normal times, with all abstracts required online at ESHRE's Central Office before 1 February, and early bird registrations available up to the end of April. Full details can be found in the table opposite.

In Helsinki last year ESHRE ran a completely paper-free meeting through its own wireless network. Similarly, this year's congress app - improved yet again - will provide full programme and abstract details for laptops and mobile devices.

The scientific programme will open with the two usual keynote lectures on Monday morning, with the first speaker representing the most downloaded article from *Human Reproduction* in 2016, followed by a presentation on non-invasive prenatal testing. These opening keynote lectures usually take place before an

attendance of more than 3000 participants. The programme will continue with one of several sessions this year on very hot topics in reproductive science - on the 'rejuvenation' of oocytes and ovarian tissue.

The former, in which injected autologous 'egg precursor' cells engerise the oocyte through the transferred mitochondria, has been commercially promoted as AUGMENT, a procedure based on the controversial discovery of oogonial stem cells by Jonathan Tilly a decade ago and on a similarly aged pilot study by US embryologist Jacques Cohen to improve IVF results in poor outcome patients by ooplasmic transplantation. In Geneva Cohen himself will review what we know so far about mitochondrial transfer and ask if it really can improve oocyte quality.

Later that same day will be an invited session on an equally controversial and ethically difficult topic, editing the germline genome by techniques such as CRISPR-Cas 9. This was a heavily discussed subject of a Campus meeting in September (see report on page 7) but in Geneva Robin Lovell-Badge, a group leader at the recently opened Francis Crick research institute in London, will review both the potential and the risks of the process. The HFEA in the UK approved a licence application from the Institute in February last year to include the gene editing of embryos. The work aimed to test the function of genes in early human development using gene editing systems.

Invited speakers on day 1 include Robin Lovell-Badge (left) on germline genome editing, and Jacques Cohen on energising oocytes through mitochondrial transfer.



REGISTRATION FEES AND DEADLINES FOR THIS YEAR'S ANNUAL MEETING

Main programme	Before 30 April 2017	After 30 April 2017	After 26 June 2017
Non-member of ESHRE	432,00	540,00	648,00
Member of ESHRE	324,00	432,00	540,00
Student or paramedical member of ESHRE	162,00	216,00	324,00
Precongress Course			
Non-member of ESHRE	216,00	324,00	432,00
Member of ESHRE	108,00	216,00	324,00
Student or paramedical member of ESHRE	54,00	108,00	216,00

* Prices are in euro and include VAT at 8%

Later that same day two presentations will examine the effects of plastics on male fertility and miscarriage. Despite fears to the contrary, the European Food Safety Authority recently concluded that bisphenol A, a chemical used in the manufacture of food contact materials and can coatings, poses no health risk to consumers of any age group. Richard Sharpe, a deputy editor of *Human Reproduction* and scientist who has long studied the association between environmental factors and reproduction, will consider the effects of these endocrine-disrupting plastics on sperm concentration and quality.

On Tuesday the programme will continue with Australia's Debra Gook, one of the pioneers of oocyte cryopreservation, asking if oocyte vitrification can yet compete for efficiency with embryo and blastocyst freezing, and Kutluk Oktay from New York reviewing the role of the BRCA genes in ovarian ageing and reproduction.

Two stalwarts of evidence-based medicine, Siladitya

Bhattacharya, editor of ESHRE's new open access journal *HROpen*, and Sebastiaan Mastenbroek will open Wednesday's invited programme in a session organised with the Cochrane group. Mastenbroek will consider evidence for procedures in the IVF lab.

The event's precongress courses are proving increasingly popular, with some courses now attracting upwards of 500 participants. This year, on Sunday 2 July, there will be 14 events, with courses on male infertility, ultrasound in early pregnancy, molecular biology for embryologists, endometrial receptivity, individualised stimulation for IVF, mitochondria, and transgenderism in reproduction. In addition there will be the exchange courses of the ASRM and Middle East Fertility Society, and a course on academic authorship hosted by the ESHRE journal editors.

'We trust that everyone will find topics of special interest - and of help for their everyday clinical practice or research,' says local organiser Anis Feki.

ESHRE's 35th Annual Meeting in 2019 to be held in Vienna



The 2019 Annual Meeting of ESHRE - the Society's 35th - will take place in the Austrian capital Vienna from 23-26 June. The event will follow Geneva later this year and Barcelona in 2018. The congress venue in 2019 will be the Messe Wien, one of Europe's major convention centres and a host to many of the world's leading medical congresses.

This will be the second time that an ESHRE Annual Meeting has been staged in Vienna, the first in 2002 when almost 4000 attended. Judging by recent events, attendance in 2019 - and indeed at all forthcoming Annual Meetings - is likely to be around 10,000.



'Best Of' congress in the best of cities

The fifth 'Best Of' meeting of ESHRE and the ASRM will be held in Paris from Thursday 23 February to Saturday 25 February at the city's Palais de Congrès. These joint meetings highlighting the best of ESHRE and ASRM recent gatherings have quickly established a tradition for bringing together world authorities in the science of reproductive medicine, with updates on the latest concepts and developments presented in a framework of lectures, debates and back-to-back sessions. The meeting is now set on a biannual track, with venues alternating between North America and Europe, with Paris the upcoming venue.

The Best Of meetings are a CME programme intended to present evidence for both established and emerging approaches to reproductive healthcare, with faculty from ESHRE and ASRM aiming to compare global approaches and technologies for diagnosis and treatment. This year's programme thus brings together sessions on gene editing, artificial gametes, energised oocytes, preconceptional genetic testing, diagnosis by RNA, and sperm DNA fragmentation. While many of these topics represent emerging concepts in reproductive medicine, more established topics in the programme include uterine

TIME	THURSDAY, 23 FEBRUARY	FRIDAY, 24 FEBRUARY	SATURDAY, 25 FEBRUARY
07:00 am – 08:00 am	BREAKFAST		
08:00 am – 08:30 am	CUTTING EDGE Ovarian imaging and Hippo signaling – Aaron Hsueh (US)	CUTTING EDGE Will artificial gametes restore fertility? – Saskia Hendriks (NL)	CUTTING EDGE Human germline gene editing – how and why? – Robin Lovell-Badge (UK)
08:30 am – 09:30 am	DEBATE 1 Is there scientific evidence for boosting mitochondrial function in oocytes? Yes – Robert Casper (CA) No – Jonathan van Blerkom (US)	DEBATE 3 Should preconceptional genetic testing be performed on all infertility patients? Yes – Rita Vassena (ES) No – Glenn Schattman (US)	DEBATE 5 Preimplantation genetic screening for recurrent pregnancy loss Pro: William Kutteh (US) Con: Mariette Goddijn (NL)
09:30 am – 10:00 am	PLENARY LECTURE 1 Diagnostic role for RNAs in reproductive medicine – Stephen Krawetz (US)	PLENARY LECTURE 3 NIPT screening for fetal aneuploidy and genetic disorders – Deborah Driscoll (US)	PLENARY LECTURE 5 Automation in the IVF Laboratory – what works and what hasn't – Jeremy Thompson (AUS)
10:00 am – 10:20 am	COFFEE BREAK		
10:20 am – 11:00 am	BACK-TO-BACK 1 Ethical and legal issues in third-party reproduction Judith Daar (US) Virginie Rozée (FR)	BACK-TO-BACK 3 Impact of uterine anomalies on clinical management ESHRE/ESGE – Griagoris Grimbizis (GR) ASRM – Samantha Pfeifer (US)	BACK-TO-BACK 4 Andrology – how best to treat The male in the clinic – Robert Oates (US) Sperm DNA fragmentation – Herman Tournaye (BE)
11:00 am – 12:00 pm	DEBATE 2 Patients' satisfaction The only satisfied patient is the pregnant patient – Siman Fishel (UK) The overall experience is more important – Janet Takefman (US)	DEBATE 4 Should aneuploid embryos be transferred or discarded? Aneuploid embryos are not necessarily bad – Siobhan Quenby (UK) Aneuploid embryos should never be transferred – Richard Scott (US)	DEBATE 6 Does the use of routine ultrasound in embryo transfer improve pregnancy or live birth rates? Yes – Candido Tomas (Finland) No – Owen Davis (US)
12:00 pm – 12:30 pm	PLENARY LECTURE 2 The walking Egg project – Willem Ombelet (BE)	PLENARY LECTURE 4 Optimal endometrial receptivity – Nick Macklon (UK)	PLENARY LECTURE 6 GnRH agonist trigger and the new concept of luteal coasting – Human Fatemi (UAE)
12:30 pm – 01:00 pm	LIGHT LUNCH		
01:00 pm – 02:00 pm	BACK-TO-BACK 2 Barriers of access to infertility care The North American perspective – Eli Adashi (US) The European perspective – Jackie Bolvin (UK)		BACK-TO-BACK 5 Education and training in ART - current and future practices and challenges ESHRE perspective – Anis Feki (CH) ASRM perspective – Catherine Racowsky (US)

disorders, automation in the IVF lab, male factor infertility, and access to fertility care.

Reflecting the meeting's

quickly growing place in the reproduction calendar, there were more than 1000 participants at the 'Best Of'

meeting in New York in 2015, and it's our hope that Paris in the early Spring will prove an equally attractive venue.

Expert workshop still urges caution in uptake of new gamete modification technologies

Mitochondrial replacement techniques, stem cell-derived gametes, and gene editing were all considered for their safety, efficiency and ethical acceptability at an Amsterdam Campus meeting.



This Amsterdam Campus, held over two days in September, proved very popular, with 108 participants. The event was jointly organised by ESHRE's SIGs Ethics & Law, Safety & Quality in ART and Stem Cells, co-ordinated by Bjorn Heindryckx (below).

The pace at which new scientific developments are introduced into everyday practice (quick, and getting quicker) has been a matter of recent concern to ESHRE, whose SIGs and journals have consistently urged caution and the weight of evidence before routine application. On the other hand, the editor of *Molecular Human Reproduction*, in lamenting the lack of long-term funding for research in reproduction, has recently described as 'unacceptable' the time it's taken 'to develop a field such as PGS'.

Three recent and fast-moving developments from basic science were under the spotlight of an ESHRE Campus meeting in Amsterdam in September and each of them reflect the speed and proximity at which clinical application is now moving behind the science. Indeed, in her review of the 'possible' applications of the CRISPR-Cas 9 genome editing system former ESHRE chairman Anna Veiga reported that at least five different companies are already preparing CRISPR technologies as gene therapies (one to treat HIV infections), all no doubt commercially packaged. Indeed, genome editing systems - 'able to knockout any gene' and presumably targeted at somatic cells - are now widely available, even as do-it-yourself kits for stay-at-home garage scientists.

It was only in 2015 that three specialists writing in *Nature* urged colleagues not to edit the human germ line. 'In our view,' they wrote, 'genome editing in human embryos using current technologies could have unpredictable effects on future generations.' But within a few months, in December 2015, an international summit meeting in Washington agreed that basic and preclinical research in the specific alteration of genetic sequences should proceed subject to legal and ethical



'oversight'. The agreement added that 'it would be irresponsible to proceed with any clinical use of germline editing unless and until the relevant safety and efficacy issues have been resolved', a cue for ethical evaluation based largely on principle and the evidence of water-tight studies. A working group of ESHRE's Ethical Committee and the European Society of Human Genetics is indeed preparing a position paper of new recommendations for basic, preclinical and clinical applications of genomic editing in the germ line (see box on page 9).

The CRISPR-Cas 9 genome editing system was one of three technologies under discussion in Amsterdam as 'safe, ethical, efficient and moral'; the other two were nuclear transfer for the prevention of mitochondrial diseases and stem-cell derived artificial gametes as an alternative to donor gametes.

Mitochondrial replacement

Bjorn Heindryckx, who as Co-ordinator of ESHRE's SIG Stem Cells was one of the organisers of this meeting, reported that the prevention of mitochondrial diseases is a key research project of his own group in Ghent and that in only a small number of labs elsewhere - as in Newcastle, UK - prevention by mitochondrial replacement therapy 'is investigated in depth'. As now seems clear, around one person per 5000 is clinically affected by mitochondrial

disorders, although around one per 200 infants inherits pathogenic mtDNA mutation. It is now reckoned that for a disease to be clinically manifest the mutational 'load' - that is the ratio of mutant to normal DNA copies - would be around 60%.

In the absence of any remedy to 'cure' mtDNA diseases, Heindryckx proposed that prevention (by prenatal diagnosis, PGD or germline nuclear transfer) is the only therapeutic reproductive option. PGD, which was later reviewed by US embryologist Jacques Cohen, is not always appropriate, according to Heindryckx: it may not be possible to find mutation-free embryos; and PGD is not suitable for patients with homoplasmic mutations or higher heteroplasmic loads.

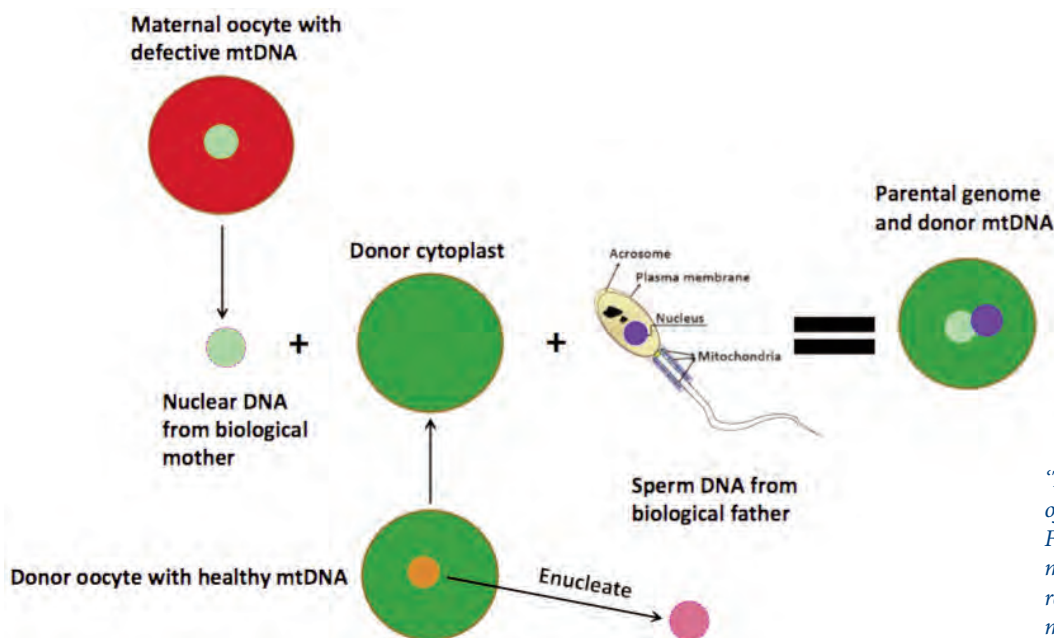
In such cases mitochondrial replacement therapy - as germinal vesicle transfer, spindle transfer, pronuclear transfer or polar body transfer - is the only alternative, although concerns remain about safety and any residual mtDNA 'carry-over'. Techniques explored in Newcastle - the so-called 'three-parent IVF' approved by the UK Parliament (though still awaiting the green light from the HFEA) - were pronuclear transfers, while announcements from the US in 2013 suggested that spindle transfer had been successfully applied in humans, with some of the ST oocytes found capable of developing to blastocysts and producing embryonic stem cells similar to controls. Then in August 2015 Zhang et al in New York reported a non-viable pregnancy from a nuclear transfer technique in a couple with repeated embryo arrest. However, in September last year, the same group of Zhang reported the successful birth of a baby born following spindle transfer in a mitochondrial case. The group disclosed that the procedure had been performed in Mexico to bypass regulatory restrictions in the US (see box on page 10).

Susana Chuva de Sousa Lopes from Leiden University said it was 'difficult to prove or disprove' the existence of oogonial stem cells.



Reviewing progress with pronuclear transfer in the prevention of mtDNA disease, specialists from the Newcastle group and others reported in *Nature* that 'PNT has the potential to reduce the risk of mtDNA disease, but it may not guarantee prevention'.¹ Thus, responding to the Zhang live birth announcement in September, Alison Murdoch from the Newcastle group cautiously told the BBC that 'the translation of mitochondrial donation to a clinical procedure is not a race but a goal to be achieved with caution to ensure both safety and reproducibility'.

As the *Nature* authors suggested, safety, as reflected in the level of mtDNA carry-over, remains of paramount concern, and in Amsterdam zoologist Klaus Reinhardt from Dresden listed six 'potential risks' associated with mitochondrial replacement therapy, not least the fact that no risk analysis has been adequately performed in the countries now heading towards clinical application. Potential risks include heteroplasmy, interacting nuclear and mitochondrial modifier genes, and epigenetic and sequence changes.



'Three-parent' embryo procedure of germline nuclear transfer. Following the injection of healthy mtDNA from a donor oocyte, the resulting embryo will have no more than 1% of the donor's DNA.

New overlaps in reproduction and genetics

A third interdisciplinary workshop overlapped with this Campus meeting in Amsterdam, bringing together as before experts from ESHRE and the European Society of Human Genetics (ESHG) to discuss recent developments in fertility and genetics - and as before the group has prepared a position paper on their interaction from research to clinical application.

There will be eight new sections to this third paper: expanded carrier screening, genetic testing and donor anonymity, the genetics of fertility disorders, preimplantation genetic testing, mitochondria from diagnosis to treatment, non-invasive prenatal diagnosis, epigenetics and germline genome editing. As with the two previous papers, this will also be jointly published in *Human Reproduction* and the *European Journal of Human Genetics*, following a consultation period on the ESHRE website.

The first meeting of the joint ESHRE/ESHG group was held in Seville in 2005 to review the interface between ART and genetics. Under consideration were genetic studies in IVF couples, PGD and screening, selection of donors based on genetic information, counselling, potential adverse effects of ART, safety and quality procedures and public policy.

The second meeting was held in Brussels in 2012 to review 'current medical issues' in ART and genetics. Discussed were cross-border



The ESHRE/ESHG group in Amsterdam, standing, Milan Macek, Joep Geraedts, Aafke Van Montfoort, Wybo Dondorp, Sirpa Soini, Heidi Mertes, Inge Liebaers, Stéphane Viville, Kelly Ketterson, Guido Pennings, Karen Sermon, Luca Gianaroli, and seated from left, Martina Cornel, Joyce Harper, Anna Veiga, Kristiina Aittomaki, Kersti Lundin. Also part of the group but not pictured Guido de Wert, Claudia Spits, Mike Morris and Joris Vermeesch.

reproductive care, genetics of male and female infertility, counselling, PGD and PGS, genomic variation in preimplantation development, accreditation of labs, consumer genetic testing, epigenetics, stem cells, and funding for IVF.

Now, with so many new topics in so few years, this field continues to move forward at remarkable pace, leaving little time in its wake for strong evidence or new recommendations of this kind.

Joyce Harper

- Soini S, Ibarreta D, Anastasiadou V, et al. The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues. *Eur J Hum Genet* 2006; 14: 588-645.
- Recommendations of the ESHG and ESHRE. The need for interaction between assisted reproduction technology and genetics. *Eur J Hum Genet* 2006; 14: 509-511.
- Harper JC, Geraedts J, Borry P, et al.. Current issues in medically assisted reproduction and genetics: Research, clinical practice, ethics, legal issues and policy. *Eur J Hum Genet* 2013; 21: 1-21.

Artificial gametes

An indication for use of gametes derived from spermatogonial stem cells was described at this meeting as 'non-controversial', unlike oocytes - or 'egg precursor cells' - derived from 'oogonial' ovarian stem cells. Indeed, no biological claim of the past decade has raised such polarity as that of Jonathan Tilly in 2004 when his group proposed the existence of female germline stem cells in the mammalian ovary which are able to support new oocyte production during adulthood. Thus, in just one or two reports, Tilly overturned the basic biological doctrine that the

number of follicles in the ovary is finite and degenerates until depletion and the menopause. Just two years ago, he described the isolation of these elusive stem cells from human ovaries and their manipulation into bona fide oocytes. These same 'egg precursor cells' are now the basis of a controversial adjunctive IVF treatment - known as AUGMENT - which seeks to energise oocytes from the mitochondria of these same egg precursor cells.

Describing her broader work in the development of gametes derived from ovarian stem cells, Susana Chuva de Sousa Lopes from Leiden University said it

was 'difficult to prove or disprove' the existence of oogonial stem cells, adding first that the Tilly findings have not been fully replicated and that many groups have cast doubt on the reliability of the antibody-based method of their isolation. 'No paper has shown that these cells can differentiate to oocytes,' said Lopes in Amsterdam. 'Indeed, it's very unclear even if they are stem cells.'

There are far fewer controversial matters in research on spermatogonial stem cells, which, said presenter Ans van Pelt from the Academic Medical Center of Amsterdam, is not yet clinically applied, although propagation and transplantation of SSCs have been successfully achieved (offspring) in mice. Van Pelt noted that human adult and prepubertal SSCs can survive and proliferate in long-term culture, and that these cultured SSCs maintain their stem cell characteristics (and chromosomal stability) following transplantation.

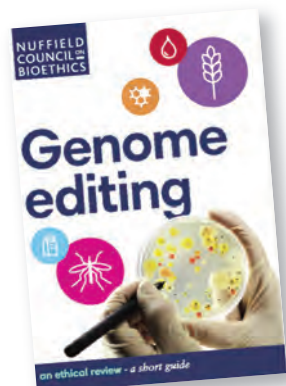
Two therapeutic routes seem possible: first, in vitro propagation and transplantation; and second, in vitro germ cell differentiation followed by ICSI. The indications, said van Pelt, seem reasonably clear - for male infertility cases not amenable to ICSI, such as in numerical and structural chromosome abnormalities or Y-chromosome deletions, and for fertility preservation in prepubertal boys following cancer treatments.

The driver for these treatments, as other work at the AMC Amsterdam has suggested, is firstly safe conception, but genetic lineage is important too, said van Pelt, which gives this work an edge over gamete donation. But ahead of any clinical application lies the prospect of ethical approvals, and particularly the European Advanced Therapy Medicinal Regulations, which recognise these and other developments as involving cells 'subject to substantial manipulation'.

An interesting angle on the social value now placed on genetic parenthood came from Ghent bioethicist Guido Pennings, who proposed that this same high value would probably justify any 'likely' increase in health problems associated with SCD gametes. 'Our society approves and contributes to this view through a devaluation of gamete donation and social parenting,' said Pennings, 'and through the development of an increasing number of techniques that have the sole goal of genetically related children.' Any objections to the evolution of SCD gametes would be difficult, he argued, because their development would be just 'one further step in an evolution that has never been questioned.'

Gene editing

Just one week after this Amsterdam Campus, the Nuffield Council on Bioethics in the UK issued a detailed opinion on the gene editing technique of CRISPR-Cas 9 and acknowledged that it is already transforming many areas of biological research, with 'the



World first spindle transfer baby



Birth of the world's first baby following spindle nuclear transfer was reported by *New Scientist* magazine in September and described in more detail at the ASRM Annual Meeting in Salt Lake City in October. The treatment was performed in Mexico by the New York group of John Zhang; the mother carries genes for Leigh syndrome, a fatal condition that affects the developing nervous system. The syndrome had been responsible for the deaths of two earlier children. When Zhang and his colleagues tested the new baby's mitochondria, they found that less than 1% carried the mutation, a level considered too low to cause any problems. In his ASRM report, Zhang said that the patient, a 36-year-old Jordanian, had elected to have spindle nuclear transfer over pronuclear transfer for religious reasons.

potential to change our expectations and ambitions about human control over the biological world?'² Reproduction, in the prevention of an inherited disease trait, was one of four areas of potential application identified by the report - alongside farming, industry and biomedicine.

However, according to Heidi Mertes from the University of Ghent speaking in Amsterdam, reproductive applications raise some of the most complex ethical concerns. Her approach was to address these concerns from the perspectives of basic research (the source of embryos) and the clinical outcomes (prevention of disease). Concerns among the latter were off-target effects (mutations) and long-term germline modifications, especially when for most of these potential applications PGD is an established alternative.

A clear presentation on the technical details of gene editing in human reproduction by Oxford biologist Ben Davies showed that there are more than 4000 known single gene conditions, which collectively are thought to affect approximately 1% of births worldwide and most of which individually are amenable to prevention by PGD. CRISPR-Cas 9, he explained, is the most widely used genome editing technique, applauded for its ease of use, low cost and reliability. 'It just works,' said Davies. 'If you just apply the protocols, it works. We're all excited by it.'

The system has two components: CRISPR, 'clustered regularly interspaced short palindromic repeats', which refers to the basis of the guide system to find the target,

Cell division without fertilisation?

Just days before this meeting took place, newspaper headlines were speculating that fertilisation was no longer necessary for childbirth. The claims followed a report in *Nature Communications* in which scientists from the University of Bath, UK, described cell division in a mouse oocyte which began without fertilisation. The oocytes were chemically treated to trick them into the beginning of mitosis and were only then - as 'parthenotes' - injected with sperm. Once transferred to the uterus, the cells developed into normal embryos and went on to grow into newborn mouse pups. According to reports, the pups appeared to be healthy and were able to produce at least two generations of their own offspring.

'Our work challenges the dogma ... that only an egg cell fertilised with a sperm cell can result in a live mammalian birth,' said Dr Tony Perry of the University of Bath, a lead author on the study.

Despite a somewhat lukewarm response in Amsterdam, the research did appear to revise the wisdom that mammalian sperm cells could only become mature sperm cells when they were inside an egg — that only the oocyte provided the environment for division to begin and an embryo to develop. But it now seems that a parthenote can serve the same function as an egg, though under the right conditions.

and Cas 9, 'CRISPR-associated protein 9', the protein which cuts the DNA at the target site. As Anna Veiga reported, these CRISPR-Cas 9 systems target specific sequences and can be produced relatively easily in the lab or obtained as commercial kits. It was the two separate reports of Zhang and Church (in the same issue of *Science*) on the use of CRISPR-Cas 9 in mammalian cells which laid the basis of a general purpose tool for editing the genome in living human cells.

According to Veiga, while PGD would be the preferable alternative for preventing autosomal recessive and autosomal dominant diseases, germline editing would be necessary when both parents are affected by the same monogenic disease (to correct the affected gene in one parent or an embryo), when one parent is homozygous for an autosomal dominant disease (such as Huntington) or when one parent is affected by a chromosomally structural aberration. Even further ahead, another potential application is to



Guido Pennings: 'Any objections to the evolution of stem-cell derived gametes would be difficult' because of the high value now placed on genetic parenthood.

reduce the risk of common diseases, or even to reshape non-medical traits. Theoretically possible is the correction of genes related to infertility (Y chromosome deletions or endometriosis), and, as Bjorn Heindryckx suggested, the elimination of mitochondrial DNA mutations present in the oocyte, as has already been shown in the mouse oocyte.

As is invariably found, there was no common conclusion to the ethical assessment of these techniques, other than an urge for caution. Some, like artificial male gametes derived from spermatogonial stem cells, seemed less controversial than others - and, as Sjoerd Repping suggested, controversy would be non-existent if proved safe and effective and if applied in iatrogenic or idiopathic infertile men. But, as others clearly noted, there is real concern over the ethics of any intervention which modifies the genome with consequences for the entire lineage. As Heidi Mertes concluded, the main concern about clinical application of these techniques is safety. And at present, she said, it would be 'irresponsible' to bring genome editing to the clinic, especially with the alternative of PGD applicable in most indications. However, she added, if the technique of genome editing of embryos is perfected and becomes safe, for those rare cases in which PGD is not possible, it would be difficult to provide a 'well-founded' reason to oppose reproduction with genome editing for the prevention of diseases.

*Simon Brown
Focus on Reproduction*

1. Hyslop LA, Blakeley P, Craven L, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. *Nature* 2016; 534: 383-386.
2. See http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf.

A year of change for ESHRE committee members

● Five new nominees for the Executive Committee and a new Chairman Elect

The General Assembly of Members, which will take place during the Annual Meeting in Geneva, will see the introduction of a new Executive Committee for ESHRE and a farewell to those members who have served two two-year terms: Petra De Sutter (BE), Georg Griesinger (DE), Grigoris Grimbizis (GR), Tatjana Motrenko (ME), and Andres Salumets (EE).

Five present members of the ExCo who have served just one two-year term, will remain in place: Mariette Goddijn (NL), Nick Macklon (GB), Basak Balaban (TR), Borut Kovacic (SI), and Rita Vassena (ES). These five will now be joined by five new members, who were nominated and selected by the ExCo in November. The five new members are Thomas Ebner (AT), Anja Pinborg (DK), Karen Sermon (BE), Thomas Strowitzki (DE), and Snežana Vidaković (RS). Each of these new members was selected following a written submission, a brief presentation to the ExCo and interview.

Also in Geneva the British gynaecologist Roy Farquharson, whose nomination was ratified at the 2015 General Assembly, will take over as Chairman of ESHRE. Farquharson, as reported in our interview on page 22, is a past member of the ExCo with responsibility for the accreditation of centres for EBCOG sub-specialist



Italian embryologist Cristina Magli will become Chairman Elect in Geneva.

training, and a past Co-ordinator of the SIG Early Pregnancy. As a clinician, he will continue the ESHRE tradition of alternating the interests of its chairmen between science and clinical medicine.

At its same November meeting the ExCo unanimously nominated the Italian embryologist Cristina Magli as the Society's next Chairman Elect. She will take over the chairmanship at the General Assembly of 2019 in Vienna. Cristina too has a long record of activity with ESHRE: she is currently a member of the ExCo and Chairman of the SIG Committee, having formerly been Co-ordinator of the SIG Embryology and a leading author of the SIG's *Atlas of Embryology*.

New election of ESHRE's Committee of National Representatives

First-round elections for membership of ESHRE's Committee of National Representatives (CNR) began last year and hopes are that the second round will be complete and members ratified by April.

The Committee, whose principal responsibility is to advise ESHRE on local matters, is made up of two representatives of each country of 15 or more members (one scientist and one clinician) elected for a period of three years, with the opportunity to stand for re-election once. Each candidacy in this latest election had to be supported by two other members.

According to ESHRE's internal rules, the CNR is in place as a 'sounding board' for the ExCo (especially on local matters), as a source from which to select future ExCo members, to review abstracts and manuscripts for the Annual Meeting and journals, and to chair sessions at the Annual Meeting. The CNR may also be asked by the Scientific Committee for suggestions on the scientific programme of the Annual Meeting.

Two ESHRE research grants awarded for projects in endometrial receptivity

Abstract applications for the 2016 ESHRE research grants closed in April and over the following seven months 91 proposals were assessed and evaluated in two rounds of review, the first for an award of €150,000 (with 51 abstract submissions) and the second for an award of €50,000 (with 40 submissions).

The committees made the €150,000 award to Guiying Nie and colleagues in Australia (Hudson Institute of Medical Research and Monash University) and Brussels (VUB) for their research proposal on elucidating a new mechanism of endometrial receptivity (glycosylated transmembrane glycoprotein removal) and its clinical significance. The review panel described the proposal as 'innovative and exciting'.

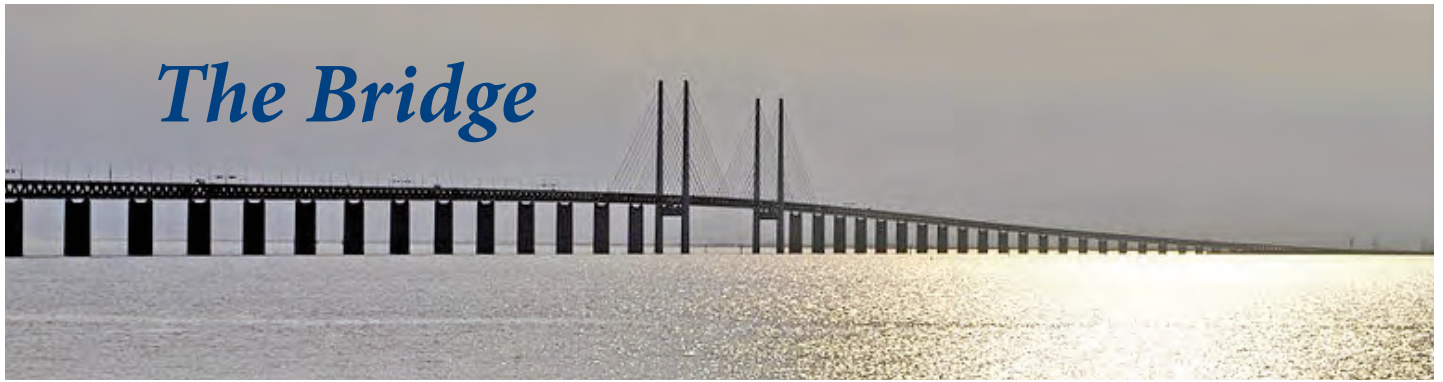
The second award of €50,000 was made to Paola Viganò and

colleagues at the Ospedale San Raffaele in Milan for their proposed project on uterine fluid exosomes as a 'liquid biopsy' in the prediction of pregnancy in ART. This too was described as 'innovative' in defining the possible correlation between uterine receptivity and proteomic profile as evident in blastocyst transfer.

The grants were available to projects running for up to three years, and were selected on the basis of scientific excellence, originality and feasibility. This year, in a bid to concentrate the scientific quality of the submissions, all research topics were related to the single theme of endometrial receptivity.

This is the second time that ESHRE has awarded its research grants, which are now on a biannual track and in the hands of a dedicated research grant committee.

The Bridge



New ESHRE fellowships in fertility training and research

● Collaboration with network of Danish and Swedish centres in reproductive medicine

ESHRE has reached an informal agreement with a Nordic network of research and clinical centres to provide fellowship funding for a number of clinical and basic science trainees working in fertility. The network - known as ReproUnion - is a consortium of 13 centres in the Copenhagen region of Denmark and Malmo and Lund regions of Sweden.

ESHRE's collaboration with ReproUnion would begin with a pilot project in 2017-2018 providing three- and six-month fellowships of €5000 and €8000 respectively. This means that ESHRE would provide fellowship funding for a trainee to cover living costs, while ReproUnion would provide the laboratory space, equipment, supervision and training.

'It's a very exciting project for ESHRE,' says ExCo member Rita Vassena. 'There are very few dedicated training

opportunities in reproductive medicine, but these fellowships can be used for all kinds of training, and not just research projects. Surgical, laboratory, clinical . . . they could all be considered.'

Applications for the fellowships would be ongoing from the beginning of the year, and ESHRE would manage a selection process every three months. Candidates would apply in the first instance to ReproUnion with their training/research projects and, if approved, to ESHRE for the fellowship. Applications would include a description of research/training plan, a CV, a motivational letter, and letters of acceptance from a ReproUnion lab and current employer/university.

ReproUnion is currently funded by a substantial EU grant to develop programmes in the management and prevention of infertility. The cross-border collaboration between Denmark



*Rita Vassena:
'Too few
dedicated
training
opportunities in
reproductive
medicine.'*

and Sweden aims to establish a common reproductive medicine centre based on a multidisciplinary concept which includes research and development, education and career development, treatment, and prevention. There are currently more than 50 PhD students working within the programme.

The fellowships in the pilot phase are for ESHRE members only and those in the early stages of their career.

ESHRE et al's appeal against European time-lapse patent decision

The saga of ESHRE's objection to the European patent awarded to Stanford University for time-lapse microscopy rumbles on, with two articles now in press following the decision of the European Patent Office to uphold and maintain the Stanford time-lapse patent.^{1,2}

ESHRE's opposition to the patent, along with that of Sterckx et al and with support of several professional organisations, was filed in 2014 largely on the grounds that patents should not be granted to treatments of the human body 'by surgery or therapy and diagnostic methods', arguing that time-lapse assessment was indeed a diagnostic procedure practised on a human body (ie, an embryo). The objection was overturned by the European Patent Office, whose reasoning last year suggested that 'diagnosis' in this case was not to determine disease but assess the competence of an embryo to develop.

Sterckx et al and ESHRE have now appealed the decision

and have argued in their *RBMO* comment that the EPO Board of Appeal's interpretation of 'medical diagnosis' was too narrow and thus unfounded and incorrect. Thus, they explain, the question of whether or not ESHRE et al will be successful in their appeal hangs on whether or not the methods to diagnose conditions which are not curable diseases are patentable - and thus whether those performing such diagnoses may be infringing patents.

In setting out his arguments why Sterckx et al might lose their appeal, UK patent lawyer David Pearce says it is now likely to take a further two years for an appeal decision.

1. Pearce D. Time-lapse microscopy patent upheld in Europe. *Reprod Biomed Online* 2016; doi.org/10.1016/j.rbmo.2016.10.012

2. Sterckx S, Cockbain J, Pennings G. Time-lapse microscopy patent upheld in Europe: response to Pearce. *Reprod Biomed Online* 2016; doi.org/10.1016/j.rbmo.2016.10.011

Online calculator to predict ART outcome

● First online predictive model with cumulative estimates and cumulative cycles

The *British Medical Journal* (impact factor 19.96) is not a natural habitat for even an eye-catching paper in ART, but that's where a report of the world's first predictive ART model with cumulative estimates over multiple treatment cycles was published in November.¹

The online calculator, developed from analysis of more than 113,000 eligible patients in the HFEA database, is claimed to estimate the individualised chance of couples having a baby both before and after their first IVF treatment, and over multiple IVF/ICSI cycles thereafter.

The researchers, from the universities of Aberdeen and Rotterdam, explain that the model will 'aid clinicians communicating to couples their personalised chances of a live birth over an entire package of IVF treatment', but warn that it 'should not be used to make decisions around whether or not couples should have IVF treatment' (because of some missing baseline data, such as BMI). They say it will also 'help to shape couples' expectations' and to plan their treatments more efficiently.

Analysis of the 113,000 eligible patients in the HFEA database showed that 29.1% had a live birth after a first cycle of treatment and 43% after six completed cycles. And it's this analysis which now provides the basis for two clinical models - one using information available before starting treatment and the other based on additional information collected during the first IVF attempt. Both models can be found on the website of the University of Aberdeen (<https://w3.abdn.ac.uk/clsm/opis>).

As expected, results show that, independent of treatment, the chances of a couple having a baby decline after the woman's age of 30 and with her increasing duration of infertility. After female age and following transfer of a fresh embryo in the first cycle, an increasing number of oocytes collected (up to 13), embryo cryopreservation and stage of embryo transfer were the next best predictors of outcome.

For example, a 30-year-old woman with two years of

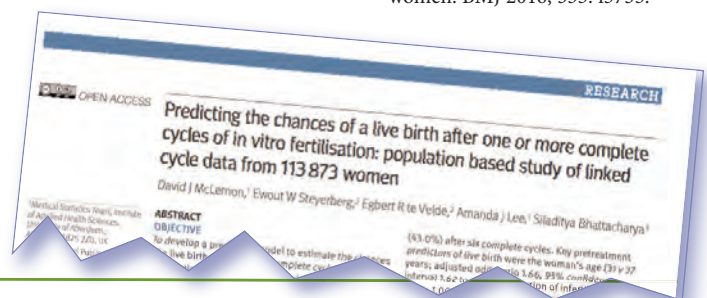
unexplained infertility has a 46% chance of having a baby from the first complete cycle of IVF and a 79% chance over three complete cycles. As expected, in this same pre-treatment model, the odds of a live birth decreased with every increasing complete cycle of treatment; thus, the odds of a live birth after cycle two was 21% lower than the odds after cycle one.

In the post-treatment model, after a fresh embryo transfer the odds of a live birth increased by 29% with the greater number of eggs collected. This doubled in cases where frozen embryos were used. Odds decreased by 9% if ICSI was used.

Explaining the logic of the two prediction models (of having a live birth over one or more complete cycles of IVF), the researchers write: 'At the point when the pre-IVF model will be used by clinicians to counsel couples as to their future chances of success, the woman's age, duration of infertility, type of infertility, previous pregnancy status of the couple, and treatment type are known. The post-IVF model revises these estimates using updated information from the first attempt at a fresh embryo transfer.'

They also add in their conclusions that, before starting IVF or ICSI, unexplained infertility and anovulation were associated with an increased chance of live birth, whereas male factor and tubal infertility had a negative association.

1. McLernon DJ, Steyerberg EW, Te Velde ER, et al. Predicting the chances of a live birth after one or more complete cycles of in vitro fertilisation: population based study of linked cycle data from 113 873 women. *BMJ* 2016; 355: i5735.



New EU traceability directive must be applied as law from April

A 2015 amendment to the 2006 EU Tissue and Cells Directive aimed to improve traceability by requiring a unique identifier applied to all tissues and cells distributed in the EU. Known as the 'Single European Code', this SEC would provide information on the main characteristics and properties of those tissues and cells.

In support of the 2015 move the Commission has now introduced a web-based coding platform for tracing donated tissues and cells from donor to recipient in the entire EU.¹ The platform is said 'to provide users with a free, simple and efficient tool to build their SEC for a tissues and cells product.'² Excluded from the directive are reproductive cells from partner donation.

According to the Commission, the requirements for the SEC as set out in the 2015 amendment should have been transposed into national law by Member States by 29 October 2016 and will become legally applicable from 29 April 2017.

The 2015 amendment, Commission Directive 2015/566/EU, was an amendment to Commission Directive 2006/86/EC with respect to 'traceability requirements, notification of adverse reactions and certain technical requirements'.

1. <https://webgate.ec.europa.eu/eucoding/>.

2. See <http://europa.eu/rapid/midday-express-06-10-2016.htm#9>.

Sperm counts of ICSI young men found lower than in naturally conceived controls

● But no close correlation between father's sperm count and son's in first follow-up study

From the very first births of the early 1990s, follow-up of its ICSI babies was always a priority at the Vrije Universiteit Brussel (VUB), from where in 1992 the group of Van Steirteghem and Devroey announced the first live birth.¹ ICSI's widespread take-up over the next few years would revolutionise the treatment of male factor infertility and finally make fatherhood possible for a large number of men with non-obstructive azoospermia. Over the past three decades, as made clear by the registry data monitored by ESHRE and SART, the use of ICSI in most regions of the world for patients with borderline or even normal semen characteristics has increased, without clear evidence of any benefit over conventional IVF.^{2,3,4}

Throughout these decades the health and development of the ICSI babies have been monitored at the VUB, and the latest report - 'the first results from the world's oldest group of young men conceived by means of ICSI because of their fathers' infertility' - published later last year show median sperm concentration, total sperm count and total motile sperm count were significantly lower than in spontaneously conceived controls.⁵ The findings came as no surprise to most commentators, particularly with the caveat that the study subjects had all been conceived by ICSI because of male factor (or idiopathic) infertility.

'These findings are not unexpected,' said Van Steirteghem in a journal press release. 'Before ICSI was carried out, prospective parents were informed that it may well be that their sons may have impaired sperm and semen like their fathers. For all the parents this information was not a reason to abstain from ICSI because, as they said, 'if this happens, ICSI can then also be a solution for our sons.'

These results do indeed suggest (but not prove) that some degree of subfertility has been passed on to the sons of fathers who had ICSI because of impaired semen characteristics.

A total of 54 men conceived by ICSI and 57 naturally conceived men were included in the study, which, after adjustment for potential confounders, showed that men conceived naturally had almost twice the sperm

concentration of the ICSIs, and more than twice the total motile count. Low sperm concentration, according to the latest WHO criteria of less than 15 million/ml, was present in 42.6% of men conceived by ICSI but only 21.1% of men conceived naturally.

However, while sperm concentrations and counts were generally lower in the ICSI men than in controls, the study did show that a low sperm concentration and total motile sperm count in fathers did not correlate with corresponding values in their sons. 'The study shows that semen characteristics of ICSI fathers do not predict semen values in their sons,' said Van Steirteghem. 'It is well established that genetic factors play a role in male infertility, but many other factors may also interfere. Correlation is not the same thing as causation.'

It was with this in mind that UK andrologist Allan Pacey (who gave last



Andre Van Steirteghem, pioneer of ICSI.

year's Annual Meeting keynote address on sperm morphology) described the results as 'quite reassuring'. 'The worry has always been that ICSI-born males were destined for a poor reproductive future that may be equivalent to (or even worse than) their fathers, whereas this paper suggests this is not necessarily the case,' said Pacey.

It was notable, however, that only 54 of the 215 young ICSI men on the VUB database agreed to take part in the study, which may also have rendered the results less than complete.

1. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet* 1992; 340: 17-18.
2. Evers JLH. Santa Claus in the fertility clinic. *Hum Reprod* 2016; 7: 1381-1382.
3. Boulet SL, Mehta A, Kissin DM, et al. Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *JAMA* 2015; 313: 255-263.
4. Grimstad FW, Nangia AK, Luke B, et al. Use of ICSI in IVF cycles in women with tubal ligation does not improve pregnancy or live birth rates. *Hum Reprod* 2016; doi: 10.1093/humrep/dew247.
5. Belva F, Bonduelle M, Roelants M, et al. Semen quality of young adult ICSI offspring: the first results. *Hum Reprod* 2016; doi:10.1093/humrep/dew245.



ART data in support of quality assurance



Members of the EIM Consortium outside the St Luc University Hospital in Brussels. In the centre foreground is the Consortium's Chairman Carlos Calhaz-Jorge, who will be succeeded in Geneva by the Swiss gynaecologist Christian De Geyter, standing on his left.

The first year of online data collection by the EIM Consortium - for the year 2013 - has seen a record number of submissions from national registries, most of which were 'consistent returns', according to ESHRE's scientific officer Veerle Goossens. She reported that data on almost 700,000 cycles had now been submitted for 2013, an increase of 8.5% on the previous year. Those data represent around 80% of total ART activity in Europe, derived from around 1200 centres in 38 countries.

Cumulatively since its formation in 1997, the Consortium has now assembled data on more than 7 million cycles and 1.3 million babies born. Describing it as 'quick and efficient', Veerle said that every country in the Consortium is now using the new online system, with only four submitting inconsistent returns (which were all amenable to repair).

Traditionally, EIM data in its annual reports have been used as a marker of outcome, availability, and safety (usually expressed in terms of multiples). But now, at the Consortium's latest biannual update held in November at the St Luc University Hospital in Brussels, there were several proposals that the very

submission of data by a clinic or the cumulative collection by a national registry or ESHRE might go even further and represent an assurance of quality in both ART performance and safety.

Indeed, ESHRE's Chairman Elect Roy Farquharson, who was present at the meeting, noted that the European Commission in informal talks with ESHRE had expressed its greatest interest in EIM data not as a reflection of outcome but as a marker of ART safety and quality. 'The EU seems far less interested in delivery rates than in adverse events,' said Farquharson, who emphasised that there is no greater demonstration of quality assurance in European ART than in the huge database of EIM. Indeed, it was suggested that a clinic's very contribution to the EIM Consortium might even be considered as a 'verification' (even 'certification') of its data collection process and quality assurance.

Indeed, it was noted by former EIM Chairman Markus Kupka that the two data collection agencies in the USA, SART and CDC, are already using their data to draw such quality conclusions far beyond their crude performance numbers.

Of course, as Kupka also noted in qualifying the claims, the EIM database does not represent 100% coverage of Europe, and the national registries from which its reports are drawn are not on a consistent cycle-by-cycle basis. There were, for example, four presentations at this meeting - from Ioana Rugescu from Romania, Carlos-Calhaz-Jorge from Portugal, Giulia Scaravelli from Italy and Dominique Royère from France - each representing registries based separately on voluntary, mandatory, summary or cycle-by-cycle data. Nevertheless, the view was clear that the value of this huge work of data collection by the EIM had worth far beyond the simple plotting of pregnancy rates or availability per million population.

It was noted from the floor, for example, that it was EIM data which first showed the diverging discrepancy between IVF and ICSI fertilisations in Europe and how this trend might have implications for cost and even safety. Although observational and

Oocyte freezing neglected in many registries

Only 17 European countries are collecting data on oocyte freezing, according to a 27-country survey carried out by ESHRE and presented here by French epidemiologist Jacques de Mouzon. While oocyte storage activity has indeed increased over the past five years, especially for egg donation, there is still little homogeneity in how that activity is recorded, even for medical indications (for which 14 of the 27 countries provide state funding). Oocyte use, said De Mouzon, 'is not very well reported'.



Jacques de Mouzon: Oocyte freezing survey.

retrospective in nature, such registry trend-spotting, it was argued, does represent real-life practice.

It was also clear in a presentation from Jesper Smeenk of the Netherlands that registry data can support - or even drive - major policy decisions, as happened in 2011 when the Dutch Ministry of Health pledged to reduce the number of reimbursed cycles of IVF/ICSI from three to just one. A counter plan from the Netherlands' 13 IVF clinics and health insurers was developed to make cost savings of €30 million a year based on an expectant management model, a policy of SET, and reduced medication cost. Now, said Smeenk, the first registry returns show that the expected savings were indeed achieved by the alternative plan - that in 2012-13 there was a 10% drop in the number of treatment cycles, and in 2013-14 a further 7% drop. The new policy has also seen a significant fall in the number of multiple pregnancies, said Smeenk, without any decline in the overall pregnancy rate.

So what next for the EIM? Incoming Chairman Christian De Geyter accepted that there was still 'a lot to do' to guarantee quality assurance through ART surveillance programmes, but he did reaffirm that 'quality assurance is the main target of collecting outcome data in ART'. Underreporting, he added, 'is the major flaw of data collection and tends to



*Incoming
Chairman of the
EIM Steering
Committee
Christian De
Geyter: 'Still a lot
to do.'*

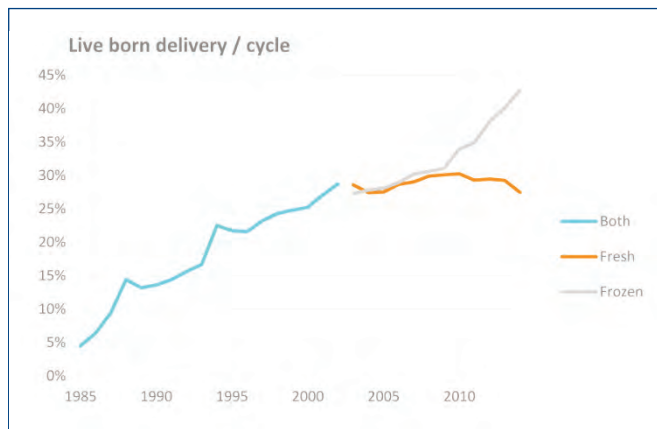
overestimate treatment effectiveness and to underestimate safety'. He described live birth rate as the gold standard measure of ART performance and similarly noted that compulsory registries are more effective than voluntary - yet many returns, as many members at this meeting confirmed, continue to be drawn from voluntary systems.

In terms of quality assurance, De Geyter identified five trends likely to compromise any hard conclusions drawn from EIM data: the patchwork of ART legislation in Europe; cross-border reproductive care; treatment by segmentation (notably freeze-all); long-term storage of gametes (such that outcome may not be reached until long after the started cycle); and the transport of biological material (in that gametes are now just as likely to 'travel' as patients).

The challenge for EIM - or any other registry - is how to incorporate these emerging trends into the online database. De Geyter suggested an individual patient code system, which could therefore follow the patient from stage to stage and site to site. But who to operate such a system? The EU . . . OECD?

Meanwhile, the immediate challenge is to ensure that national registries provide as full and accurate data to EIM as possible, and in this the online data submission system seems already to be playing a useful part.

US fresh delivery rate declines in latest SART update



A 2016 update on the activities of SART in the USA reports that membership comprises 375 clinics (83% of all those required to report) and 91% of all reported ART cycles.¹ The update notes that the number of clinics in the USA continues to rise, but at a slower rate since 2000. Most clinics still report through SART (80%) and to the CDC using the National ART Surveillance System (NASS) system, but a few do not report at all. All SART clinics also report to CDC but apparently without the need for duplicate data entry.

Among the other trends identified in the update is a continuing rise in the number of treatment cycles performed. The USA's continuing high overall delivery rate is now considerably driven by the high success rate of frozen cycles, which now, says SART, exceeds that of fresh, 'likely due to a combination of factors,

including the more physiological endometrial development of a non-stimulated cycle, and the improved embryo selection following PGS/PGD'. By contrast, the update found a slight decline in the fresh delivery rate, 'likely due to increasing use of single blastocyst transfers'. Maternal age, however, remains 'the strongest influence' on the success of the cycle. The rate of single embryo transfers continues to rise (to around 30%), and with it a decline in the twin rate to just under 25%.

The update also identifies three trends not yet manifest in the SART reports: PGS for aneuploidy screening in thawed embryos; embryo transfers with embryos 'accumulated' from more than one retrieval; and freeze-all approaches for varying indications.

● Speaking at the EIM meeting in Brussels reported above, Aaron Levine from the School of Public Policy at Georgia Tech and a 'guest researcher' for the CDC also highlighted the difficulty of accommodating cross-border treatments within national registries. Levine said that almost 3% of all US ART cycles in 2013 were in non-US residents, though adding that registry attempts to collect cross-border information from clinics 'have suffered from low response rates and incomplete data'. His disclosures followed a study of NASS data between 2006 and 2013 of cross-border treatments in US clinics which found a high traffic in 'specialised' procedures such as oocyte donation, PGD and surrogacy. However, the study found no bias in outcome, reporting comparable rates of embryo transfer and live birth for US and non-US residents.

1. Toner JP, Coddington CC, Doody K, et al. Society for Assisted Reproductive Technology and assisted reproductive technology in the United States: a 2016 update. *Fertil Steril* 2016; 106: 541-546.

Fertility preservation in females

Risk assessment and family discussion essential to define strategy

ESHRE has staged two Campus meetings on fertility preservation in the past few months, the first in Germany on procedures in males and the second in Paris on comparable techniques in females. Both were well attended - there were more than 150 present in Paris in November - reflecting today's widespread intent to restore quality of life in cancer patients, especially those diagnosed at a young age. As Hamish Wallace from the very active Edinburgh group said in Paris: 'Cure is not enough. We must pay attention to quality of life.'

Behind his assertion lay a pattern of increasing cancer incidence - especially in those under 19 - but a 'steady decline' in mortality, such that around 80% of cases are now long-term survivors. Thus, while there is still 'a very low chance' of children getting cancer, a proportion of those who do are at high risk of infertility. However, said Wallace, it's not the diagnosis itself which determines that risk, but the stage of the disease. It's the stage of disease which determines the treatment - and that's where the risk lies.

Overall, the options for fertility restoration in males - as the Edinburgh algorithm below suggests - are fewer and more simple than in females. Semen collection and storage in post-pubertal boys are relatively straightforward, although testicular tissue biopsy and cryopreservation, the only option for prepubertal boys, remain experimental. Similarly, the options in females depend on puberty and the level of ovarian function in post-pubertal females. Necessary in all cases, said Wallace, is careful risk assessment and sympathetic family discussion. A starting point for

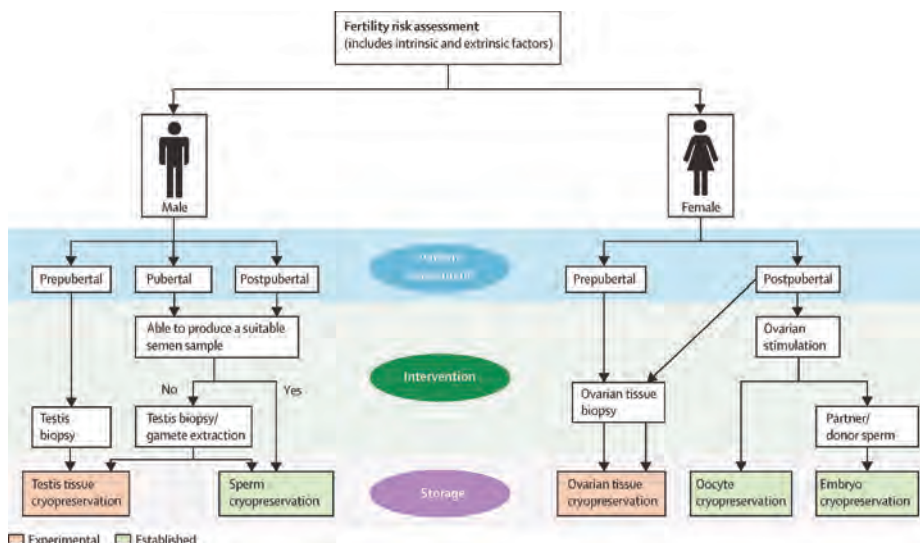


This well attended meeting in Paris in November was organised by ESHRE's SIG Safety & Quality in ART.

that discussion, said Wallace, might be the Edinburgh selection criteria for gonadal tissue cryopreservation (see box below).

Ovarian tissue cryopreservation remains the only viable option for prepubertal girls, while a 2015 review of more than 50 transplantations in 41 adult women in Copenhagen showed that grafted ovarian tissue is effective in restoring ovarian function in a safe manner. The pregnancy rate in this series was about 30%. So far, around 60 babies are believed to have been born worldwide following ovarian tissue cryopreservation, some from spontaneous conceptions and some from IVF - and more than half of them in Copenhagen.

In December the world's first birth was reported in the UK in a 24-year-old woman born with beta-



Algorithm for fertility preservation in male and females.¹

- Age younger than 35 years
- No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy is acceptable if younger than 15 years
- A realistic chance of 5-year survival
- A high risk of premature ovarian insufficiency (>50%)
- Informed consent (parent and, when possible, patient)
- Negative HIV, syphilis, and hepatitis serology
- Not pregnant and no existing children

The Edinburgh criteria for ovarian tissue cryopreservation.

thalassaemia whose ovarian tissue was frozen pre-treatment and before her onset of puberty. The cryopreservation was performed in Leeds, and the transplantation in Denmark.

In these difficult prepubertal cases, Wallace explained that AMH is detectable before puberty and may thus be important in risk assessment. AMH levels fall during cancer treatment (in pre- and pubertal girls) and recover in those deemed at low or medium risk of gonadotoxicity. Only when AMH levels fail to recover might the risk be indicative of future ovarian failure.

Depending on risk assessment, Michael Grynberg from the University of Paris described oocyte cryopreservation as 'the best option for sure' in female cancer patients, an established procedure recommended in guidelines but one clearly contraindicated in patients recently exposed to chemotherapy (within six months). Given that ovarian stimulation would be necessary to generate sufficient follicles, Grynberg also noted as contraindications a diagnosis of estrogen-sensitive tumours and ovarian or cervical cancers. He advised that patients should be referred as early as possible for ovarian stimulation and egg collection before their cancer treatment - and that stimulation should be performed in an antagonist protocol (with agonist trigger to avoid OHSS).

Presentations at this three-day meeting, which was organised by ESHRE's SIG Safety & Quality in ART, covered preservation of the whole range of gametogenesis, from primordial and growing follicles to mature eggs. In vitro maturation, according to the meeting's organiser Daniela Nogueira from the Clinique Saint Jean Languedoc in Toulouse, is best applied in cases where cancer therapy cannot be delayed and ovarian stimulation is contraindicated. Follicles, said Nogueira, can be collected either in vitro or ex vivo, with comparable maturation results if collected in the luteal or follicular phase of the cycle, but oocyte development potential seems related to the size of the collected follicle. For example, studies have found inconsistent patterns of developmental competence from small antral follicles. However, while more studies are needed to confirm protocols, Nogueira described IVM as 'a necessary tool' in urgent cases of fertility preservation in postpubertal women, with IVM better completed before (and not after) vitrification.

On the emerging question of using oocytes for IVM collected ex vivo, Ingrid Segers from the VUB Brussels group - and based on very limited data - agreed that these oocytes taken from ovarian tissue do seem of 'true benefit to fertility preservation patients', but efficiency and safety data remain very limited. She reported a 37% maturation rate (27% in prepubertal girls and 39% in adults) in Brussels.

Of course, underlying most of these presentations



Local course organiser Daniela Nogueira described IVM as a necessary tool in fertility preservation.

was this question of safety and whether malignant cells are or remain present in the cryopreserved material. Mikkel Rosendahl, whose group in Copenhagen probably has the world's greatest experience of ovarian tissue cryopreservation, said 'there will always be a risk', though so far the real life outcome data seem 'reassuring'. He reported three distant relapses from 41 transplantations in Copenhagen, a 7% chance of relapse, with the risk apparently highest in leukaemia patients. He thus recommended evaluation of all cells before transplantation, even if the histology was normal, with xenotransplantation of ovarian cortex likely to be the most accurate of several methods. Isabelle Demeestere from the Erasme Hospital in Belgium, who reviewed the accuracy of markers of

malignant cells in preserved tissue, also stressed the importance of screening for malignant cells, especially in patients with normal histology.

With so many of these safety studies described as anecdotal and limited, there was much talk at this meeting of the need for a comprehensive registry to monitor activity. Arianna D'Angelo, Co-ordinator of the organising SIG Safety & Quality in ART, in her presentation on setting up a fertility preservation service, noted the Oncofertility Consortium established a decade ago in the USA (<http://oncofertility.northwestern.edu>) and other national registries in Australasia, Brazil, Japan and FertiPROTEKT in Europe representing activity in 100 centres in Germany, Austria and Switzerland (<http://fertiprotekt.com>). The monitoring and auditing associated with such registries are essential safety requirements, said D'Angelo.

While most of the cryopreservation techniques described over the three days of this Campus were essentially exercises in fertility *restoration*, there was one presentation on true fertility preservation through the adjunctive use of GnRH agonists during chemotherapy. However, Zev Blumenfeld in presenting a huge amount of data conceded that the evidence for ovarian protection during chemotherapy with agonist co-treatment was still controversial, despite its recent incorporation into several guidelines, notably last year in the clinical consensus of ESMO (European Society of Medical Oncology). The 'pendulum' of evidence, said Blumenfeld, had thus swung towards a positive effect, with 'quite convincing' evidence displayed in meta-analyses. Indeed, he said, failure to offer GnRH agonist co-treatment 'may disadvantage many patients who could benefit from such a clinical combination'.

Simon Brown

Focus on Reproduction

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The British gynaecologist Roy Farquharson will become Chairman of ESHRE in Geneva. He talks to Focus on Reproduction about his career in Liverpool and his view on the challenges and opportunities now facing ESHRE.

Taking the wider view

‘We must still look at the global nature of reproductive science and medicine.’

FoR: You'll be taking over the chairmanship of ESHRE in Geneva. Will that affect your clinical career?

RF: I retired a year ago as a full-time clinician in O&G - 30 years as a consultant in Liverpool. I was clinical director for gynaecology with a £25 million turnover and had a hand in the design of the new Liverpool Women's Hospital, which opened in 1995. My main clinical and research interests were - and still are - in early pregnancy and recurrent pregnancy loss. We set up a miscarriage clinic in 1987, which became a national referral centre with around 250 new referrals a year.

And do we now have a good explanation for recurrent pregnancy loss?

We are certainly able to diagnose chromosome disorders more accurately, and that's reinforced our understanding that chromosome disorders are the commonest cause of random miscarriage. But for recurrent pregnancy loss, there are other disorders to exclude, so the chromosome abnormality rate is lower. But it's still substantial and requires testing.

And prevention? Would you recommend PGS in recurrent cases?

Well, *HR* recently published a study from Stanford suggesting that expectant management is as effective as PGS. The main theme of recurrent pregnancy loss is a high spontaneous cure rate, which was first

recorded by Percy Malpas in Liverpool in 1938. So treatment intervention is not always needed and should not necessarily replace counselling and patience.

So now you are moving from a life dominated by these clinical and research interests to be Chairman of ESHRE. Will your life be different now?

Yes, different, certainly, but ESHRE is still a comparable and exciting challenge. There's a lot of good work still to be done in reproductive medicine, and ESHRE, as the world's leading organisation in the field, can make a big contribution - in education, practice, research and teaching. ESHRE can't do it alone, and there's much to be said for increasing collaboration with all our partners, especially those outside Europe. So I think ESHRE now has to take more of a global view of its function and strategy.

How has a clinical career in Liverpool prepared you for this?

Today, the Chairman of ESHRE is in a senior executive position, and believe me there's a lot of strategy, change and implementation required in Britain's NHS. I've also worked a lot for the RCOG, and with NICE - so all this has given me a solid foundation for an executive role in ESHRE.

You've also been very active with ESHRE, so there's been a hands-on preparation too.

Yes, I've been involved in education, teaching, improving practice and research. In 2005, I became Co-ordinator of the SIG Early Pregnancy when it was clear that we needed a real update. Our first challenge was to standardise the terminology - and then we moved on to an ESHRE guideline. After this, we began our first original work, and slowly developed an international network of research centres. This would culminate in the randomised trial recently published in the *New England Journal of Medicine* on progesterone support in women with recurrent miscarriage. We can't say it was exclusively a SIG study, and funding - £1.6 million - came from the research arm of the NHS. But several of the main study centres in the trial did originate from the SIG Early Pregnancy.

It's been a very successful SIG in ESHRE's recent history?

Yes certainly. Our guideline on the investigation and medical management of recurrent miscarriage was one of ESHRE's first guidelines, and shortly after we began collaborations with other groups in Campus meetings and pre-congress courses, both at ESHRE and the ASRM. So we've been active in research, guidelines and education. We now have plans for ultrasound training.

And your next big step in ESHRE was the invitation to be Chairman Elect. Did you have any second thoughts?

I saw it as a challenge, yes, but don't forget that I'd also spent four years before that as a member of the Executive Committee. These were very informative years for me. Being given responsibility for the accreditation of training centres helped me understand what ESHRE was all about in terms of progress, collaboration and ambition. So the truth is I was very keen to be approached for Chairman Elect. The Executive Committee's first formal question was whether I'd wear my kilt at the Opening Ceremony. Of course, I said yes - so I guess that was the right answer.

I suppose that raises the question about your Scottish heritage.

Scotland, of course, has always played a big part in the history of reproductive medicine, and in the history of ESHRE - David Baird, David Barlow as editor of *Human Reproduction*, Nick Macklon on the present Executive Committee . . .

Is there a Scottish characteristic that we should be looking out for?

I left Scotland more than 30 years ago, so I have become quite anglicised. However, early on I was told by a colleague that 'you Scots are just like haemorrhoids - once you're down you stay down and are a constant source of irritation!'

Well, you will certainly be the first Scot to become chairman of ESHRE. Do you see any obvious challenges ahead?

Inevitably, there will be many challenges during my chairmanship, because that's what being a chair is all about. Trying to foresee them all is difficult, so being ready for them is essential - and that requires a quick response and flexibility.

So no specific challenge?

One of the biggest in my view is to be a WHO-recognised organisation. We need to be a non-state actor and be sure we have a role. WHO is currently investing in infertility as a clinical problem and we have to respond to that. The WHO definition of infertility is not just the inability to conceive but also to maintain a pregnancy and carry it to a live birth. So we're talking about inability to conceive *and* pregnancy loss, and this reflects a bigger agenda. It's a whole new portfolio for WHO with investment, and that's why ESHRE has to be at the table.

But ESHRE has broadened its scope over the past few years.

Yes, ESHRE is a mature organisation but it must become a more active participant in the global setting. There are many countries which look to ESHRE for leadership and we have to respond to that.

But where does that leave ESHRE members - especially when most are from Europe?

The challenge is to listen to the membership and address the areas they have prioritised. In that way we must still look at the global nature of reproductive science and medicine and also at the young people who are the future of the Society. I feel there's been an underinvestment in the young membership of ESHRE in terms of attention and support.

So how would you hope to be remembered as an ESHRE chairman?

Two years as Chairman is a short time to achieve big changes, but I would like us to have improved our relations and activity with other major societies. That might be simply in the form of workshops or guideline development, but with further growth and consolidation thereafter. A future young members forum would also allow them an open channel to the Executive Committee.

PROUST QUESTIONNAIRE*

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

Laziness

● **And in others?**

Lack of clarity

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

Akaroa, New Zealand

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

Good wine

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

'Better to travel in hope than expectation'
(RL Stevenson, *Travels with a Donkey*)

● **Which talent would you most like?**

To play a musical instrument

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

New Zealand

● **Your favorite non-working pastime?**

Ballroom and Latin dancing with my wife Karen, reading and poetry

● **Your most treasured possession?**

A home

● **Your favourite writers?**

Many, but no single choice

● **The last film you saw?**

The Shawshank Redemption
. . . again!

● **Beer or champagne?**

Champagne

● **Strict exercise or a leisurely stroll?**

Both in moderation

● **Sporting interests?**

Rowing and watching football

● **Your greatest achievement?**

Being a grandfather

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



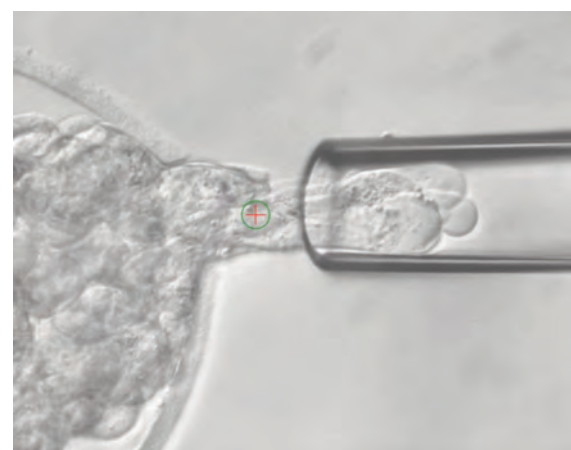
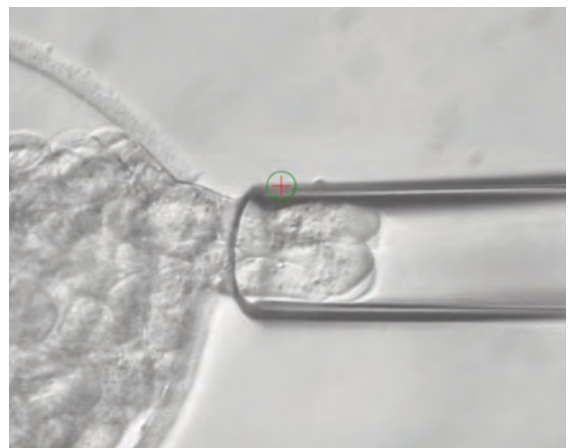
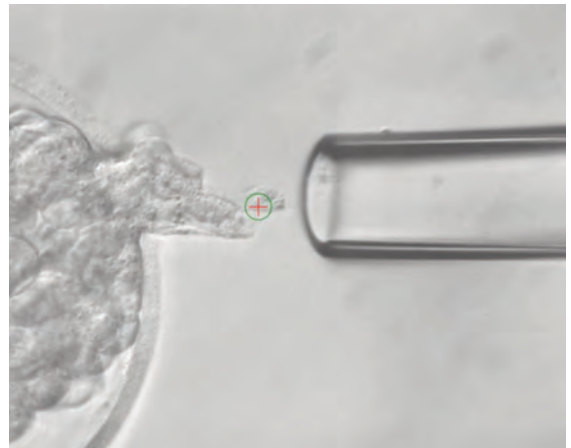
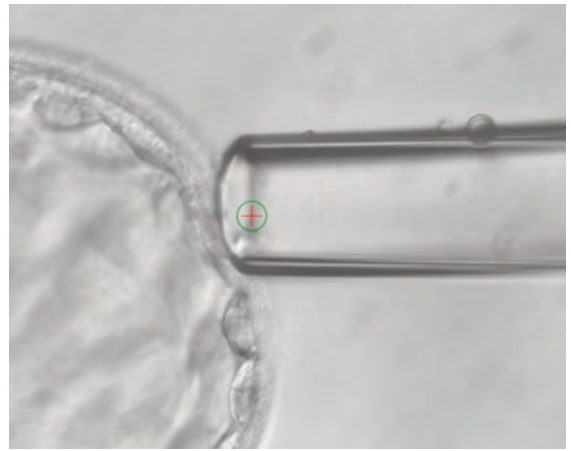
PGS in the clinic

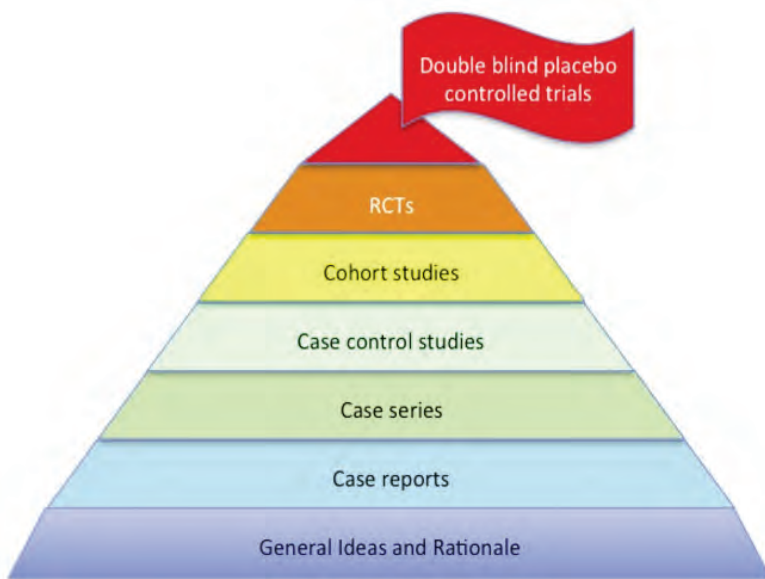
‘Jacob’ vs ‘Giuseppe’

The opposing sides in the great PGS debate seem no closer together, even ten years after the Amsterdam trial showing lower live birth rates in PGS subjects. Is there a way round this impasse such that PGS has a legitimate place in today’s IVF clinic? Darren Griffin and Sally Sheldon propose that a revised ‘gentler’ model of evidence-based medicine may bring together ‘Jacob’ and ‘Giuseppe’, two protagonists still ideologically apart in this PGS debate.

Preimplantation genetic screening (PGS, aka PGD-A), assaying for chromosomal abnormality in IVF embryos followed by the selective transfer of those thought to be euploid, has been controversial from the very beginning. Reports in the UK press and in a BBC investigation programme in November mention PGS as one of the candidates for ‘unnecessary add-on’ treatments offered by fertility clinics, along with immunology, time lapse imaging and endometrial scratch.^{1,2,3} On the other hand, both the Preimplantation Genetics Diagnosis International Society (PGDIS) and the Controversies in Genetics (CoGEN) forum have issued statements about the sensible use of PGS, along with guidelines on what to do when mosaicism is detected. Ten years ago the proponents and opponents of PGS were passionately arguing their case. Little changes.

The basic rationale behind PGS is sound, and few contest this point. We know that a large proportion of embryos are aneuploid (and would not develop, would lead to miscarriage or would produce an affected child) and we have had, for several years, the technology to detect aneuploidy in single cells. The question is whether PGS works in practice given the complications of mosaicism, for example, and the possible effects of biopsy on embryo development.

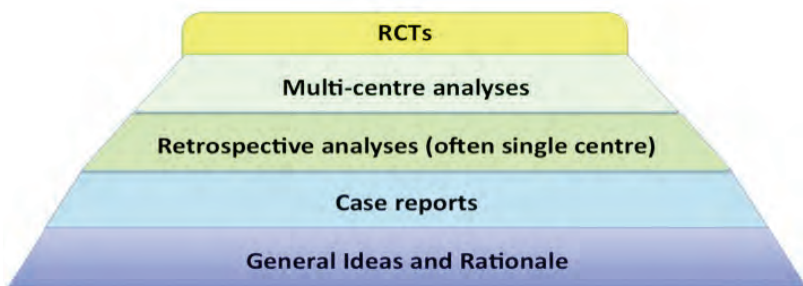




The standard model of evidence-based medicine, with the summit flagged at its peak by the double-blind placebo-controlled trial.

benefits of the treatment may already be apparent and the appetite to perform the trial may have waned. A contemporary example here is the ESTEEM trial on the efficacy of array CGH for PGS.¹⁵ This is an excellent study in principle, but one that may never be published because of criticisms of its recruitment strategy and mixed skill variance in its methodology. In any event, ESTEEM has taken so long that the field has in the meantime moved away from array CGH and towards sequencing. Conversely, a motivation to be seen as innovative (and one associated with charging patients for ‘the latest’ therapy) is proposed by some to be sufficient reason for clinics to offer new treatments, regardless of the evidence supporting their efficacy. We thus await the outcome of the most recent STAR trial.¹⁶

So where are we with the PGS debate and what’s its place in the modern IVF clinic? Whatever the evidence, it seems that the opposing sides are still no closer to agreement. So, to take a ‘straw man’ approach, we mischievously represent the argument of each of the sides by creating two imaginary characters (Jacob and Giuseppe) at the extreme ends of the debate. While such individuals may not represent real world characters, they do perhaps usefully offer an extreme example of the practices and mind-sets that are all too present in our clinics.



Our proposed ‘gentler’ model of evidence-based medicine, developed for the purposes of reproductive medicine.

Our first straw man, ‘Jacob’, is a medical statistician who opposes PGS. In this imaginary world, Jacob gets very angry when he reads any evidence in support of PGS and will usually find an excuse to criticise it. His mantra is ‘evidence-based medicine’, advocating that more and more complex analyses must be done before PGS is put into clinical practice. In his own publications, he will be selective about evidence in support of his point of view.

Our second straw man, ‘Giuseppe’, is a clinician who advocates PGS. He is motivated in part by good press for his IVF unit and generating income to keep it open. His mantra is ‘I will always do what I think is best for my patients’ while maintaining that PGS is effective, whatever the evidence. In his own publications he is selective about evidence suggesting that PGS is ineffective and has made a career out of treating patients with PGS, always publishing his findings that show it in a positive light.

In a reasonable world, we may not always agree, but we would try to find common ground. Why then do the Jacobs of this world continue to criticise or disregard the mounting evidence of the efficacy of PGS? Why do the Giuseppees not listen to the warnings of the advocates of EBM? In short, too many people have built their careers on their own point of view, and backing down is not an easy task.

So what is the solution? First of all, we are not in a position to apply the ‘mountain model’ of EBM with the goal of capturing the ‘flag’ that is the placebo-controlled clinical trial. A placebo is near impossible to achieve. The skill of the operator (or lack of it) can negate any beneficial effect of the treatment and any randomisation can thus be rendered meaningless. IVF is more reliant on ‘good gardening’ skills than many other areas of medicine. There is rarely such a thing as a ‘blind’ study - do the embryologists performing micromanipulation not know they’re doing it? We need to consider that the accumulation of results (for example, retrospective) from single centres may be just as useful to the big picture as randomised trials. We need also to be aware that meta-analyses may mask particularly bad (or good) practice by individual clinics.

We thus propose the model of a ‘gentler hill’ (rather than a mountain) as an approach to visualising EBM for PGS and reproductive medicine generally. Rather than just simply chopping off the top of the mountain this model gives more weight to retrospective analyses and case reports to gain a bigger picture of the evidence base.

Provided patients are kept informed about the state of the art with respect to the evidence base for any particular treatment (PGS included) and, when carefully explained to them what the pros and cons are at each point on the hill, then they are more in a position to make their own decisions.

Of course, a reliance on informed consent does not entirely solve the problem. It is important to recognise that patients may not always be good at dealing with complex information; this is a

particularly vulnerable patient group and there are significant financial implications for many in pursuing further treatment. We do not pretend that this is a perfect solution, but it may be the best on offer.

We need to apply careful scientific judgment and robust evaluation to consider the broader definition of EBM, namely:

An approach to medical practice intended to optimise decision making by emphasising the use of evidence from well designed and well conducted research.

But, in the context of reproductive medicine generally (and PGS specifically), what do 'well designed' and 'well conducted' mean? We should perhaps not automatically assume that EBM = RCT to the exclusion of all else. Indeed, even the model of the 'gentler hill' pictured opposite could be seen as deceptive in its acceptance of a clear hierarchy of study methods. Although RCTs will, and should, remain the gold standard, nonetheless just because a study is an RCT does not mean it is necessarily a good study (especially if badly executed). Equally, just because a study is not an RCT does not necessarily mean it's a bad study: a well designed study can be badly executed and vice-versa. We need to appreciate that RCTs have already been performed on the most recent versions of PGS, mostly showing it in a positive light.

We thus need to understand better and stratify the patient groups who would ultimately benefit from PGS. So we should constantly improve our external quality assessment schemes and consider appropriately staged introduction protocols for new innovations such as blastocentesis and karyomapping.

We also need to consider the mechanisms of mosaicism better in the light of the role of meiotic vs. post-zygotic errors. It is incontrovertible that a significant proportion of embryos are mosaic. But mosaicism can either arise from a meiotic aneuploidy in which some cells became normal or from a normal conceptus that acquired

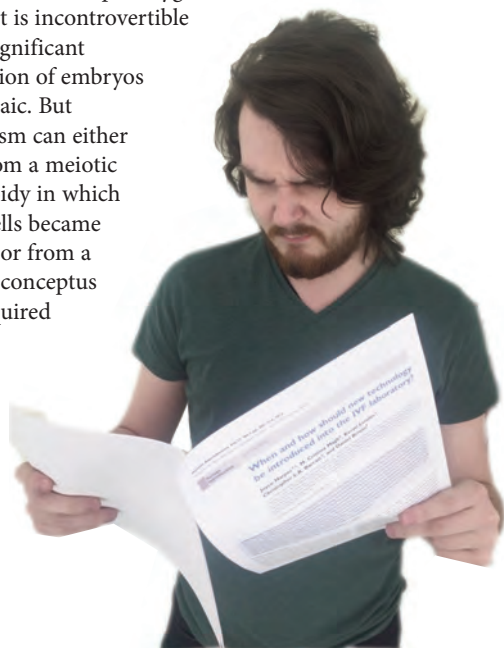
aneuploidy post-zygotically. A mosaic embryo with a meiotic aneuploidy will either not implant, lead to a miscarriage, lead to obstetric complications or lead to an affected child. It may also display uniparental disomy in the 'normal' cells. Similarly, an embryo with multiple chromosome abnormalities will not develop, regardless of how it arose. We should not be transferring these embryos.

Equally, some post-zygotic mosaic trisomies will be normal and we need to get better at detecting these, asking whether they will lead to normal live births or have an altered reduced chance of implantation. SNP chip analysis (eg, karyomapping) has, in conjunction with sequence analysis, the power to distinguish these mechanisms. In reality, despite the promising results of the current PGS trials, the basic question of the level of aneuploidy in each germ layer in human blastocysts has not been satisfactorily answered.

So, our call to the committees (who often form the arbiters of what is meant by EBM) is to reconsider the EBM model that supports IVF innovation in general (and PGS in particular) in this unique setting, taking into account the relative value of anecdotal and retrospective studies and the possible pitfalls surrounding reliance on RCTs alone. We should not automatically assume that an RCT, however well designed it was, has necessarily been well performed.

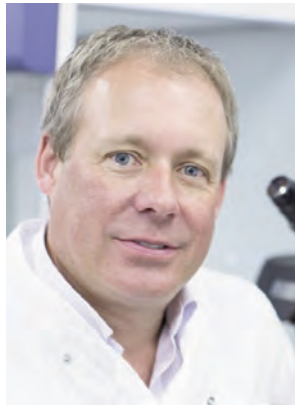
There is much debate on the statistics that need to be used (for example, those which consider that an embryo, once transferred, is an independent variable, which it is not). Innovations are, by definition, new and we may be missing something. The Jacobs of this world need to realise that the majority of the IVF

community appear to be convinced by the evidence (RCT and retrospective analyses) supporting PGS (if the overwhelming results of polls at recent PGDIS and CoGEN meetings are anything to go by). They need to apply their expertise in refining the technique and making the evidence base



Our men of straw, Jacob, left, and Giuseppe. Jacob is a medical statistician whose mantra is 'evidence-based medicine' and who is steadfastly opposed to PGS. Giuseppe is a clinician who always puts his patients first and believes PGS is effective.

Darren Griffin and Sally Sheldon: 'We need to understand better and stratify the patient groups who would ultimately benefit from PGS.'



even stronger. The Giuseppes of this world must not be complacent and should realise that we can, and do, often get things wrong.

A final parting shot is this. Against the potential harms caused by offering a therapy of disputed benefit, we need always also to consider the implications of *not* offering it. A failure to offer PGS means a failure to offer the opportunity for a patient to avoid a range of adverse outcomes. Weighing potential harms against potential benefits is never easy, nor is it quick. However, with rigorous study and minds that are appropriately open to new evidence, we will get there.

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Acknowledgments

We would like to thank Professor Simon Fishel for his comments on the manuscript and would particularly like to thank the 'real' Jacob and Giuseppe (PhD students in DKG's lab) for being good sports and allowing their images to be used.

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A new Steering Committee appointed and now in place

A new Steering Committee of the PGD Consortium is now in place. We are grateful to Jan Traeger-Synodinos (past Chair) and Sioban SenGupta for their contributions over the past years. Edith Coonen stepped down as Chair in November and will stay on as Past Chair. Martine De Rycke is the new Chair. Georgia Kokkali remains for another term of two years, while Celine Moutou becomes a special advisor for the online database. New members of the Steering Committee are Madelon Meijer-Hoogveen, Filipa Carvalho and Carmen Rubio. Cristina Magli remains as representative of ESHRE's Executive Committee and will be appointed in the coming months.

Data collection

We are in a time-lag phase and a catch up plan has been worked out. Data collections XIV and XV (covering 2011-12) will be combined in one manuscript, while summary data for 2013-2015 will be combined in another. Both papers are on course. The new online database for prospective data collection should be available at the end of this year.

Education activities

In April last year we organised a well attended and well received Campus workshop in Maastricht titled **All about preconception, preimplantation and prenatal genetic testing**. This was the first workshop to be organised in collaboration with the European Society of Human Genetics (ESHG), combining the best of both groups. A little over 130 participants from 34 different countries enjoyed three days of excellent scientific lectures and the renowned Burgundian life. Topics covered in the preconception genetic testing part included the need for carrier screening, genetic counselling, what results to report, and testing/reporting strategies.

The prenatal genetic testing parts included a state-of-art lecture on NIPT and a debate on whether all pregnant women should be offered prenatal genome-wide testing. The meeting further highlighted important topics such as EQA and physician liability, and non-invasive genetic testing. Finally, the preimplantation genetic testing section comprised an update lecture on application of genome-wide analysis techniques alongside lectures on blastocoelic fluid as source of DNA for PGD, predictive value of mitochondrial DNA, predictive value of cumulus cell analysis, metabolomics/proteomics and EQA.

Following an interactive webinar on trophectoderm



The new Steering Committee of the PGD consortium met in Brussels in November. The committee comprises, from left to right, Filipa Carvalho (PT), Veerle Goossens (ESHRE), Carmen Rubio (ES), Celine Moutou (FR), Edith Coonen (NL, Past Chair), Martine De Rycke (BE, Chair), Madelon Meijer-Hoogveen (NL) and Georgia Kokkali (GR).

biopsy hosted by Georgia Kokkali in December, another two webinars have been selected for PGD Consortium members; a first about NGS-based technologies in PGD/PGS and a second on blastocentesis planned for early 2017.

As 2017 marks the 20th anniversary of the PGD Consortium, a celebration Campus event is planned in December. Here we will pay tribute to many key players in the field - and also look back to the early days from the perspectives of counselling, biopsy and technologies. The meeting will also be an opportunity to report on the current state-of-the-art, and to look ahead at what the future holds for PGD and PGS.

*Martine De Rycke
Chair, PGD Consortium*

New members



Filipa Carvalho is Assistant Professor of Genetics at the University of Porto, Portugal. She is a previous Deputy of ESHRE's SIG Reproductive Genetics.



Madelon Meijer-Hoogveen, is Medical Coordinator for PGD and a fertility physician at the University Medical Center, Utrecht. She has worked in PGD since 2009.



Carmen Rubio is Director of the PGS and molecular cytogenetics laboratory at IGENOMIX Valencia, Spain. She has long experience in the field of PGD and PGS.

Testing for the ECRES certification in endoscopy: The skills and theoretical exams explained

● ESHRE certification programme now moving into its fourth year

ECRES, the ESHRE Certification of Reproductive Endoscopic Surgery, remains the only international certification programme in reproductive endoscopic surgery and is now moving into its fourth year. The electronic certification platform enables the quick insertion of data by applicants, and fast and accurate administration by ESHRE Central Office. The programme's e-log books, as well as the 'e-loading' of unedited videos, works very well and the system facilitates efficient reviewing, which is performed by at least two reviewers; if there is more than a 30% scoring difference, a third reviewer is asked to score.

At last year's Annual Meeting in Helsinki 21 colleagues applied for ECRES, 16 applicants at the Primary level and five at the Master level. The ten endoscopic stations used for the certification process have also been used for training and testing sessions - and more than 30 doctors received the 3-hour training session in hysteroscopy and laparoscopy. The participants were happily surprised by their rapidly acquired skills in such a short time of training and asked for further information about proper training sessions. Thus, ESHRE's SIG Reproductive Surgery provides twice yearly courses in Leuven on reproductive endoscopic surgery, with lectures and hands-on-training. A reading list and an e-learning platform are provided on the ESHRE website for ECRES applicants.

The ECRES committee has increased the number of programme tutors, who in 2016 included Professor Stephan Gordts, Professor Grigoris Grimbizis, Professor Anis Feki, Dr Sylvie Gordts, Dr Pietro Gambadauro, Dr Jaana Seikkula, Mrs Sanna Mustaniemi, Dr Razvan Socolov, Professor George Pados, Professor Michelle Nisolle and Professor Vasilios Tanos.

ECRES certification programme

ECRES now offers TESTT, 100 multiple-choice questions designed to test theoretical knowledge in fundamental areas of endoscopy and in specific areas of expertise according to the level. As with the online MCQs of the Winners Project for gynaecological endoscopy, the TESTT questions are constructed according to universally accepted rules and guidelines and were centrally reviewed by European experts.

Practical endoscopic skills exam

Testing endoscopic skills includes three training



models: Laparoscopic Skills Training and Testing package (LASTT®); Suturing Training and Testing package (SUTT®); and Hysteroscopic Training and Testing package (HYSTT®).

LASTT®. Three exercises measuring the ability of an individual to correctly handle the laparoscopic instruments. The exercises have proven construct and content validity.^{1,2,3} Results are expressed as the time needed to perform the exercise correctly. This single, objective parameter reflects both judgement error and movement efficiency. Misplacements or inappropriate object handling result in time delay and reduce performance scores. Thus, time limits are imposed during testing. When an exercise is not completed within the time limit, the last accomplished task is recorded. Each exercise has to be performed three times to be able to calculate the mathematic algorithmic final score. Both the consecutive runs and score calculation are based on a large benchmark database of expert laparoscopic surgeons.

SUTT®. The SUTT module tests for complex and fine laparoscopic skills, like needle manipulation, intra-corporeal knotting, cutting, and tissue approximation. The candidate must use both the dominant and non-dominant hand. The exercises are performed in a standard pelvi-trainer with a 0°, 10-mm optic and two

needle holders. The trainee can initially locate and insert the trocars as preferred, but thereafter they cannot be repositioned. The camera is manipulated by an assistant. The SUTT II pad is designed for the ECRES Primary level. It provides four exercises: stitching with both the dominant and non-dominant hands targeting eight dots in a predefined pathway; stitching and knot tying with the right and left hand; vertical stitching, tissue approximation; knot tying with the dominant hand. The exercises are evaluated with several criteria: the time to perform the full exercise, correct needle manipulation through a pathway of predefined dots, knot quality, tissue approximation, and absence of trauma. Test proficiency confirms that the candidate possesses sufficient, fine LPSs, including stitching and intracorporeal knotting.⁴

HYSTT *. Two exercises measuring the psychomotor ability to perform hysteroscopy. The HYSTT model simulates a normal uterus, with correct spatial distribution and orientation of the different planes and angles. The exercise is done with a 2.9 mm 30° optic, housed within a 5 mm hysteroscopic operative sheet, using a 5 French grasping forceps, and without the use of distention medium.

The first exercise, camera navigation, consists of identifying and correctly positioning several different small targets which are placed in random order within the model. The trainee must manipulate the optic such that the depicted character is displayed within a ring positioned on the monitor. The assistant or mentor indicates the anatomical position of the target and accepts the correctness of target positioning before going to the next one. In order to provide a score, the exercise needs to be done three times and the final score is calculated using the same principle as described for the LASTT calculation.

The second exercise measures instrument handling and hysteroscopic skills. Fourteen pin objects are available in the trainer model and must be picked up and released within the cavity of the model. Again, time for correct performance is the outcome measure.

The +he Academy online scoring system

All results are registered in a cloud-based online platform and the scores are calculated automatically. During testing sessions the individual receives detailed information on each exercise performed.

Testing session

The Academy has developed a unique and dynamic online scoring platform to register participants' data and test results in a central database. For each

participant, the previous exposure to gynaecological laparoscopy is registered and documented according to a scoring system of three groups: G1, one or less than 30 procedures as an assistant (= minimal); G2, more than 30 procedures as assistant but less than 50 as first surgeon OR more than 50 as first surgeon but less than 200 (= intermediate); G3, more than 200 endoscopic interventions as first surgeon (= major)

All tested individuals with large experience (G3) are used as reference values to calculate the group allocation.

The central database provides an online calculation of the results and an appreciation of the skills of the participant with a colour code. The green code indicates an excellent level of proficiency and is assigned to results within two standard deviations of the reference values. The yellow code indicates fair skills and is assigned to results between 2 and 4 SD of the reference values. The red code indicates that there is still a lot of room for improvement and is assigned to results more than 4 SD of the reference values. Thus, the final skill passport provides a global picture of psychomotor skills and can be used as an objective criterion to enter different training programmes. The benchmark database is continuously supplied with test results of the first test of an individual and saved in relation to its score of exposure to laparoscopy at the time of the test procedure. Therefore, the database is dynamic and the cut-off values can change over time

Certification and scoring

The online scoring platform provides the examiner with results of all tests performed. If more than two red scores are present, no deliberation is possible and a fail is automatically generated. In case of one red score the examiner or the committee has to make a judgement individually. The ECRES committee reviews all individual complaints every September. The overall result is displayed with a colour code to indicate the competence level.

Vasilis Tanos

Co-ordinator ECRES, for the ECRES Committee

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2. Campo R, Reising C, Belle Y, et al. A valid model for testing and training laparoscopic psychomotor skills. *Gynecol Surg* 2010; 7: 133–41
3. The European Academy of Gynaecological Surgery. http://www.europeanacademy.org/Gynaecological_Surgery.html (accessed Dec 27, 2014).
4. Campo R, Molinas CR, De Wilde RL, et al. Are you good enough for your patients? The European certification model in laparoscopic surgery. *FVV in ObGyn* 2012; 4: 95–101.

The urgent need for reliable up-to-date data

In an attempt to catch-up on previous delay in our data collections and annual reports on ART activity in Europe, we have now published our reports on 2011 and 2012 data.^{1,2} Their results show that the overall number of ART cycles in Europe continues to grow year by year, that pregnancy rates in 2012 remained stable when compared with those reported for 2011, and that the number of transfers with multiple embryos (3+) and multiple delivery rates were lower than ever before.

Now, taking advantage of the new electronic platform designed specifically for EIM data submission, the 2013 report is almost ready and we hope to have it published in the first months of 2017. It will break an EIM record, with 38 countries contributing with their registry data. Data collection for 2014 is now well on its way and we will be pleased to see data from a more complete registry in Spain.

As reported in last September's issue of *Focus on Reproduction*, a new requirement for all Spanish clinics to submit cycle data to a Ministry of Health registry run by the Spanish Fertility Society has seen a huge escalation in the number of clinics reporting data and in the number of cycles recorded in Spain. Provisional EIM data presented in Helsinki for 2013 recorded just 78,152 cycles submitted from Spain (and 164 clinics). Now, in the latest figures for 2014 calculated by the Spanish Fertility Society, the number of clinics reporting (ART and IUI) has risen to 278 and the number of ART cycles performed to a remarkable total of 116,688.

Data requirements for an effective registry

In support of our continuing efforts to help countries with a non-robust or even non-existent national registry, a 'core dataset' as a prerequisite for registry development has been defined by Markus Kupka and colleagues from the EIM Steering Group. The three-page PDF, with simply described fields and parameters, is now posted under open access on the EIM page of the ESHRE website.

A complete and reliable European ART registry in the future is a very hot topic for EIM. At the political level we have stressed to the ESHRE Chairman and the Executive Committee the importance of convincing the European Commission and its institutions that our expertise and experience with registry data make ESHRE a natural partner of the Commission in evaluating the safety and quality of ART in Europe. This idea has been well received by the ExCo, and both informal and formal contacts have made between ESHRE and Commission representatives on this subject in recent months.

However, we have a very real concern that the great changes now taking place in the clinical performance



*EIM Consortium
Chairman Carlo Calhaz-Jorge: A concern that the clinical changes now taking place in ART raise the risk that traditional registry parameters will become obsolete*

of ART may run the risk of making the classical type of registry obsolete. A forward-looking paper on this subject has now been published by some of the EIM Steering Committee members under the initiative of Christian De Geyter, Chairman Elect of the Consortium.³ The report argues that ART now includes so many more diverse approaches with 'sequential' results (eg, short- or long-term freezing of gametes, gonadal tissues or embryos, and cross-border reproductive care) that the conventional parameters of ART registries may no longer be comprehensive. Thus, long-term cumulative treatment rates and an international approach are urgently becoming a necessity.

As reported on page 16 of this issue, most members of the EIM Consortium met in Brussels to exchange experiences, confront their different problems and try to find solutions for them. Dealing with such rapidly changing parameters in ART was just one such problem.

In our activities next year - in addition to an ever greater collection of data and publication of our 2014 annual report - we plan to perform a survey on the different legal and public funding provision of ART in Europe. We will also co-host an ESHRE Campus meeting in Helsinki with the SIGs Safety & Quality in ART and Global and Socio-cultural Aspects of Infertility. We hope this initiative will highlight the relevance of data collection in the field and the need to improve the quality of registries in European countries.

*Carlos Calhaz-Jorge
Chairman EIM Consortium*

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2. Calhaz-Jorge C, de Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. *Hum Reprod* 2016; 31: 1638-1652.

3. De Geyter Ch, Wyns C, Mocanu E, et al. Data collection systems in ART must follow the pace of change in clinical practice. *Hum Reprod* 2016; 31: 2160-2163.

Upcoming events planned for a busy 2017

SIG's support for WERF harmonisation project

The SIGEED has a full and exciting programme of educational events planned for 2017. In Sofia, Bulgaria, from 27-28 January, we are hosting a Campus workshop on **Effects of ART and endometriosis on pregnancy outcome**. This is a joint venture with the SIG Implantation and Early Pregnancy.

On 17 May we are running a joint

ESHRE/ASRM precongress course prior to the 13th World Congress on Endometriosis (www.endometriosis.ca/wce2017) in Vancouver, Canada. This is a half-day course titled **Unravelling the mystery of infertility and endometriosis**.

Registration for the congress (early bird) closes on 31 January.

On 2 July we will be holding our own annual precongress course ahead of the ESHRE Annual Meeting in Geneva on **Endometrial receptivity**.

From 18 -19 September this year we are running a Campus workshop on **Methodological approaches for investigating endometrial function and endometriosis** in Edinburgh, another joint venture of the ASRM and SIGEED.

And to close the year we are joining the SIGs Early Pregnancy and Safety & Quality in ART to run a hands-on practical Campus on **Ultrasound in assisted reproduction technologies (ART) and early pregnancy: blended training approach**. This will take place on 16-17 November 2017 in Cardiff.

STEERING COMMITTEE

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

Our SIG Steering Committee had a very successful and productive meeting in October in Milan where we were able to review our plans for meetings throughout 2017 and beyond, discuss proposals for plenary sessions and our precongress course for the 2018 Annual Meeting, and review and update the contents of our website. If any SIGEED member has any feedback about our educational events or our

website please contact a member of the committee. Our next face-to-face meeting is planned for July in Geneva.



The WERF Endometriosis Phenome and Biobanking Harmonisation Project tools

As many of you will be aware, we supported the WERF Endometriosis Phenome and Biobanking Harmonisation Project (EPHect). This aims to enable large-scale, cross-centre, epidemiologically robust research into the causes of endometriosis, novel diagnostic methods, and better treatments, through the development of (1) standardised detailed clinical and personal phenotyping data collection instruments, and (2) Standard Operating Procedures (SOPs) for collection, transport, processing, and long-term storage of biological samples.

Initial development involved collaboration between 34 academic institutions and three medical/diagnostic companies. The resulting data collection instruments and sample collection protocols were published in *Fertility and Sterility* in 2014 (*Fertil Steril* 2014; 102: 1213-1222, 1223-1232, 1233-1243, and 1244-1253). and are freely available at <http://endometriosisfoundation.org/ephect>. The tools are designed to facilitate the design and interpretation of collaborative studies across the entire endometriosis research field, including studies into its pathogenesis and identification of disease sub-types, biomarker and targeted treatment discovery, and assessment of treatment outcome/effectiveness in clinical trials.

Based on user feedback, as well as further systematic searches, the tools are reviewed every three years and updated where necessary. The next round of review is happening this year, with results to be presented at the World Congress of Endometriosis in May. If you are using the tools and would like to provide feedback, we would like to hear from you at <http://endometriosisfoundation.org/ephect/#3>.

Andrew Horne
Co-ordinator

SIG Endometriosis and Endometrial Disorders



SIGEED Steering Committee members in Milan, left to right, Gerard Dunselman, Krina Zondervan, Andrea Romano, Andrew Horne, Carla Tomassetti, Lone Hummelshoj and Antonio Simone Laganà.

Consideration of guidelines on ultrasound standards

Involvement in a new EU 'work package' on tissue and cells in ART

We aim to achieve our educational goal by promoting scientific information on safety and quality through the events we organise, mainly pregress and Campus courses. We hope that participants will learn to identify and mitigate risks with user-friendly tools to drive improvement in ART practice.

Recent and upcoming events

We held a very exciting Campus course in September with the SIGs Ethics & Law and Stem Cells on **Novel gamete manipulation technologies in ART: SEEM (safety, ethical, efficient, moral) OK?** The meeting took place in Amsterdam and focused on some of the recent breakthroughs in gamete manipulation publicised as possible new treatments for infertile patients. The meeting, which is reported in detail on page 7, proved very interactive, with much time for stimulating discussion.

On a more clinical subject, we organised in Paris in November a very well attended course on **Innovative care and technologies for female fertility preservation**. The course, again reported in this issue of *Focus on Reproduction*, had a pragmatic emphasis and described the development of multidisciplinary cryobiological platforms and the use of different fertility preservation approaches dependent on gonadotoxic urgency. Different strategies appropriate to specific patient groups and oncology conditions were described along with their risk/benefit balance and ethical considerations. Oncofertility, although a specific sub-speciality in fertility centres, is still an extremely topical subject and draws much attention among fertility and non-fertility specialists.

Both these events are now available on the e-learning ESHRE platform.

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



Plans for our pregress course in Geneva - Transgenderism and reproduction: **State of the art in fertility options for transgender and people with sex reassignment** - are now complete. The course has been jointly organised by the SIGs Safety & Quality in ART, Psychology & Counselling, Ethics & Law and Global and Socio-cultural aspects in ART. Despite pervasive discrimination and

invisibility, transgender people have in recent years experienced significant advances in social acceptance and media attention. Reproductive transgender care is a true niche in the ART community, and it is clear that more and more people are 'coming out as trans' and will make their wishes known at ART centres. Our pregress course will be a first for ESHRE to bring together experts in this speciality.

A Campus course titled **What can we learn from ART disparities in Europe? Safety, quality and socio-cultural factors** is being organised with the EIM Consortium and the SIG Global and Socio-cultural Aspects of Infertility to take place in Helsinki on 28-29 September this year. It aims to provide up-to-date information, interpretation and discussion on treatment patterns and trends in fertility treatment in Europe. Data buried in national registries have the power to reveal many interesting perspectives on fertility treatment, not only from laboratory/clinical point of view but also economical. Outcome parameters can be linked to health of the children and global socio-cultural trends.

Finally, on 16-17 November the first hands-on Campus course on ultrasound in ART and early pregnancy will take place in Cardiff (UK). This course is a joint venture between ESHRE and the British Society of Gynaecological Imaging (BSGI) and will use simulators to learn or improve USS skills. Because of its practical nature the course will be limited to 70 participants on a first-come first-served basis.

Ultrasound guidelines, EU project

We have plans to develop a new ESHRE guideline on professional working standards in ultrasound practice. Ultrasound plays an important role in the management and treatment of women with gynaecological problems, with difficulties to conceive and in early pregnancy. However, it seems that current standards in performing basic ultrasound examination and interventions are not well defined. Safety and quality aspects of interventional ultrasound guided procedures (cyst drainage, follicle reduction, HyCoSy/saline sonography) and



SQART Steering Committee at the Paris Campus: Willianne Nelen, Iona Rugescu, Arianna D'Angelo, Kelly Tilleman, Daniela Nogueira, Zdravka Veleva, and Augusto Semprini.

transabdominal embryo transfer are not covered in a uniform way across countries. Three SIGs (SQART, Endometriosis and Endometrial Disorder, and Implantation & Early Pregnancy) have met to explore the possibility of developing a guideline to standardise practice. Before embarking on such an ambitious project, we would like to ask your opinion on this matter. Is there a role for ESHRE to collate the different recommendations given by the other societies and develop standards in interventional ultrasound that could be implemented in Europe and beyond? Please answer the quick questionnaire and let us know your views. Complete the questionnaire at <https://www.surveymonkey.co.uk/r/ESHRESurveyUSS>.

We are also pleased to report that ESHRE will be involved in a very important EU project, Euro GTPII



(www.goodtissuepractices.eu), a three-year project to set up a schedule of good practices applied to tissues and cell preparation and patient follow-up procedures. Our deputy, Kelly Tillemann, is work package leader for ART in this project and together with ESHRE and an international team, she will embark on this project later in 2017. The project aims to provide practical tools to assist tissue and cell centres in the implementation of requirements defined for the assessment and verification of the quality, safety and efficacy of therapies using human tissue and cells. The specific ART work package - 'good practices for demonstrating safety & quality through recipient follow-up in ART' - aims to determine essential criteria for the implementation of ART products or clinical ART applications, including a risk assessment tool for ART.

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

SIG PSYCHOLOGY & COUNSELLING

'Fertility awareness' is our pregress topic for Geneva

A recent highlight of the SIG Psychology & Counselling was a Campus basic training course for infertility counselling held in Vienna, at the end of October. The course covered many of the issues related to counselling in infertility, providing highly attractive content to psychologists and counsellors.

The hands-on workshops were a good opportunity to discuss counselling in third-party reproduction, gender differences, bereavement in the course of infertility process and the evidence-based approaches to infertility counselling. High-quality speakers contributed to an increase in the knowledge of everyone present in the workshops.

A diverse group of participants was present: clinicians, nurses, students and others. Most were very satisfied with the content of the course. The majority reported that what they had learnt was important and would have an impact on their work. The group discussions were perceived as very useful for their own practice. For those unable to be present, all the content will be available for members on the ESHRE website.

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



Upcoming events

Please don't forget to submit your abstract for the next Annual Meeting in Geneva, which must be done before 1 February. I am sure that the Annual Meeting will yet again be a great opportunity to share experiences and learn more about very recent research in the area (and also to taste the Swiss chocolate).

Our pregress course in Geneva will be on fertility awareness and should provide (a) an understanding of why fertility awareness is linked to infertility prevention, (b) an in-depth understanding of the levels of fertility awareness among people of reproductive age in Europe, (c) an update on evidence-based interventions to increase fertility awareness, and (d) an update on evidence-based interventions for fertility decision-making. We are looking forward to seeing you there. We are also preparing other Campus meetings, and will have definite news soon.

Juliana Pedro
Junior Deputy SIG Psychology & Counselling

The full cycle of germline development in vitro

Recent and upcoming activities

Our recent Campus event on **Novel gamete manipulation technologies in ART** held in Amsterdam in September was very well received with close to 100 attending. As our report on page 7 indicates, three of the currently hot research topics in ART were covered (nuclear and mitochondrial transfer, stem cell derived gametes and genomic editing), which led to a lively debate and discussion.

This year, the SIG Stem Cells pre-congress course in Geneva will concentrate on the crosstalk and overlap between 'human embryology' and 'human embryonic stem cells'. First presentations will be on the influence of embryo quality and culture conditions on both human embryonic development and embryonic stem cell derivation. Next, recent genome wide transcriptomics performed at the single cell level in human embryos by two pioneer labs (in the Netherlands and in Sweden) generated fascinating new insight into how human embryonic development is regulated.

We are now planning a further symposium in late 2017/early 2018 on **In vitro modelling: from embryo to gametes** behind which lie the many and better systems now being developed which allow the study of processes such as embryo implantation in vitro.

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Mieke Geens (BE), Junior Deputy
Rita Vassena (ES), Past Coordinator



Breakthroughs

In a real tour de force, the Japanese group of Katsuhiko Hayashi working in a mouse model has produced eggs from which fertile pups could be obtained in a germline cycle starting from pluripotent stem cells. Through a fascinating three-step in vitro culture system, both embryonic stem cells and induced

pluripotent stem cells were developed to generate functional oocytes - and embryonic stem cells derived from these IV-developed eggs could in turn generate eggs, thereby completing the reproductive cycle

This is a remarkable achievement, to enable in vitro the production of functional mouse oocytes over and over again entirely in a petri dish, and to achieve this completely in vitro without in vivo steps.

If the process can be translated into the human, which is thought to be more difficult than in the mouse, de novo eggs from patient's own stem cells could be produced, which would revolutionise the entire field of female infertility. However, we still need to recognise that the efficiency of obtaining offspring from these in vitro generated oocytes was much lower than their control counterparts. So much more research is warranted before we can even think of possible clinical applications in human.

*Björn Heindryckx
Co-ordinator SIG Stem Cells*

SIG IMPLANTATION AND EARLY PREGNANCY

Ultrasound a focus of this year's training programme

In October the SIG Implantation & Pregnancy represented ESHRE in developing and hosting a pre-congress course at the ASRM's 49th Annual Congress in Salt Lake City. The course, titled **Optimal Prevention and Diagnosis of Miscarriage**, was an update of new advances in imaging and clinical concepts of miscarriage diagnosis and prevention. There were some excellent interactive presentations on nomenclature, miscarriage diagnosis and the management of recurrent pregnancy loss.

On 27-28 January we will host our Winter Symposium, this year in collaboration with the SIG Endometriosis and Endometrial Disorders. The meeting, titled **Effects of ART and endometriosis on**

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Maria Krog (DK), Basic Science Officer



pregnancy outcome, will take place in Sofia, Bulgaria, and will explore the effect of ART and endometriosis on pregnancy outcome. Both local and international speakers are participating.

One of the SIG's main current aims is to improve education and training in the ultrasound diagnosis of early pregnancy problems. We are therefore pleased to announce our first theoretical course on **The role of ultrasound in early pregnancy** as part of the pre-congress programme at this year's Annual Meeting in Geneva in July. The first practical course is planned for November in Cardiff, UK.

*Emma Kirk
Co-ordinator SIG Implantation & Early Pregnancy*

Key performance indicators in the IVF lab

ESHRE/Alpha KPI project

The SIG Embryology, designated ESHRE members and the Alpha scientists in embryology are sharing their best expertise to formulate a consensus on key performance indicators (KPIs) in the IVF laboratory. A meeting was held in September in Vienna where definitions of KPIs were proposed for oocytes, sperm, fertilisation, cleavage, blastocysts and PGS/PGD. The workshop included expert opinion and data from questionnaire responses from IVF labs and national embryology societies. A consensus was established, with minimum performance levels for each KPI representing the basic competency and aspirational benchmarks of each as a best practice target.

At this stage, a consensus document on the outcome of the workshop is being finalised by ESHRE and Alpha. We would like to thank Alpha and the representatives of national societies for their collaboration in this major and ambitious project. We are also grateful to the ESHRE Chairman Kersti Lundin, the SIG Committee Chair Cristina Magli, ESHRE's scientific officer Nathalie Vermeulen and ESHRE members Arne Sunde and Alison Campbell for their participation and support.

Optimising IVF success

Our collaboration with the Paramedical Group in a Campus meeting in Gothenburg in November proved a valuable opportunity for the 108 participants - laboratory technicians, embryologists and paramedics - to improve their understanding of basic biology and embryogenesis and update their knowledge of laboratory techniques. Participants also had the opportunity to attend hands-on workshop sessions in

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 Susanna Apter (SE), Deputy
 Debbie Montjean (FR), Junior Deputy
 Roger Sturmey (GB), Science Officer
 Maria José De los Santos (ES), Past Co-ordinator



time-lapse and cryopreservation, and to discuss quality control in the IVF lab. Overall, a very large panel of topics was addressed during the three-day programme, with additional sessions on basic statistics, how to review and write an article, and troubleshooting.

Forthcoming activities

The beautiful city of Milan will be host to our next Campus on 11-13 May covering those aspects of gamete development to implantation which are sensitive to the time factor. Carlos Plancha and David Albertini will provide a comprehensive overview of the kinetics of oocyte development and how ageing does adversely affect its quality. Chris Barratt will also explain how culture may have an effect on sperm over time with a potential impact on fertilisation and embryo development. The target audience covers clinical embryologists, reproductive biologists and ART specialists. Places are still available and the deadline for abstract submission is 9 April.

Cellular and molecular biology for clinical embryologists is the topic of our pre-congress course for Geneva. This advanced course is planned to be of major scientific interest and will be open to embryologists, andrologists, technicians and clinicians aiming to improve their understanding of the cellular and molecular factors in gamete and embryo function. David Albertini, Keith Jones and Marie-Helene Verlhac will review molecular function in oocyte division and maturation while Chris Barratt will address the changes which sperm must undergo before fertilisation. Catherine Combelles will describe the fertilisation process and why fertilisation failure occurs in IVF. Eva Hoffmann, Roger Sturmey and Antoine Peters will consider the preimplantation embryo.

From gametes to blastocyst is a Campus taking place in Edinburgh on 12-14 October and co-organised with the SIG Reproductive Genetics. This collaboration has designed a high-level scientific programme covering all aspects of gamete maturation and selection for IVF through embryo development and function to fertilisation. This three-day meeting will also be marked by breakout sessions on clinical cases led by Danny Sakkas and Chris Barratt. These sessions will address lab problems seen in daily practice - fertilisation failure, atypical embryo development, etc.

Giovanni Coticchio
 Co-ordinator SIG Embryology



Milan, host city for our May Campus on the time factor in gamete and embryo development.

Moving forward with ovarian stimulation guideline

The year 2016 was very active for the SIG RE. With a very well attended pregress course on **Managing the difficult IVF patient**, a combined Campus meeting with the SIG Reproductive Surgery, and a very enthusiastic start for the guideline development group on *Ovarian Stimulation For ART*, first in Helsinki at the Annual Meeting and then for a start on the real work in Brussels in November, the SIG RE has continued its efforts in promoting education and consensus in good infertility treatment practice.

Business matters

Following directives from ESHRE's Executive Committee, we have welcomed two new members to broaden the scope of the Steering Committee. Roy Homburg, as International Advisor, and Jenny Visser, as Basic Science Officer, have accepted a role in fields where decisions may be difficult and to promote basic research in our educational programmes.

Lastly, and notably, Michael Grynberg and Dror Meirou, two members of the International Society for Fertility Preservation, have joined the SIG RE; their knowledge not only of fertility preservation *per se* but also of ovarian function and the effects of oncology treatment on folliculogenesis and ovarian reserve will be invaluable in developing our future programmes.

This year will also see the effects on daily practice of the two large IVF trials on the individualisation of FSH dosage on ovarian stimulation. Both, the ESTHER and OPTIMIST trials, were presented at the Annual Meeting in Helsinki last year.

Presenting new evidence on do's and don'ts, both studies may well provide important information for the process of developing the ESHRE guideline on ovarian stimulation. It will be an extensive work package and much of it has already been planned at a very constructive and laborious meeting in Brussels in November. With various new members on board, reflecting expertise from many EU member countries, topics such as FSH dose, protocol type, response monitoring and OHSS prevention have all now been rephrased into PICO questions (population, intervention, comparator and outcomes) and first results of the literature searches discussed. Practice variation here is tremendous, and this first guideline will aim to reduce that variation - to cut expenditure on medication, to enhance safety and patient compliance with treatment, and possibly to improve on the most important outcome, the chance of an ongoing pregnancy and live birth achieved within a ONE-year treatment time frame. Our plans are that the guideline working groups will complete their review and analysis in the summer, so that a first draft of the text will be

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 Daniela Romualdi (IT), Deputy
 Georgios Lainas (GB), Junior Deputy
 Roy Homburg (GB), International Advisor
 Jenny Visser (NL), Basic Science Officer
 Stratis Kolibianakis (GR), Past Co-ordinator



available for review early in 2018.

Upcoming events

It was unfortunate that the Campus meeting organised by Bulent Urman for Istanbul in December had to be postponed. But now this same workshop on **The multifaceted challenge of female reproductive ageing**, with a focus on the physiology of ageing and the

management of couples with age-related fertility decline, will take place in Athens on 5-6 May.

Our pregress course in Geneva will consider how ovarian stimulation can be optimised by individualisation (using tools such as response prediction and patient profile), the pharmacodynamics of stimulation drugs, and the physiology of folliculogenesis.

Later, in Vienna on 15-16 September we are hosting a Campus workshop on the impact of adjuvant treatments on pregnancy potential in IVF. This symposium will offer update information on the rationale for adjuvant treatments at the level of ovary, oocyte, spermatozoa, embryo and endometrium, provide scientific evidence on treatment efficacy and potential risks, and look ahead to future developments in this field.

Altogether, the year is buzzing with activities, and the SIG RE is looking forward meeting you all and each other in Geneva in July.

Frank Broekmans
 Co-ordinator SIG Reproductive Endocrinology



Historical perspective in Helsinki: Past and present SIG RE Co-ordinators (Kolibianakis, Griesinger and Broekmans) with Junior Deputy Georgios Lainas.

Italy faces up to a fertility 'apocalypse'

● Ad campaign branded 'sexist and patronising'

According to Eurostat, the statistical office of the EU, Italy now has the lowest crude birth rate in Europe. As of January 2016, Eurostat put Italy's birth rate at 8.0 per 1000 residents, just below that of Portugal (8.3 per 1000) and Greece (8.5 per thousand). These depressed figures were in contrast to those found in Ireland (14.2 per 1000, the highest in Europe) and France (12.0 per thousand) - but still well below the EU average of 10.0 per 1000.¹

Italy's birth rate has more than halved since the 'baby boom' of the 1960s, with the number of births now falling lower than at any other time since the modern state was formed in 1861.

Italy has introduced some measures to try and stimulate its birth rate, but an €80-a-month 'baby bonus' for low income families in 2014 has done little to reverse the decline. In May last year Italy's health minister pledged to double the amount to avoid what she described as a 'catastrophic' fall in birth rate, an 'apocalypse' for the Italian economy.

Later, as a further incentive for more *bambinos*, the Italian government planned a 'fertility day' campaign for the autumn which now, in its promotion and schmaltzy advertising, has been branded so patronising that even pre-resignation Prime Minister Matteo Renzi appeared embarrassed. 'As far as I know,' he said, 'none of my friends had their kids after seeing an advert.'

The fertility ads in question prompted a venomous outcry in Italy, particularly against an image of a bemused young woman touching her stomach with one hand and holding an ever emptying egg-timer in the other - which many took to imply that women had only themselves to blame for putting off pregnancy for too long. Reaction was fierce, prompting the beleaguered health minister to withdraw the promotion - though not the concept and activities of 'Fertility Day'.

The public outcry also drew accusations that Italy's demographic decline deserved more than just a few patronising and sexist ads. And raised too the question of whether the state



even had a role in the encouragement or not of procreation.

Most European countries - including the EU itself and Italy - do have population policies, which recognise that the reasons why couples are not having children are not just biological (even if partly explained by a social trend of delayed pregnancy). Child care,

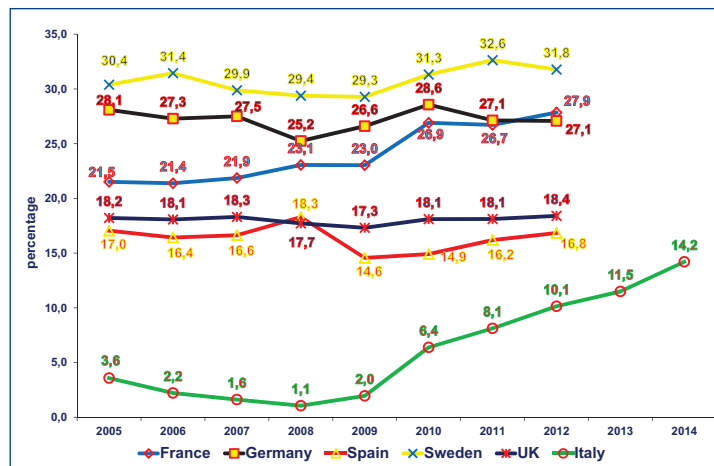


'Beauty has no age. But fertility does,' ran the saccharine caption, which many took to imply that women had only themselves to blame for putting off pregnancy too long.



working hours, paid maternity (and paternity) leave, affordable housing, family tax allowances, and nursery schooling all combine to influence the rates of conception. The place of ART within those policies - with reimbursement, state funding and greater access - has been controversial, but the experience of Denmark suggests that a generous reimbursement system for ART can be considered in the mix of several explanations for a buoyant fertility rate.

Continued over page



Trends of FER cycles as percentages of total transfers in six European countries. Italy's steady increase in ART has been largely driven by FER following its rehabilitation in 2009.

PARAMEDICAL GROUP

More than 100 take part in training workshop

The Paramedical Board in collaboration with the SIG Embryology were pleased to host a Campus course in Gothenburg in November on **Optimising IVF success.**

The course attracted 108 delegates from around Europe and beyond, with presentations on basic biology, embryogenesis, what to do when sperm and oocytes fail, embryo development and time lapse, basic statistics and information on how to review and write an article. A panel discussion chaired by Kersti Lundin allowed participants to 'Ask the expert'; here there was much healthy debate, which continued on into the evening.

An afternoon of hands-on workshops gave delegates the opportunity to access time-lapse systems, vitrification and quality control. This practical session was well received, so thank you to all the speakers who gave time out from their schedules and special thanks to local organiser Cecilia Westin.

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Certification

The Nurses and midwives certification committee met in September and have reorganised the reading list. The committee are preparing questions for the next exam, scheduled for 1 July 2017 in Geneva.

The Paramedical Laboratory Technicians are creating a helpful study guide using many of the archived e-learning lectures available via the ESHRE website for

the Embryology Certificate course.

As mentioned before we are always keen 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
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Paramedical hands-on training in Gothenburg.

Giulia Scaravelli, head of Italy's National ART Register, says that ART has never been considered as part of a population policy in Italy - until now. 'But today things are changing and ART techniques should be included in the LEA - the essential level of assistance - in the next finance bill. So the situation might steadily improve.' EIM data show that ART availability in Italy (at less than 1000 cycles per million population) is consistently settled among Europe's lower provision rates.

However, Giulia also told *Focus on Reproduction* that the use of ART in Italy continues to grow, driven largely by an increase in frozen embryo transfers (if not fresh). Embryo freezing was banned in Italy under 2004's Law 40 and was only reintroduced in 2009 after the draconian legislation of 2004 was declared 'unconstitutional'.

Meanwhile, Italy, the world's ninth biggest economy, seems still reeling from a long period of economic austerity; unemployment remains high and

domestic demand low. A higher birth rate as an economic expedient may well offset some of the demands of an ever-ageing population in Italy, but they seem unlikely to be met by misguided advertising or even the unsteady hand of the state in matters of procreation.

Simon Brown
Focus on Reproduction

1. See <http://ec.europa.eu/eurostat/documents/2995521/7553787/3-08072016-AP-EN.pdf/c4374d2a-622f-4770-a287-10a09b3001b6>

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