focus on REPRODUCTION

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SCIENCE MOVING PEOPLE MOVING SCIENCE

The maturity of in vitro maturation

- Sperm banking: crisis, what crisis?
- Reproductive genetics: 2015 in review

// JANUARY 2016

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CHAIRMAN'S INTRODUCTION

I have now been Chairman of ESHRE for half a year and have already found that it's a big job, but very interesting and extremely rewarding. I meet so many positive people working inside or in collaboration with ESHRE, and it's fantastic to see their knowledge, commitment and enthusiasm. It becomes very obvious from these meetings that ESHRE is not a static Society. We are constantly evolving, and necessarily must change and adapt to the nature of our environment and to the needs of our members.

Although we are a European Society, one-third of our members are from non-European countries and one of these needs is to think increasingly global. Fertility is being taken more and more seriously in low resource countries, which raises ever more demands on educational and policy matters. It is also important that we as the largest society in reproductive medicine and science keep a critical eye on what is happening in our field. It is without doubt becoming increasingly commercialised, with some new techniques introduced very rapidly and without sufficient evidence of effect or safety.

We are slowly adapting the structure of ESHRE to keep pace with these changes. We have for a number of years had Task Forces in place to deal with a defined question, ranging from the role of basic science in our Society to guidelines for viral screening, from clinical and educational policies in low resource countries to implementation of the EU tissue directives or management of fertility units. These Task Forces have now concluded their specific tasks, and I would like to thank the groups and their co-ordinators for all their expertise and the work they have done. Their closure, however, does not mean that their questions will be less important or forgotten. Many of these matters still need consideration and will therefore be directed into our existing SIGs or to a committee.

It is because of these emerging demands on our Society that we are also putting new structures in place. The importance of being politically aware and connected is continually increasing. This is why we are involved in the Alliance for Biomedical Research in Europe (BioMed Alliance), which represents the interests of 21 leading research-oriented medical societies with European institutions. ESHRE also collaborates more and more formally with organisations such as the European Union, Council of Europe and WHO. Similarly, new directives, guidelines and regulations are being proposed and implemented, and it is clearly important that we are heard and involved in these political and regulatory decisions. This is why we are now setting up a new European affairs committee, to keep special watch on matters arising and be present in the political arena. Similarly, a new ethics committee is already in place and we plan to establish a certification committee to make sure that our booming certification programmes each works towards harmonised and common goals. It is our hope and conviction that these changes will enhance and simplify communication within ESHRE and with the rest of the world - and in so doing further strengthen the place of ESHRE in reproductive science and medicine.

Kersti Lundin
ESHRE Chairman 2015-2017

// JANUARY 2016

Helsinki abstract submissions: Must be with ESHRE by 1 February 2016

ESHRE's next Annual Meeting - from 3 to 6 July - will be held for the first time in Helsinki, Finland. After Lisbon's altered schedule, Helsinki moves back to early July and as a consequence deadlines for abstracts and registrations are later than last year - and back to normal, with early bird registrations available up to the end of April. Full details can be found in the table opposite.

For the first time in Lisbon, ESHRE replaced the traditional paper programme and abstract books with electronic options. Now in Helsinki, ESHRE will have its own wireless network. The congress app will offer improved features, and will be available for laptops and mobile devices. We believe that participants, even those with only moderate experience of apps, will be pleased with the result.

The scientific programme will start with the two usual keynote lectures, with the first speaker representing the most downloaded article from *Human Reproduction* in 2015, followed by a presentation on the long-term consequences of maternal obesity for the health of offspring. The programme will continue with a session on the genetics and development of the early embryo regulated by newly discovered genes. Other interesting topics on Monday cover human stem cells, optimised monitoring of ovarian stimulation, cellular interactions in oocyte physiology, anonymity in donor conception, sequencing of the embryo, reproduction and 'rhythmicity', and consequences of an extra X-chromosome.

On Tuesday the programme will continue with several interesting topics covering standard IVF treatments, epigenetic remodeling in embryos, and Klinefelter and Turner syndromes. Paramedical sessions are no less interesting, with presentations on ART monitoring, twinning, ultrasound imaging, the role of oxygen in embryo culture and insulin

REGISTRATION FEES AND DEADLINES FOR THIS YEAR'S ANNUAL MEETING

Main programme	Before 30 April 2016	After 30 April 2016	After 26 June 2016
Non-member of ESHRE	496,00	620,00	744,00
Member of ESHRE	372,00	496,00	620,00
Student or paramedical member of ESHRE	186,00	248,00	372,00
Precongress Course			
Non-member of ESHRE	248,00	372,00	496,00
Member of ESHRE	124,00	248,00	372,00
Student or paramedical member of ESHRE	62,00	124,00	248,00

* Prices are in euro and include VAT at 24%

sensitisers in reproduction.

Wednesday starts with molecular elements in male infertility, the contentious matter of endometrial injury prior to embryo transfer, and embryo transfer exclusively in FET. Other topics include the molecular regulation of implantation, premature ovarian insufficiency and endometriosis. This final day - and the entire meeting - will end with the traditional award and closing ceremony.

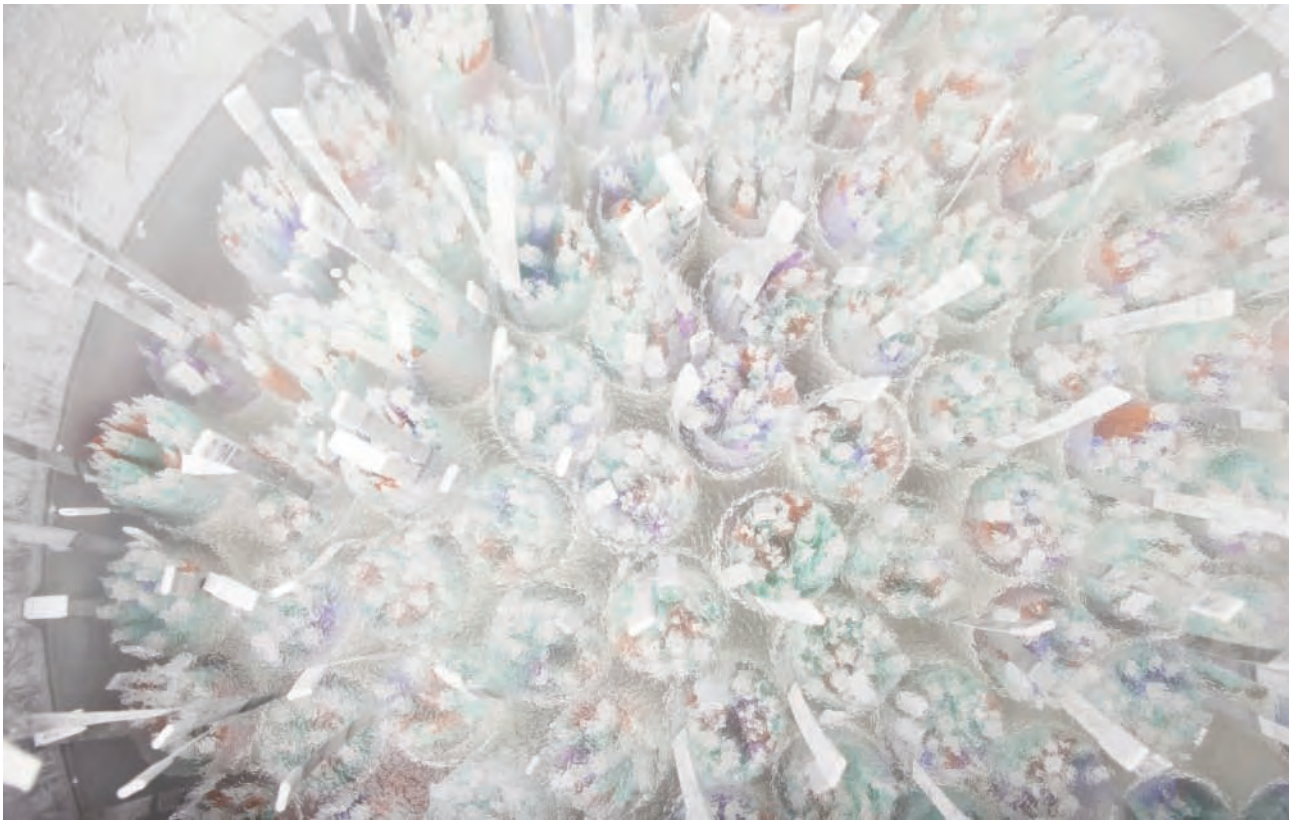
We trust that everyone will find many topics of special interest - and of help for their everyday clinical practice or research work.

The event's social programme will begin with the opening ceremony on Sunday, where all participants can enjoy Finnish (but also international) entertainment. The meeting's official charity run will take place on Monday afternoon and will be as 'serious' as always. This year the meeting's get together will be held separately from the run and will take place on Tuesday evening, an affordable community event for all participants at Kaivohuone, a well known Helsinki entertainment venue in Wells Park. Our local organisers are doing everything to ensure that the event is lively, relaxed and interesting to all. Food, live music and excellent company are guaranteed in this seaside park landscape.

The weather in July in Finland is usually sunny, and the organisers are confident that you'll need only sunglasses - and, just in case, a very small umbrella.

Local organising committee
Juha Tapanainen, Aarne Koskimies,
Anne-Maria Suikkari, Aila Tiitinen, Timo Tuuri

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



THOMAS FREDBERG/SCIENCE PHOTO LIBRARY

Crisis? What crisis?

- Fears associated with screening and consanguinity are largely misplaced
- No strong evidence for identity disclosure: the donor is not a parent

There's a perception that sperm banking in Europe is in crisis: a chronic decline in the number of donors (who are only in it for the money), long waiting lists for treatment, and ethical controversies too difficult to deal with. Yet those perceptions, said UK andrologist Jackson Kirkman-Brown speaking at a well attended Campus meeting in December, belie the real facts - for the facts are that there continues to be a steady increase in the number of donors (who are motivated more by altruism than money), many clinics, both state-run and private, have a good supply of donors and sperm, and any fears about screening and inherited disease are largely misplaced. In fact, the only perception widely accepted as fact by this meeting's large audience was that sperm banking is nevertheless 'difficult'.

The other truth universally acknowledged was that sperm donation in Europe is a patchwork of different regulations and practice. A 2015 survey performed by Willem Ombelet, one of the course organisers, found that only 14 of 22 European countries allowed donor insemination in lesbian and single women (still outlawed in Italy and France), around half only allowed anonymous donation, and cross-border care (including the import of sperm, which is not allowed in France) is a complication to any national legislation.

The subtitle to this Campus event was 'medical, socio-cultural, ethical and juridical considerations', and that largely defined its content. Those hoping for a few practical clues to overcome any practical difficulties might have been disappointed, for there was little on the recruitment of donors (other than examples of advertising) or on the demand for donor sperm. There was an assumption that demand was increasing, driven largely by lesbian, single and cross-border patients, but

With more than 160 registrations, this was among the best ever attended Campus meetings of ESHRE. The event, which took place in Leuven in December, was organised jointly by the SIGs Andrology, Ethics & Law, Socio-cultural aspects of (in)fertility, and Task Force Developing Countries.

little evidence to quantify the extent. Nathalie Dhont reported that the number of DI cycles in Belgium had increased from 8766 in 2008 to 13,048 in 2011, while UK figures presented by Kirkman-Brown showed comparable increases in the use of donor sperm in IVF. But otherwise, supply and demand remained in the background, and the issues under this meeting's spotlight were donor screening, consanguinity and anonymity.

Course joint organiser Willem Ombelet found a patchwork of legislation.

Donor screening

Donor selection criteria for the prevention of inherited disease were among several 'minimal standards' for sperm banking listed by Nicolás Garrido, sperm bank director at IVI Valencia. He was largely of the view that current guidelines for the prevention of infectious disease were adequate, but, with the greater (and cheaper) availability of more comprehensive tests, there may be scope for more rigorous genetic screening.

He reported that screening for HIV, hepatitis B and C, syphilis, CMV and other transmissible diseases (depending on the donor's origin) were common to most legal requirements and, with a quarantine freezing period to detect any seroconversion, appeared to provide a high level of safety. However, he saw greater scope for the prevention of Mendelian diseases, whose consequences, however rare, can be devastating for the offspring and family.

Nicolas Garrido: Genetic screening 'as safe as reasonably possible'.

Garrido cited two benchmark standards for safety: first, that donor conception should be as safe as natural conception between two healthy partners (as claimed by the French national sperm bank CECOS); and second, that donor conception should be as safe as reasonably possible. Thus, said Garrido pursuing the latter, if any risks of transmitting serious disorders can be tested for at reasonable cost, then this should be done. Partners cannot be replaced, he said, but donors, as providers of gametes, can be.[1]

This call for wider screening was also addressed by Dutch bioethicist Wybo Dondorp, who was also first author of ESHRE's 2014 consensus on the genetic screening of donors.[2] Dondorp suggested there was agreement that donors should not have major Mendelian disorders, major malformations, significant familial disease with major genetic component, or any chromosomal rearrangement which could result in chromosomally unbalanced gametes. However, he found inconsistency in screening for some autosomal recessive disorders and even for chromosomal abnormalities (with only France and UK requiring karyotypes of all donors).

Harmonisation of recommendation was thus one of the ESHRE conclusions reported by Dondorp, while risk profiling through wider screening (via next generation sequencing or array-based technologies) was described 'at the moment' as 'fully disproportional'. Dondorp thus proposed that donors should be treated as 'interested stakeholders' and not merely as providers of genetic material. Indeed, the ideal of the 'perfect donor', free of any genetic mutation or gene variant, was a recurring theme of this meeting. The idea of avoiding all risks is impossible, said Dondorp, and testing should remain 'proportional'.

Consanguinity

There was much less debate about the risks from consanguinity, with Dutch biologist Pim Janssens claiming categorically that the 'spread of genetic disease is not affected by the number of offspring per donor'. However, within the context of 'responsible care' and minimal standards, he acknowledged that some form of quota in terms of sperm donation and offspring was desirable, 'to recognise the *potential* harm *possibly* resulting from a large donor quota'. It thus seems reasonable, said Janssens, 'to have some reasonable limit'.

A calculation based on Dutch national data found that with 200,000 births and 1250 donor children per year the chance of a consanguineous relationship for a donor child was 0.011% when one donor was responsible for 10 children, and 0.101% when responsible for 100 children. French calculations indicated that inbreeding as a result of DI is around half that resulting from other 'accepted forms of mating'. Janssens thus concluded that offspring number per donor should be 10-100 families, and that counting should be of families, not individual children.

Anonymity

The presentation by ethicist Guido Pennings on disclosure or anonymity proved a masterclass in ethical debate - clear, structured and unequivocal. His argument rested on a basic distinction between need and desire, and that 'parents' are those who raise the child, not necessarily conceive it. Pennings could find no evidence of a 'need' for children to know the identity of the donor, and certainly no evidence of the need for a relationship - just as it became clear a decade ago that there was no 'need' for a father in the development of a child.

The reasons claimed in favour of donor identity were, said Pennings, largely spurious and insufficient to remove any requirement of anonymity. He thus proposed consideration of a compromise system which allowed the exchange of identifying information only if desired by all parties. But to indulge the wishes of the child alone and assume that interaction with the donor is preferable and correct would be on the slope of a 'slippery evolution' (as is now happening in Australia), and just one step away from acceptance of the 'donor as parent'.

There was of course more to this meeting than agonising over ethical considerations which may or may not encourage the smooth running of a sperm bank. However, it was clear that screening and the possibilities raised by identity disclosure could have a practical effect on donor recruitment. Both Nathalie Dhont and Jackson Kirkman-Brown reported a low conversion rate (of around 10%) from initial enquiry to sample provision in their own centres. Extended testing would increase the number of rejections and lower the recruitment rate even further - and this, said Nicolás Garrido, should thus be taken into account in any 'risk/cost/benefit' calculation.

So what about the benefits? A prospective study described by Genk PhD student Annelies Thijssen of more than 900 donor IUI cycles in 306 couples found an overall pregnancy rate of 15.6%. But, when multivariate analysis had deconstructed the results, a pregnancy rate of 38% was found likely if the recipient was around 25 years old, and had IUI in a low-dose stimulated cycle with motile sperm. The three defining factors for high success, said Thijssen, were female age, type of ovarian stimulation, and grade A sperm motility. BMI and smoking did not affect outcome.

Nor did the meeting ignore the impact which such treatments might have on patients. A qualitative study of 23 single women in the UK made it clear that solo motherhood was no simple choice - plan Z rather than plan B, said Cambridge investigator Susanna Graham.

Simon Brown
Focus on Reproduction

1. See, for example, Garrido N, Bosch E, Alama P, Ruiz A. The time to prevent mendelian genetic diseases from donated or own gametes has come. Fertil Steril 2015; 104: 833-835.
2. Dondorp W, De Wert G, Pennings G, et al. ESHRE Task Force on Ethics and Law 21: genetic screening of gamete donors: ethical issues. Hum Reprod 2014; 29: 1353-1359,

SART data study questions viability of cryopreserved oocytes

In what may be a modest blow to the many clinics now offering oocyte freezing for social reasons or egg donation via egg banks, a study of all donor cycles performed in the USA in 2013 has found that the use of frozen oocytes was associated with a lower but statistically significant live birth rate than fresh oocytes.[1] The report, published as a letter to *JAMA* from the group of Gleicher in New York, was an analysis of SART data involving 11,148 oocyte donation cycles, of which 2227 (20%) were cryopreserved.

The analysis found live birth rates per started cycle of 50% with fresh and 43% with cryopreserved oocytes, and 56% per transfer with fresh and 47% with cryopreserved. However, 12% of started cycles were cancelled in fresh oocyte cycles vs 8.5% in cryopreserved.

The authors suggest that the reasons for lower LBRs with cryopreserved oocytes remain to be established. However, they note that one possibility is a reduced opportunity for embryo selection because of a smaller starting numbers of oocytes. They also note that the added convenience and lower cycle costs with cryopreserved oocytes must be balanced against the lower live birth rates.

'If you start with 10 embryos rather than 5 , you have a better chance of selecting the best embryo,' investigator Vitaly Kushnir told *Time* magazine. 'But it could also be that freezing and thawing diminish the quality of the egg.'

He noted that while oocyte vitrification is no longer considered 'experimental' in the USA (the ASRM lifted that tag in late 2012), it's still not a foolproof procedure, said Kushnir - although this study did not specifically identify the cryopreservation technique.

A separate study - from the large oocyte cryobanking programme at IVI Valencia - found implantation, clinical and ongoing pregnancy rates per donation cycle of 39.0%, 48.4%, and 39.9% respectively, following an analysis of more than 3000 donations of cryopreserved oocytes over six years.[2] Noting that 'efficient oocyte cryobanking has eliminated the need for synchronization between donor and recipient', the authors report that vitrified oocytes are now used in many egg donation programmes throughout the world. Two conclusions to emerge from this huge study were 1) that there is as yet no way to predict oocyte survival potential from baseline characteristics, and 2) as Cobo herself reported at ESHRE's Annual Meeting in 2014, the probability of live birth using vitrified oocytes increases progressively with the number of oocytes consumed.

1. Kushnir VA, Barad DH, Damon SK, Gleicher N. Outcomes of fresh and cryopreserved oocyte donation. JAMA 2015; 314: 623-624.
2. Cobo A, Garrido N, Pellicer A, Remohi J. Six years' experience in ovum donation using vitrified oocytes: report of cumulative outcomes, impact of storage time, and development of a predictive model for oocyte survival rate. Fertil Steril 2015; doi: 10.1016/j.fertnstert.2015.08.020

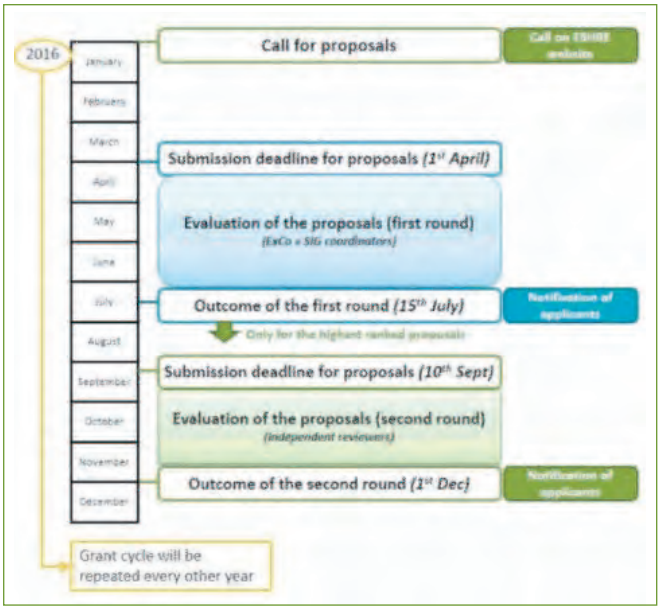
Applications for ESHRE's second research grant now open

Two awards available; proposals must be on the theme of endometrial receptivity

Applications for the second ESHRE Research Grant are now open, and all proposals must be with ESHRE by 1 April. All first-round abstract submissions will be evaluated blind by three ESHRE reviewers, after which applicants whose proposals have passed this first-round assessment will be asked to submit a second full proposal. First-round evaluation will be completed by 15 July and a final decision made by 1 December 2016.

This year, two grants will be awarded, one for €150,000 and a second for €50,000. The grants will be awarded to projects running for up to three years, and will be selected on the basis of scientific excellence, originality and feasibility. This year, however, in a bid to concentrate the scientific quality of the submissions, all research topics must be related to the single theme of endometrial receptivity.

All proposals for the first evaluation should be submitted as an abstract through the online portal on the ESHRE website. This portal is only accessible to ESHRE members - and co-ordinators of the projects should thus ensure that they are indeed an ESHRE member.



Collaboration between research groups is encouraged, but not obligatory. For each proposal, a maximum of six associated investigators can be listed, and both single-centre and multicentre studies are eligible. The grants will be awarded to the host institution.

The ESHRE Research Grant is now in the hands of a dedicated grant committee, and full details of the submission and selection processes as agreed by the committee are available on the ESHRE website (www.eshre.eu/grant) and in the grant guide downloadable as a PDF.

All proposals for the first round will be blinded before review and scored by visual analogue scale by at least three reviewers. The reviewers will be selected from ESHRE's Executive Committee and Co-ordinators of the SIGs based on the topic of the proposal.

Chairman Elect Roy Farquharson described the grant as ESHRE's bid to sponsor and reward research.

ESHRE's Chairman Elect Roy Farquharson has described the grant scheme as ESHRE's bid 'to sponsor and reward' research.

The 2014 grant of €150,000 was awarded to a project submitted by the Universities of Edinburgh and Rome Tor Vergata, led by Professor Norah Spears, to test the viability of tyrosine kinase inhibitors in protecting the ovary against loss of fertility during cancer treatment.

Responsibilities of ESHRE's Task Forces shifted to SIGs

ESHRE's five Task Forces have been disbanded. The idea behind the original formation of all ESHRE Task Forces was to address a specific question through the assembly of data or consensus. However, in the case of ESHRE's five last remaining TFs the Executive Committee has agreed that the initial objectives behind their formation have now been met.

Some of the ongoing activities of the TFs will be absorbed into other working groups or SIGs. For example, a basic science interest will still be reflected in the composition of SIG steering committees, and some of the interests of the TF Developing Countries will be taken up by the new SIG Socio-cultural aspects of (in)fertility. The latter TF, it was noted, has been particularly active, having first raised the social (and clinical) extent of infertility in resource-poor countries, and latterly, under the guidance of Willem Ombelet, having set in motion the protocols for very low-cost IVF. Ombelet reports on the first low-cost pilot project about to start in Ghana on page 31 of this issue.

Some of the responsibilities raised by the TF EU Tissue and Cells will be transferred to a new ESHRE committee aiming to forge better relations with the EU.

ESHRE reaffirms commitment to ESTEEM trial

● Recruitment incentive to centres in study of PGS by polar body analysis

ESHRE's commercial partner in support of the ESTEEM trial has pledged €70,000 as an added incentive for the further recruitment of patients into the study. The study, which is the first to assess oocyte viability by polar body analysis, has two primary aims: to improve live birth rates in women of advanced maternal age, and to estimate the likelihood of having no euploid embryos in future ART cycles.

Illumina is already providing the materials needed for the trial's genetic analysis and will now provide the extra incentive funding for recruitment at study centres. According to the study's steering committee co-ordinator Karen Sermon, about 300 patients are still needed to complete recruitment; this means that centres will receive around €230 per recruited patient. Illumina has agreed to pay these sums to ESHRE for distribution among the seven centres.

The study's target recruitment for a meaningful result was a total of 560 cycles randomised to polar body analysis or no screening. However, says Karen, patient recruitment remains slower than anticipated and she is keen to emphasise ESHRE's commitment and the new financial incentives to bring recruitment back on target. And to this end she has written to all centres reaffirming the added values of the trial, that:

- ESTEEM is the methodologically correct way to address the important scientific question of polar body analysis
- ESTEEM is the only RCT recruiting patients of advanced maternal age for analysis of polar bodies
- While there is no good evidence showing that polar body biopsy is inferior to, for example, blastocyst biopsy, there is no scientific proof yet in support of biopsy at any time point
- Scientifically, ESTEEM will give an unprecedented insight into the genetics of human female meiosis
- Participating centres in the study have a long track record of conducting these types of study, and setting a benchmark for progressive clinical care.

ESTEEM co-ordinator Karen Sermon

Karen also emphasises that ESHRE, as the main sponsor of the study, has reaffirmed its commitment to funding, agreeing at its Executive Committee meeting in Lisbon to continue financial support until the end of 2016. This too, says Karen, is the cut-off date for Illumina's incentive payments. 'That will be the end of funding,' she says, 'not a day longer.'

Already, adds Karen, recruitment at the seven study centres seems to be picking up, and ESHRE's renewed commitment has been an encouragement. However, some centres have had their own local difficulties, not least Athens struggling at the heart of the country's financial crisis. The original study design was for each centre to complete 82 cycles, but so far only the Vrije Universiteit Brussel has met this target.

'It's an important trial,' says Karen, 'with much needed results. So I hope the other centres can meet their objectives. The outcome will be crucial for embryo selection, and this is a once-and-for-all opportunity.'

Testing the uneasy relationship between science and commerce

The relationship between commercial interest and good medicine becomes increasingly uneasy. Few of the world's large-scale clinical trials are now without manufacturer involvement and in recent years a whole literature has evolved on the process of publishing results. A recent study of 1224 cardiovascular trials published in the top eight journals between 2001 and 2012, for example, found that results from those sponsored by industry were more than twice as likely to be 'positive' than government-sponsored studies.

Reproductive medicine has neither the volume of such studies nor the huge industry involvement, but it is fair to say that few developments in the field are now without a commercial edge. This has most evidently been seen - and debated - in the introduction of 'new' techniques, most of them without preclinical safety studies or early phase human studies - and many promoted directly to patients as the next big thing in IVF.

This and the whole gamut of reactions to commercialisation in reproductive medicine will be the subject of a closed expert meeting to be staged by ESHRE in February. Any conclusions drawn from the many expert presentations and the discussion will hopefully find their way into a consensus paper not unlike the recent proposal from the SIG Ethics & Law on distinguishing between experimental, innovative and established treatment in reproductive medicine.[1]

The main two topics of this meeting will be 'responsible innovation' and 'advertising and promotion', of which the latter will even consider the implications of sponsorship for ESHRE and other medical societies. Other sessions will cover advertising directly to consumers, reporting study results and the journals.

1. Provoost V, Tilleman K, D'Angelo A, et al. Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment. Hum Reprod 2014; 29: 413-417.

Update on ESHRE guidelines

Three completed, implementation next

Three ESHRE guidelines have so far been completed, the latest in December on the **Management of women with premature ovarian insufficiency**. In her report to ESHRE's Executive Committee in November Research Specialist Nathalie Vermeulen, pictured right, noted recurrent miscarriage, Turner syndrome, and implementation as the priorities for 2016.

- **Management of women with endometriosis**

The guideline has been briefly evaluated and was apparently well received. As the SIG explains on page 24, next task is to develop of a set of quality indicators based on patient and professional input to monitor the management of endometriosis in European hospitals. Results are expected this year. Meanwhile, a full update to the guideline is scheduled for 2017.

- **Routine psychosocial care in infertility and medically assisted reproduction: A guide for fertility staff**

Finalised in March 2015; a short version was published in *Human Reproduction* in September 2015. A patient version of the guidelines has been circulated recently to all ExCo members and the document has been approved.

- **Management of women with premature ovarian insufficiency**

Final comments on the full text were made in December, with approval by guideline development group and ExCo before year's end. A summary paper has also been drafted and sent for approval before submission to *Human Reproduction*.

Nathalie also reported that ESHRE had been invited by the European Society of Endocrinology to collaborate on a guideline on Turner Syndrome, which has been agreed by the ExCo. ESHRE's revised guidelines on good practice in IVF labs has been finalised and published for review on the ESHRE website. The document was approved by the ExCo in December and will be ready for publication early in 2016.

With an increasing number of European guidelines in place, their implementatiion has been put in the hands of a small working group, whose aims are the evaluation of current indicators for implementation, how dissemination can be improved, and the development of tools to increase the impact of ESHRE guidelines.

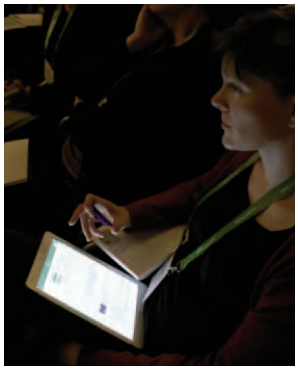
New ESHRE ethics committee will have impartial advisory role

ESHRE's Executive Committee has agreed to the formation of an Ethics Committee whose role would be advisory and whose judgement would be impartial. The Committee would thus be asked by the ExCo to provide opinion on ethical questions in reproductive medicine, help determine ESHRE's position on controversial subjects, or give advice on legal matters. The Committee might also be called upon to provide an opinion on matters involving conflict of interest.

The ExCo is now concluding the composition of the Committee, which will comprise a mix of clinicians, scientists, paramedics and ethicists. At its meeting in November the ExCo agreed that the committee would advise on matters in reproductive medicine and science with potential impact on patients, professionals and society.

The Ethics Committee is one of several new committees proposed by ESHRE; others include a Research Grant Committee and Certification Committee, both developed from existing working groups, and a European Affairs Committee.

An ESHRE events app: Campus courses in the palm of your hand



Up and running. The ESHRE events app, now a single access point for all Campus information.

Those attending ESHRE's last four Annual Meetings have been able to read the abstracts, browse the programme and take notes with their smartphone or tablets via an ESHRE app, which aims to improve congress experience by providing all relevant information – updated in real-time - in an easily accessible way.

Now, the app's function will be extended to all Campus courses, with the same objective in mind: to provide a simple tool to help maximise benefits from the meeting.

The events app will be the single-access point to all course information, with centralised scientific (programme, syllabus, abstracts, speakers) and logistic details (venue, maps, hotel).

ESHRE Campus events are also about networking so attendees can check the participants lists to send messages and exchange their electronic business card contained in the app. Other useful functions include note-taking, answering surveys, and the latest news about the course and ESHRE.

The app was introduced in December at ESHRE's last Campus course of 2015, on sperm banking, in Leuven, Belgium. More than 100 participants there (from 165) downloaded the app, with users praising its convenience.

The app will be available to all those attending each Campus course in 2016, and will be accessible for Android and iOS devices, as well as a desktop version.

SIG raises safety doubts over widely publicised mitochondrial transfer technique

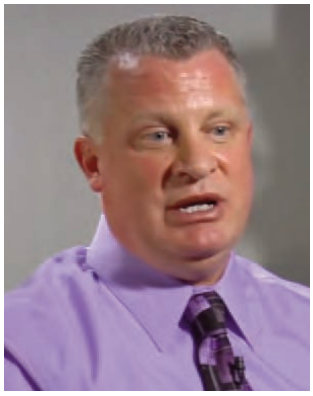
- First data published as 'physician reported outcomes'
- SIG urges caution in interpretation of results

One of the talking points along the corridors of last year's Annual Meeting in Lisbon was a technique of energising IVF oocytes with mitochondria from the patient's own 'egg precursor cells'. The technique had been publicised a few weeks before by announcements of the first live birth and press reports of 'a new chapter in medical history'. *Time* magazine said that the birth would be 'the first in a wave of babies expected to be born this summer through a technique that some experts think can dramatically improve the success rate of IVF'.

Björn Heindryckx, Co-ordinator of ESHRE's SIG Stem Cells, which produced the opinion in November last.

There appeared to be two historical preludes to the treatment, each of which were somewhat controversial at the time: first the work of Jacques Cohen and others in the late 1990s to improve oocyte quality by the injection of cytoplasm from healthy donor eggs (with resulting pregnancies); and second, the discovery by Jonathan Tilly and colleagues of 'oogonial' stem cells ('egg precursor cells') in the lining of the ovarian cortex. Thus, in terms of improving oocyte quality, any ethical or procedural problems inherent in the former (a third-party source of mitochondria) might apparently be resolved by the rewritten biology of the latter (an autologous source).

Tilly himself is described as one of the 'scientific founders' of OvaScience, a US company established in 2011 which has commercialised the use of mitochondria from egg precursor cells as 'Augment'. At the time of the first-baby press reports in May and an off-programme symposium in Lisbon in June, there were no peer-reviewed papers to describe the technique or its outcome. But that changed in August when Fakih et al published their 'physician reported outcomes' of Augment treatment in the open access *Journal of Fertilization: In Vitro, IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology*.[1] The report, which described treatment in two series of poor prognosis patients at two centres, one in Canada and one in Dubai, had been much anticipated; use of Augment treatment, it said, is based on case reports of donor egg cytoplasm injection and animal studies demonstrating 'that the addition of mitochondria during IVF treatment is safe, improves the quality of the embryos, and increases the success of IVF'.



Jonathan Tilly explaining his work on oogonial stem cells in 2012.

A statement recently issued by ESHRE's SIG Stem Cells has considered the publication and, after raising five unresolved safety concerns, 'urges all stakeholders to perform extensive safety studies and prove the beneficial effect of mitochondria transfer on infertility before considering the possible clinical applications'.

The statement notes a lack of quality assessment in the report (reagents, the isolated mitochondria, oocytes) and an ill-defined minimal threshold number of mitochondrial copies. One study has even found that excessively high copy numbers can have detrimental effects in mice - while recent studies from Fragouli et al appear to support an adverse correlation between mtDNA copy number and blastocyst quality and implantation rate in the human.[2]

The SIG statement notes potential sources of bias in the study methodology and timing anomalies in the studies cited to support some of the investigators' claims. It also raises reasons for caution in the lack of any evidence of a direct beneficial effect of transferring mitochondria from egg precursor cells on embryonic development, even in animals - and that there is still controversy over the very existence of egg precursor cells in adults.

The SIG's concluding advice is that the results of the published study should be interpreted with caution and that more safety reassurance is needed before clinical introduction. So far, the OvaScience website notes, the treatment is only available in limited countries, and not in the USA where, apparently, the FDA considers such treatments as 'gene therapy' and thus subject to a high bar of regulatory approval.

1. Fakih MH, Shmoury MEl, Szeptycki J, et al. The AUGMENTSM Treatment: Physician Reported Outcomes of the Initial Global Patient Experience. JFIV Reprod Med Genet 2015; 3: 154. doi:10.4172/2375-4508.1000154

2. Fragouli E, Spath K, Alfarawati S, et al. Altered levels of mitochondrial DNA are associated with female age, aneuploidy, and provide an independent measure of embryonic implantation potential. PLoS Genet 2015;11(6): e1005241.

As you were in treating unexplained infertility

- Letrozole has 'no advantages over clomiphene' in large RCT
- IVF more expensive than IUI, but no more effective

One of the largest reported randomised trials for several years has found that ovarian stimulation for unexplained infertility is most effectively performed with gonadotrophins. The study, conducted by the NIH in 12 US centres and published in the *New England Journal of Medicine* in September last, involved 900 couples with unexplained infertility given (injectable) gonadotrophins, or (oral) clomiphene and the aromatase inhibitor letrozole before IUI.[1]

As background to the report the investigators note that aromatase inhibitors have already been used successfully to induce ovulation in women with PCOS, and in multiple reports have been proposed as effective alternatives for ovarian stimulation in unexplained infertility, with monofollicular development reported in many cases and lower rates of OHSS.

Following treatment for up to four menstrual cycles in this study, a pregnancy rate of 35.5% was found in the gonadotrophin group, 28.3% in the clomiphene group, and 22.4% in the letrozole. Live birth rates were 32.2%, 23.3%, and 18.7%, respectively. The pregnancy rates with letrozole were significantly lower than the rates found with standard therapy (gonadotrophin or clomiphene) or gonadotrophin alone, but not with clomiphene alone.

The clomiphene group had the fewest multiple pregnancies, at 1.3%, followed by 2.7% in the letrozole group and 13.4% in the group receiving gonadotrophins. All multiple pregnancies were twins in the clomiphene and letrozole groups; for the women receiving gonadotrophins, 24 multiple pregnancies involved twins and 10 involved triplets.

Thus, because gonadotrophins resulted in the most multiple pregnancies of the three treatments, and letrozole resulted in the lowest pregnancy rate, the study authors concluded that clomiphene is the most appropriate to stimulate ovulation in unexplained infertility treated with IUI.

In a press statement issued by the NIH, study author Esther Eisenberg said that letrozole treatment offered no advantages over clomiphene. 'Women in the letrozole treatment group had fewer live births, but four times as many multiple pregnancies as women in the clomiphene group,' she said.

Another large-scale trial involving stimulated IUI in unexplained infertility - this time from the Netherlands - has confirmed that IVF strategies are significantly more expensive than stimulated IUI without being significantly more effective.[2]

'No evidence in support of IVF as a first-line treatment in unexplained infertility.'

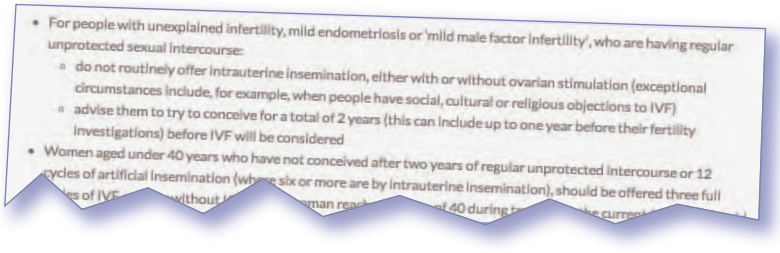
This was a cost-efficiency analysis performed alongside a randomised non-inferiority trial in 602 couples with unexplained infertility and a poor prognosis at 12 Dutch centres. The couples were randomly allocated to three cycles of SET IVF plus subsequent frozen embryo transfers, six cycles of modified natural cycle IVF or six cycles of stimulated IUI - and followed for 12 months after randomisation.

There was a delivery rate of 52% in the SET IVF group, 43% in the modified natural cycle group, and 47% in the IUI group. However, the mean costs per couple were €7187 for SET IVF, €8206 for modified natural cycle IVF, and €5070 for IUI. The costs for both IVF approaches were significantly higher than for stimulated IUI.

As a result, the investigators concluded that there is no evidence in support of IVF as a first-line treatment in unexplained infertility. 'Both IVF strategies are significantly more expensive when compared with IUI-COH,' they write, 'without being significantly more effective.' And they thus recommend that stimulated IUI remains the first-line treatment.

It is noteworthy too that they draw attention to the latest NICE guidelines in the UK and their controversial recommendation to proceed immediately to IVF in such cases after two years 'expectant management'. Roy Homburg, speaking at last year's 'Best of' ESHRE and ASRM meeting in New York, described the UK recommendations as incomprehensible, and they are now branded 'unsustainable' by the Dutch.

1. Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. NEJM 2015; 373: 1230-1240.
2. Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PMM, et al. Is IVF—served two different ways— more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod 2015; 30: 2331-2339.



NICE guidelines updated in 2013. Described as 'unsustainable' following a large-scale cost efficiency analysis in the Netherlands.

No fertility problems for women of the Tsimane people of Bolivia infected by parasitic roundworms.
Picture: Michael Gurven

Worms may have immunological effect in fertility - at least in the Amazon valley

What turned out to be one of the most remarkable fertility stories of last year came in the journal *Science* in November in a report from California that parasitic roundworm infection can increase the reproduction rate in (Amazonian) women - while hookworm infection can decrease it.[1]

Apparently, parasitic worms infect 2 billion people globally and, while it's known that some parasites can cause cognitive and nutritional impairment, this new study now suggests that reproduction rates can also be affected. The investigators propose a hot-topic mechanism behind this correlation: the immune system. 'Infection with intestinal helminths results in immunological changes that influence co-infections,' they write, 'and these might influence fecundity by inducing immunological states affecting conception and pregnancy.'

Helminths are parasitic worms that feed on a living host for nourishment and protection, while causing poor nutrient absorption, weakness and disease in the host. These worms and larvae live in the small bowel, are usually referred to as intestinal parasites, and include nematodes or roundworms.

To test the effects of these parasites on reproduction rates, Aaron Blackwell and colleagues from the University of California at Santa Barbara used data collected over nine years from Tsimane women in the lowlands of Bolivia, a population with an average birth rate of nine children per woman. The analysis was performed in 986 Bolivian forager-horticulturalists with proven natural fertility and a 70% helminth infection prevalence.

'Women infected with a species of roundworm were found to have up to two more children than those without infections'

'We found that different species of helminths - a family of parasitic intestinal worms - could have either positive or negative effects on the timing of a Tsimane woman's next pregnancy,' said Blackwell. 'Hookworm infection tended to increase the length of the intervals between births . . . consistent across all ages. But younger women infected with roundworm had shorter birth intervals.'

They similarly found that women who were repeatedly infected with hookworm were likely to have up to three fewer children in their lifetimes than uninfected women, while women infected with a species of roundworm were found to have up to two more children than those without infections.

Infection with roundworm (Ascaris lumbricoides) was thus associated with earlier first births and shortened interbirth intervals, whereas infection with hookworm was associated with delayed first pregnancy and extended interbirth intervals. Helminths may thus have important effects on human fertility reflecting immunological consequences of infection, the authors write.

These two parasites, they explain, are known to invoke different immune changes; the changes following roundworm infection happen to be reflective of those that occur during pregnancy. Specifically, as a woman proceeds through her menstrual cycle, levels of type 2 (Th2) T-cells increase and, if conception occurs, this increase continues through pregnancy and helps suppress type 1 (Th1) T cells. Because roundworms are known to increase Th2 levels, and hookworms have been reported to evoke a mixed Th1/Th2 response, the authors suggest that these parasites are indirectly affecting reproduction rates by changing immune cell balances.

'Reproductive immunology' has become a hot topic in recent years, based on the idea that the developing embryo can be 'rejected' by these immune cells. Adjunctive treatments - usually given in cases of previous implantation failure - have included steroids, intravenous immunoglobulin (IVIg), tumour necrosis factor-a (TNF-a) blockers, and intralipid infusions. Trials of these treatments are virtually non-existent and, in the case of one of several examples, the UK's Royal College of Obstetricians and Gynaecologists said last year that 'there is no rationale for the use of intralipid infusions in fertility treatment'. Similarly, a recent review of several clinical trials found that IVIg treatment did not increase IVF success rates, while another recommended that IVIg for recurrent miscarriage should not be offered unless it is done as part of a clinical trial

1. Blackwell AD, Tamayo MA, Beheim B, et al. Helminth infection, fecundity, and age of first pregnancy in women. Science 2015; 350: 970-972.

The last ESHRE pioneer to step down from his university post

Arne Sunde's 30-year involvement with ESHRE

It's a sign of the times that most of those ESHRE pioneers who formed the Society in London in 1984 and went on to join the first Executive Committee have either retired from their university posts or are no longer with us. ESHRE is now in the hands of a new generation, though the past is never forgotten.

The last of those earliest pioneers to step down from his academic post - though not to 'retire' - is Arne Sunde, the Norwegian biologist who was gently coerced into ESHRE's first temporary committee by Bob Edwards himself and would within a few months be given responsibility for ESHRE's training programmes. Eighteen years later - in 2003 - Sunde was named as the tenth Chairman of ESHRE.

His retirement from St Olav's Hospital in Trondheim was marked by a short symposium in September last, with presentations from his Norwegian colleagues Jarl Kahn and Berge Solberg, and from ESHRE's past and present chairmen Juha Tapanainen and Kersti Lundin.

Sunde was appointed professor in cell biology at the University of Trondheim in 1994 but before then had been part of the team responsible for the first IVF babies in Norway (in 1984) and the first baby in the Nordic countries born after embryo cryopreservation (in 1988).

As with many other IVF 'retiremens' in recent years, Sunde will now head to the private sector and a new clinic in Trondheim, to serve as a senior embryologist and consultant. For ESHRE he will continue his membership of the culture media working group, campaigning for greater clarity in the composition of different media and aiming to produce a summary report.

Over the years Sunde has been one of the most active and influential ESHRE members, notably in the development of the Campus programmes, precongress courses and strategic directions. Yet his introduction to ESHRE had been nothing but fortuitous, when he wandered into a meeting room (to pass a little time, he said) at the third World Congress of IVF in Helsinki in 1984. There he would find Edwards and a bunch of keen Europeans determined to set up a society to rival the Americans and it was they who made him welcome.

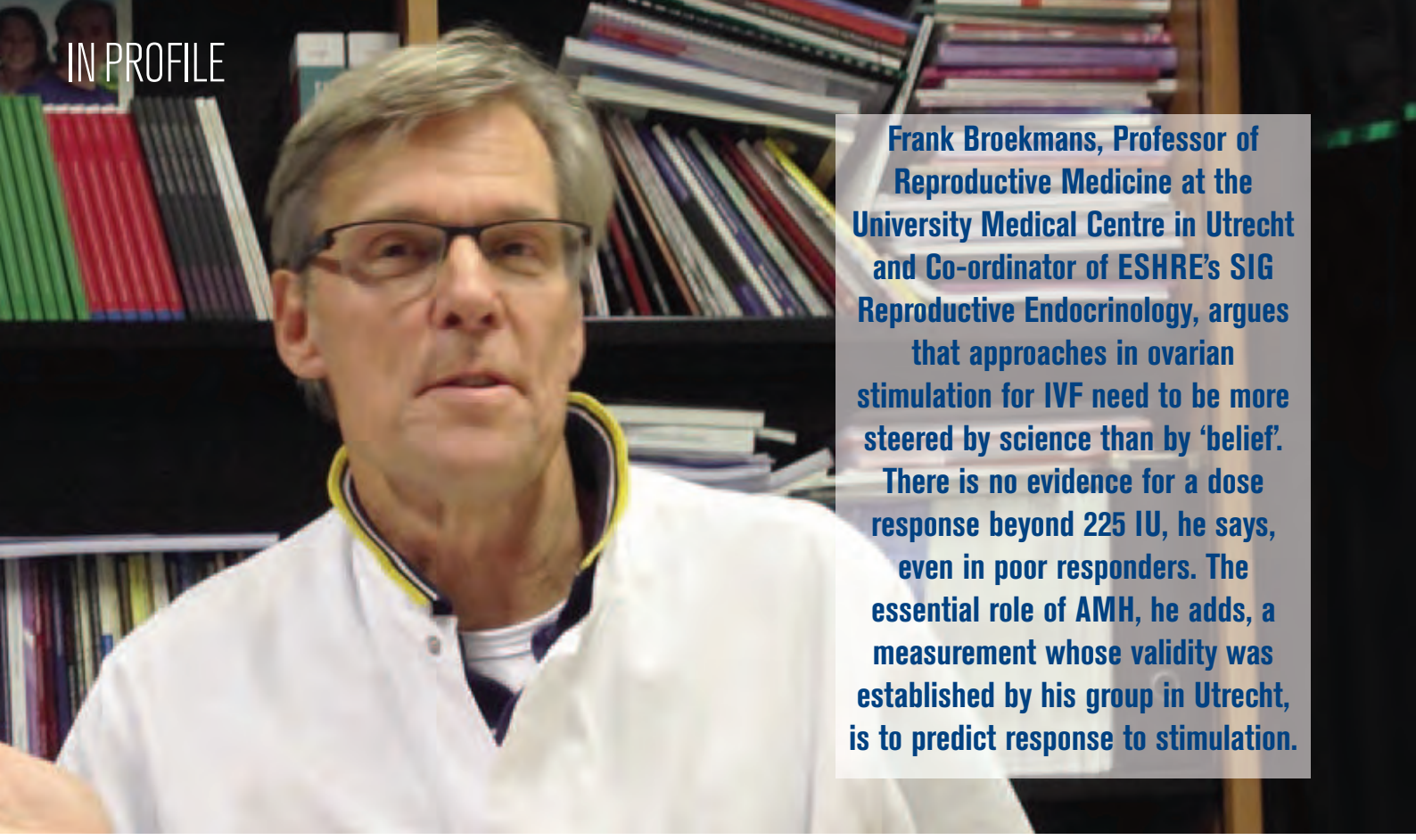
It was during Sunde's chairmanship of ESHRE from 2003 to 2005 that the Society found itself in a far more political environment than ever before. Under his leadership the Society formally opposed the restrictive legislation proposed in Italy (enacted in 2004), and formally supported embryo and stem cell research (which appeared under threat from EU funding and a 'rumoured' tissue and cell directive). It was also under Sunde's chairmanship that ESHRE finally bought its own Central Office in the suburbs of Brussels. It was, said Sunde, as if ESHRE were now acting more as a business, without actually being a business.


Arne var først ute


- Kjempeinnsats av teamet

Sunde's group in Trondheim was the first in Norway to achieve a live IVF birth, a baby girl born in July 1984.

Arne Sunde, seated left, became ESHRE's tenth Chairman in 2003. He is here seen with his nine predecessors, from left to right standing, PierGiorgio Crosignani, Basil Tarlatzis, José Egozcue, Lynn Fraser, Klaus Diedrich, Jean Cohen, Robert Edwards, André Van Steirteghem and, seated, Hans Evers.



Frank Broekmans, Professor of Reproductive Medicine at the University Medical Centre in Utrecht and Co-ordinator of ESHRE's SIG Reproductive Endocrinology, argues that approaches in ovarian stimulation for IVF need to be more steered by science than by 'belief'. There is no evidence for a dose response beyond 225 IU, he says, even in poor responders. The essential role of AMH, he adds, a measurement whose validity was established by his group in Utrecht, is to predict response to stimulation.

The science of stimulation

'You cannot change the fate of poor responders. You can predict, but you cannot change the outcome.'

FoR: You're running one of the world's most active research groups in reproductive medicine here in Utrecht.
FB: Well, we certainly have a powerful group - although our research in reproductive ageing and PCOS is really a collaboration with Rotterdam. We also do a lot of research on cost efficiency - and that's a real Dutch enterprise, which we do with many other hospitals nationwide.

So how many papers do you produce a year?
Up to 30 or 40 in total, many of them published in high ranking journals.

And how many research projects are going on at any one time?
In this hospital we're always involved in three to five national trials in reproductive medicine, and one of them will be directed by us. On top of that there are five or six projects which we run alone, with a PhD student allocated to each one.

It's clearly a huge responsibility. Is there any obvious pattern to your working day?
The only pattern is that Monday, Tuesday and Wednesday I collect a lot of work, coach my PhDs and do my clinics. Then I resolve this accumulation of work with a home working day on Thursday and on Friday there's either the operating theatre or a symposium or my activities as Chairman of the Dutch Society of ObGyn.

You're also Co-ordinator of ESHRE's SIG Reproductive Endocrinology. It's been a big year for them with publication of the first major guidelines on premature ovarian insufficiency. What are their main recommendations?
First, that the diagnosis of POI is important and that its causes need long-term management - especially in terms of other health threats to these young women. It's not a diagnosis and goodbye condition, but diagnosis and take care.

And hormone therapy?
Yes, the guidelines advise that this is the best choice - for its general health benefits - although the hard evidence is not always there on the balance of side effects.

And in practical terms how is a diagnosis of POI confirmed?
Absence of cycles, elevated FSH and low estradiol. AMH can provide further confirmation if there's any doubt.

Which brings us nicely on to AMH and work which is very closely associated with your group here in Utrecht. So where do you see AMH right now - has the fundamental work been done?
AMH is still a concept of promise. It's a very high promise, but we still need to consider a few things. We are still waiting for a

universally acceptable assay for speedy reliable results. We still need an international standard for AMH measurement where we have cut-offs for different clinical conditions. And then we have to be clear what those measurements mean - and here we're mainly talking about response prediction in IVF and individualised treatment.

So only response to stimulation? The prediction is not taking you as far as pregnancy or live birth?
No, it's about predicting response in IVF and the individualisation of management. There are now two big trials which will report later in 2016 - the OPTIMIST trial on the cost effectiveness of individualised FSH dosages and the ESTHER trial, and both will probably show the same - that you cannot change the fate of poor responders. You can predict, but you cannot change the outcome. High responders are different - you can predict and you *can* alter their fate in terms of efficacy and safety.

OK, so risk prevention justifies prediction in high responders, but what's the benefit in poor responders? Why do we want to know?
Many centres today, in predicted or observed poor responders, still use 300, 450, 600 units day after day and it doesn't work. You can easily use 150 units in these cases to get the same results. But don't spend all that money on a poor responder. These trials will demonstrate once and for all that using huge dosages in these patients just doesn't work.

But don't we know that already?
Yes, but it seems we don't really believe it.

So AMH as a test will give us the best idea of how a patient will respond to stimulation, but nothing more?
Well, the question is, what will it do for your whole programme, and the answer is that it will probably not create more pregnancies. But it *will* create lower cost and greater safety.

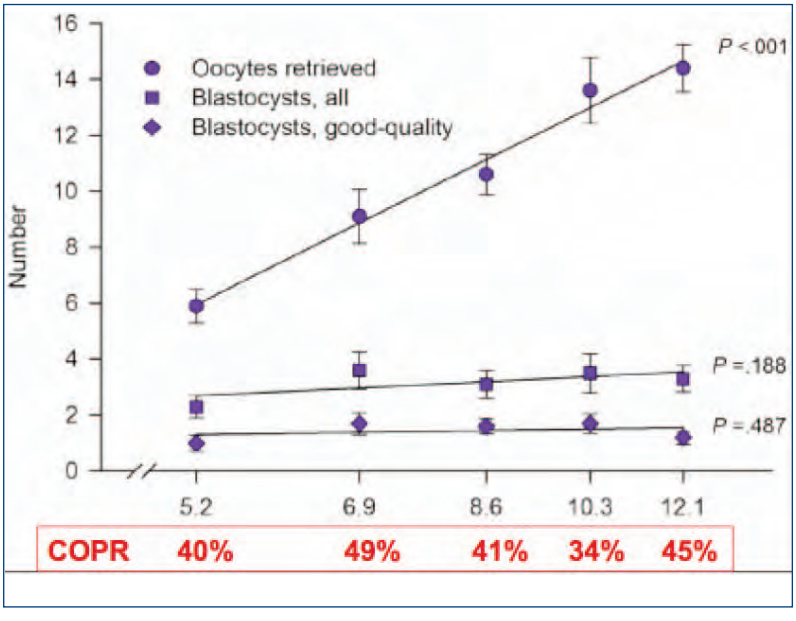
So the best predictor of pregnancy remains female age?
Yes, age - and a little bit of AMH! Within certain age categories AMH may identify cases with a very poor prognosis - but this is only in older women and the estimates are mostly based on a one-cycle observation.

And counting follicles?
Counting follicles could be another test. We have learnt that both tests, AMH and AFC, could be similar in their prediction, but only if you have rigorous quality control on your antral follicle count. Here in Utrecht we only do AFC with two specialists, otherwise we feel we are moving away from precision. So AMH is probably the best way to go, because we can leave quality control to the lab.

Going back to this question of poor responders, there's some discussion about the ESHRE criteria, and whether poor, normal and high are too simplistic.
One of the interesting features of those Bologna criteria is that they put in high age as predictive of poor response. But what we missed here is that a 'poor responder' who is young is probably not a 'poor' responder. She's just somebody with not many eggs but still young enough to get a pregnancy. I've recently reviewed a huge dataset from China, and I wrote back saying this is your chance to show that a poor responder below the age of, say, 36 is not actually a poor responder. Here's a chance to make the Bologna criteria more explicit. I think we're looking at a group here of the same age - 30 to 36 - with a different number of eggs but only a very marginal difference in pregnancy prospects.

You're saying that these so-called poor responders - or even the genuine poor responders - will not be helped by higher doses of FSH. But isn't there anyway a general move towards milder stimulation in IVF; isn't this the explanation?
My view on the outcome of stimulation is that it doesn't depend on dosage but on the number of follicles capable of responding. So there's always a group of follicles which are capable of responding - and which may be different in number from patient to patient. There is a dose response curve, but it only goes from about 100 to 200 units, and above that dose will make no difference. So response is not mathematics, it's not volume - what you get is simply what the ovary has in stock. It depends a little bit on dosage, but mainly on the ovaries of the patient. So our message is, get eggs, but whether it's a little more or less doesn't really make any difference. And why do we say that? Because of the study of Juan Carles Arce in 2014, who demonstrated in a dose response study that you get increasing follicle numbers and oocytes between 100 and 200 units, but you don't see any effect on the number of good quality blastocysts or on the number of ongoing pregnancies, even when measured cumulatively with fresh and frozen together. You can argue that those with many eggs get more frozen embryos, so have better cumulative pregnancy rates, but it's not true. Of course, the Arce study is a pharma study, performed in a more optimal patient group, but it helps us rethink our beliefs.

That seems counterintuitive to me. How do you explain the higher cumulative rates of pregnancy? Is it not true that the more eggs you have, the better your chances?
The Arce study clearly demonstrates that this may not be true. In fact, this goes back to a concept first proposed by Esther Baart and Bart Fauser, who said that, if you have three or four eggs instead of ten, you will still get the good eggs. You'll get a lot of rubble from those ten eggs, and that will keep you busy - you have to fertilise them, freeze them, replace them. It's time consuming but at the end of the day fresh plus frozen doesn't give better results in terms of babies. This is a real change in our views on ovarian stimulation.



Fundamental to Broekmans' argument is the study of Arce et al (Fertil Steril 2014; 102:1633-40.e5), which showed that an increasing FSH dose yielded more oocytes but the same number of good quality blastocysts - and the same cumulative ongoing pregnancy rates.

You believe that, but won't you need more data to make everyone else believe it? How are you going to convince the world?
Well, I'm lecturing on Friday, and probably the week after that. And there will be results from the OPTIMIST and ESTHER trials which could further support this view.

So you'll keep talking?
Yes, keep talking and discussing. In fact we're also doing some studies on the effect of FSH bioavailability on ovarian response . . . how levels of FSH in a poor responder or normal responder are the same. So it's not true that a poor responder is a poor responder because she didn't get enough FSH in her system. What you also see is that the FSH measurements themselves are highly variable. And what does this mean? A difference in bioabsorption of the drug? The assay not picking up the FSH properly? But in terms of dosage and response there is no relation between what you get in serum and what you get in the lab.

This sounds like a crusade for you, something you're evangelical about?
Well, I'm trying to steer a proper discussion. As clinicians with a scientific responsibility we have to rely on a strong evidence base. Our work is too much driven by belief. The results of Arce et al are remarkable. They are the kind of studies which we as specialists should be doing. But we lack the spirit and the resources to do them. Even the studies which have been done have not been embraced in the field. That study found a dose response relationship, but after 225 units it had gone. We have accepted that in the Netherlands, and are committed to using no dose higher than 225 IU.

So if dose has no effect on the number of good quality blastocysts, what does? Age, chromosomes?
Well, here we enter a very enigmatic area. If you have ten eggs how many of these eggs are chromosomally competent? We can guess the answer in different age groups, but who has the evidence? We don't know how large the variation in euploidy rates is in women of the same age group. So if you have ten eggs at age 35, how large is the variation in the number of normal embryos? It could be one normal blastocyst to five normal blastocysts, or maybe ten in rare cases.

So are you a believer in screening embryos?
I've been following this discussion for many years. And I personally conclude that we have failed to deliver the proper evidence that routine comprehensive chromosome screening of either cleavage or blastocyst stage embryos will create more pregnancies than conventional selection. We've failed to prove that. Here in the Netherlands we're not in commercial IVF, but elsewhere there are incentives which force you to offer new developments. Nobody in the Netherlands does aneuploidy screening. All we are doing is a large trial of time-lapse, another tool which could replace invasive techniques - but so far, where is the evidence? It's not there, and we really need it. We are trying to contribute. We have government funding for a large trial on these time-lapse systems, and we hope to add to the literature to see if it really makes a difference.

Do you think it will?
I personally have high hopes. Time-lapse can improve lab conditions and we can observe the embryos without disturbing them. That's one possible gain. It's always been a frustration in the Netherlands that we don't have the resources to improve our labs.

So it does make a difference here that you do your IVF in a public health system?
We've shown that we can do the same with our lab quality as other clinics do commercially. Our cumulative live birth rate is 32-36% per started cycle, which I think is much more comparable with outside the Netherlands than ten years ago. And that's mainly because we're much more rigorous in all lab procedures.

But you've also had to show that you can do IVF efficiently, to prove it to the Ministry.
Yes, we had to put a lot of effort into maintaining three reimbursed cycles by cutting back our budgets - and that was achieved by cutting the costs of FSH and lowering the rate of twin pregnancies. Our current twin rate nationwide is 4% in ART pregnancies, which represents a huge saving.

And your plans for ESHRE? A new guideline on ovarian stimulation?
I think this is a real possibility. The new trials are likely to show that our views on stimulation will change, and we need guidelines to reflect these views. There are several groups already busy in this area, including WHO, but I believe ESHRE needs to take this up. There is so much that is new, so many myths that can now be broken down without jeopardising a couple's chances. But we need to move away from the view that we're harming our patients if we don't get 20 eggs. If you get one egg, you don't beat nature, but if you get three, four, five eggs, that might already be optimal.

PROUST QUESTIONNAIRE*

- **Your greatest personal strength?**
Connecting with others

- **What trait do you dislike in others?**
Stubbornness and an inability to accept new ideas

- **What's your greatest extravagance?**
A sailing boat used mainly for day trips

- **Who do you most admire?**
Barack Obama

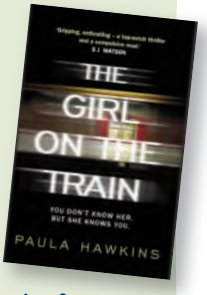
- **What quality do you most admire in others?**
A focus on ambition

- **Which words do you most overuse?**
Winners have a plan, losers have excuses (ask my kids)

- **What do you most value in friends?**
Openness and support

- **If not the Netherlands, where would you most like to live?**
Italy

- **What book are you reading now?**
The Girl on the Train by Paula Hawkins



- **Where did you spend your latest vacation?**
Peru

- **What is your favorite pastime?**
Sailing and biking

- **And your favourite writer?**
A F Th van der Heijen

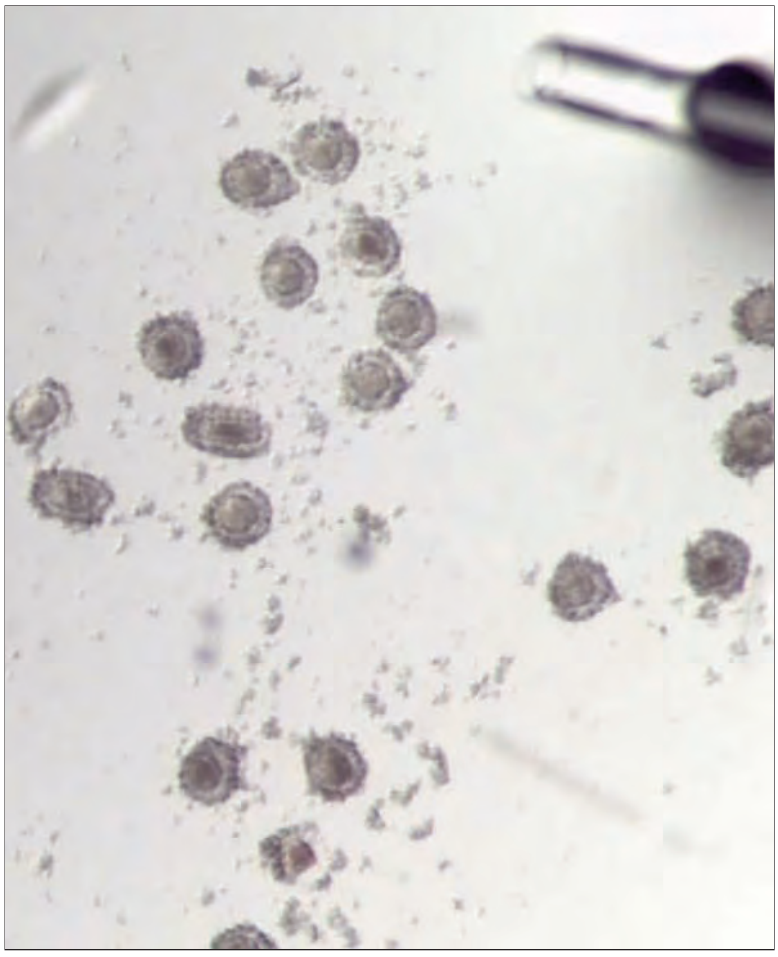
- **The last film you saw?**
La Famille Bélier

- **Your favourite composer?**
Rachmaninov

- **Beer or champagne?**
Champagne

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

The maturity of in vitro maturation



Immature oocytes from antral follicles after minimal or no gonadotrophin administration

A shift at last from hype to hope

Following Europe's first IVM live birth in Brussels, programme leader Michel De Vos argues that it's now time 'to embrace IVM' as a useful approach in modern ART.

Studies now indicate that individualised ovarian stimulation programmes in modern ART practice can produce cohorts of mature oocytes able to yield cumulative live birth rates above 40% after fertilisation in vitro. However, the picture is not all sunshine and rainbows. There is a substantial proportion of infertile patients who decline conventional 'hormone driven' IVF and seek alternative approaches. They may consider IVF as too cumbersome - the need for frequent monitoring of ovarian stimulation or because of hormonal side effects. These side effects range from abdominal discomfort and emotional disturbance to full-blown ovarian hyperstimulation syndrome (OHSS).

Some patients have a narrow window of optimal ovarian response to gonadotrophins, either because of a non-linear dose-response, as observed in patients with polycystic ovary syndrome (PCOS), or because of premature luteinisation leading to endometrial advancement. Others may find it hard to combine fertility treatment with everyday life and struggle to commute between home, work and the fertility centre. Some may live in rural areas and have to travel long distances, or may face hours of dense traffic in metropolitan areas.

Any or all of the above may be reasons for IVF's lack of appeal, or may lead to treatment termination before a successful pregnancy is achieved.[1] Some patients will prefer an alternative simplified, low-burden ART. However, whether they would accept this at a cost, or with a lower chance of pregnancy, is currently unknown.

Current status of IVM

Oocyte in vitro maturation (IVM) has been proposed as one alternative to conventional IVF, and, because of its reduced hormonal burden for the patient, has been described as a 'patient-friendly' treatment. But how did IVM evolve and what is its current status in human reproduction?

IVM is a fertility treatment which obviates the need for ovarian stimulation with gonadotrophins to produce mature oocytes ready for fertilisation. The

concept that immature human oocytes can resume meiosis spontaneously and reach metaphase II within 36 hours was acknowledged 50 years ago by Robert Edwards, who remained an advocate of IVM throughout his entire career.[2] Indeed, the historical observation of Edwards and others that approximately 50% of human oocytes, when removed from their follicular environment, reach metaphase II spontaneously is still valid and constitutes the basis of oocyte maturation in vitro as we apply it today.

So it is disappointing to realise that maturation rates of oocytes incubated in currently available IVM systems registered for clinical use have not really evolved since those early experiments of Edwards back in the sixties, and low maturation rates are still a major obstacle to the efficiency of IVM.

In contrast, the technology of hormone-driven ART has seen tremendous advances in the past decades, fuelled by the development of pharmaceutical compounds to produce high quality oocytes following ovarian stimulation. The development of stimulation protocols has led to major improvements in conventional hormone-driven ART results since the beginning of the nineties. Similarly, GnRH antagonist protocols with GnRH agonist trigger and efficient vitrification systems have seen an overall reduction in the incidence of OHSS in high responders. Thus, a lack of incentive to develop alternative methods to ART has been one major impediment to the progress of IVM.

However, it would be unfair to say that IVM is an orphan technology and neglected by the scientific community. For IVM is widely applied in animal breeding, where maturation rates after IVM appear to be much higher than in human IVM; indeed, yearly cattle embryo production using IVM has been estimated to exceed 500,000. Furthermore, IVM has attracted enormous interest from reproductive biologists keen to unravel the complexity of human oocyte maturation and translate the physiological process to the in-vitro setting. Finally, the improved success rates of IVM treatment in patients with PCO/PCOS reported by some groups and the succesful use of IVM in fertility preservation programmes have fuelled renewed interest in this technology.[3,4]

How it works

Strictly speaking, IVM involves the aspiration of immature oocytes from antral follicles after minimal or no exogenous gonadotrophin administration. Oocyte collection is typically performed from follicles of up to 12 mm and selection of a single dominant follicle is avoided to prevent any negative impact on development of subordinate follicles.

Oocyte maturation rates in vitro are generally lower than maturation rates of oocytes retrieved in a conventional IVF programme after administration of an ovulation trigger, suggesting that a considerable proportion of immature oocytes from small antral follicles are still meiotically incompetent and would have required more time within their follicular environment to accomplish physiological nuclear and cytoplasmic maturation.

Higher oocyte maturation rates can be obtained when a bolus of hCG is administered, typically 36-38 hours before oocyte retrieval. In these cases, meiotic resumption is initiated in vivo and a proportion of oocytes are found to have reached metaphase II at the time of oocyte retrieval - they are oocytes which have thus completed meiosis in vivo and can readily be inseminated. As such, the hCG triggered IVM system may represent a semantical contradiction, but it is applied more often than the 'pure' non-hCG triggered system, where all oocytes are at GV stage at the time of egg collection. Nevertheless, there is ongoing debate as to the most efficient clinical and laboratory protocol for patients undergoing IVM.

Because of the lower maturation rate and lower developmental potential of in vitro matured oocytes retrieved from antral follicles - at least using registered IVM media - IVM is currently not a suitable option for every patient requiring IVF. Thus, the cornerstone of an efficient IVM programme is proper patient selection - and it seems that women with polycystic

Patient selection criteria for IVM

- **IVM as an alternative, minimal approach ART for infertile patients with polycystic ovaries:**
  - **AMH correlates with pregnancy rate through its association with the number of aspirated immature oocytes**
- **Fertility preservation:**
  - **IVM of transvaginally aspirated immature oocytes**
  - **IVM following oophorectomy: combination of techniques may enhance the potential of cryopreserved tissue**
- **Patients whose ovaries have antral follicles unresponsive to FSH**

Robert Edwards remained an advocate of IVM throughout his career. His observation that approximately 50% of human oocytes, when removed from their follicular environment, reach metaphase II spontaneously is still valid and the basis of oocyte maturation today.

ovaries (PCO-like ovaries and women with PCOS) are the best candidates for IVM. They yield sufficiently high numbers of immature oocytes to compensate for the inherently lower efficiency of IVM compared to standard IVF.[5] Serum concentration of AMH, a biomarker which correlates well with the severity of the PCOS phenotype, is a strong predictor of the number of immature oocytes retrieved by follicle aspiration, and, by proxy of oocyte number, AMH correlates with the probability of pregnancy after IVM.[5]

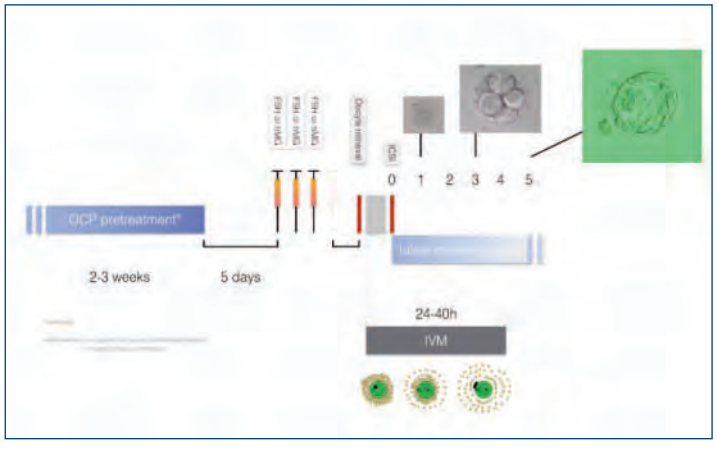
There may be a learning curve for egg collections from small antral follicles, and closed-circuit needle flushing systems have been developed to avoid blood clots in the aspirated follicular fluid, although the optimal technique of immature oocyte collection from antral follicles requires further study.[6]

What's driving IVM today?

However, despite its lower efficiency than standard IVF, a number of fertility clinics have continued to use IVM for several years, for a variety of reasons - to avoid OHSS, to circumvent local regulations on the number of oocytes that could be fertilised in vitro, and to reduce costs related to gonadotrophins. And even though OHSS has almost become extinct after the introduction of GnRH agonist triggering and elective embryo cryopreservation, interest in IVM as a minimal-burden alternative has not disappeared. A number of key developments can be identified as major drivers of this interest:

1. Favourable clinical outcomes

Athough the patient series are small, live birth rates of 40% and higher in patients with polycystic ovaries have been reported from Western Australia.[7] Key elements contributing to the success of this non-hCG triggered IVM protocol include FSH priming and blastocyst culture. However, in comparison with conventional IVF, IVM has not been able to generate an equal amount of blastocysts, although the implantation rate per embryo appears similar in both approaches. One could therefore state that IVM is a less wasteful system in terms of embryo production



Current clinical protocol of IVM in Brussels.

MICHEL DE VOS: 'A LACK OF INCENTIVE TO DEVELOP ALTERNATIVE METHODS TO ART HAS BEEN ONE MAJOR IMPEDIMENT TO THE PROGRESS OF IVM.

than conventional ART.

We launched an IVM programmme at our centre in Brussels in 2010. It was embedded within a research project aimed at improving IVM outcomes through modification of the clinical approach and culture system. Our initial results in patients with polycystic ovaries were disappointing, but, contrary to what happened in a number of pioneering IVM centres, we did not abandon the programme. First, we learnt that transfer of warmed IVM embryos after vitrification three days after ICSI performed better than fresh embryo transfer. Second, we reduced the IVM incubation period from 40 to 30 hours and applied extended embryo culture to the blastocyst stage in a subset of patients. By doing so, consistently good clinical outcomes were obtained, comparable with those published by the Australian group. Nevertheless, sufficiently powered clinical trials investigating the true potential of current IVM systems compared with conventional IVF are still lacking.

2. Reassuring safety scores of IVM systems

At both a cytogenetic and epigenetic level, in vitro matured oocytes and embryos generated after IVM do not carry more chromosomal or methylation defects.[8] Data from these studies mitigate concerns with efficiency and safety of IVM technology (as proposed by the ASRM and SART), although follow-up of children born after IVM remains mandatory.[9] Previous studies had shown abnormal methylation in oocytes after IVM, but the immature oocytes used in these studies were derived from conventional IVF cycles and had failed to complete meiosis after an ovulation trigger. There is now compelling evidence that attempts to 'rescue' these immature oocytes are not recommended, as they have a high prevalence of DNA damage, and embryonic development is grossly compromised.[10]

3. In fertility preservation for cancer patients

Immature oocytes can be obtained from antral follicles in the follicular and luteal phase of the cycle when there is not enough time to stimulate the ovaries and harvest mature oocytes. Oocytes can even be retrieved from extracorporeal ovarian tissue, matured in vitro,

Europe's first live birth in Brussels

- **Nulliparous 26-year-old patient with serum AMH of 2.3µg/L before gonadal trauma**
- **Diagnosed with pelvic arteriovenous malformation requiring intravascular coiling with predicted impact on ovarian perfusion**
- **Cryopreservation of the cortex of the ipsilateral ovary + identification of 13 cumulus-oocyte complexes during ovarian cortex processing**
  - **IVM of 13 GV oocytes, resulting in six MII oocytes**
  - **insemination of mature oocytes with partner sperm using ICSI, resulting in three 2PN oocytes**
  - **vitrification of three embryos on day 3 after ICSI**
- **Ovarian insufficiency after interventional radiological treatment - serum AMH 0.04µg/L**
- **Request for embryo transfer after warming:**
  - **first FET: one embryo warmed, 6/8 blastomeres survived, no pregnancy ensued**
  - **second FET: one embryo warmed, 9/10 blastomeres survived, pregnant**
  - **delivery at term of a healthy child in July 2015**


IVM-BABY'S

Europese primeur in UZ Brussel: eerste baby geboren uit 'onrijpe eicel'

Zijn IVM-baby's de toekomst?

13-08-15, 06.00u - ELINE DELRUE

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fertilised - and result in live births.[11] This combined application of fertility preservation methods may increase hope of delayed childbearing to young cancer patients who undergo ovarian cortex cryopreservation before gonadotoxic treatment.

4. IVM of oocytes can be a last resort in infertile patients who have consistently high circulating levels of FSH and a normal antral follicle count with antral follicles unresponsive to FSH.

Although IVM research has not yet revolutionised IVM systems in the clinical setting, improved IVM systems are under way. Lessons have been learnt from experiments in animal models, where modulation of the maturation process in vitro through cAMP-mediated systems or the addition of oocyte growth factors, such as Growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15), can result in substantially higher numbers of blastocysts. However, progress is slow, partly because of licensing and regulatory hurdles required in the development of culture media.

Nevertheless, it's my belief that the time has now come to embrace IVM as a useful additional tool in modern ART practice. IVM requires no major modifications in the ART laboratory; however, because of the complexity of physiological oocyte maturation, our current IVM systems, which are not physiological, do require further refinement. The promisingly good clinical outcomes obtained in some pioneering IVM centres, after proper patient selection, illustrate how IVM has the potential to grow to full maturity in the future.

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SIG's precongress course proves popular at ASRM

US audience largely committed to oocyte cryopreservation for non-medical reasons

While we are finalising the first report from our European oocyte cryopreservation survey - to which we are now adding ovarian tissue cryopreservation - we successfully organised the ESHRE postgraduate course in October at the ASRM annual meeting in Baltimore. The topical subject was the pros and cons of oocyte cryopreservation versus embryo freezing.

We had 150 in attendance, and our speakers included embryologists Laura Rienzi and Cristina Magli on science and practice in the lab, followed by clinical outcomes and sociocultural and ethico-legal considerations from Professor Siladitya Bhattacharya and myself.

This was a very well attended course, with many questions asked. With vitrification now established as the favoured cryopreservation method in many parts of the world, the practical message from Laura was 'keep it simple and keep it fast' - and do not disturb the cells, whether oocytes or embryos, by adding components or extra steps to protocol. She concluded that vitrification best maintains the oocyte's competence to develop in vitro and is most effective for improving clinical results, and that evidence is accumulating that the outcome and safety of oocyte cryopreservation are similar to embryo freezing .

Cristina discussed the value of genetic diagnosis and screening for both the oocyte and embryo. She reported that the chromosome analysis of oocytes has revealed that more net errors in aneuploid zygotes occur in meiosis II and that premature chromatid separation is the prevalent form of errors at meiosis I. The chromosome analysis of embryos has revealed high levels of mosaicism at the cleavage stage, which, she said, can cause misdiagnosis, and low levels of mosaicism at the blastocyst stage. However, in regularly developing embryos, biopsy at previous stages is highly predictive of the blastocyst's chromosome condition. Cristina also reviewed her own group's work on the analysis of blastocyst fluid as a marker of viability.

Siladitya Bhattacharya outlined the value of meta-analysis, and how the removal of one study may change the final picture. Going back to the original data and not taking any meta-analyses for granted was a valuable tip. On the question of outcome, he concluded from the data that frozen-thawed embryo transfer lowers the risk of preterm babies, increases maternal safety but could be associated with large-for-gestational age offspring - whilst the pregnancy rate in poor prognosis women was unclear.

The debate about freezing oocytes for non-medical indications was very energetic, as was the discussion on what medical reasons other than the classical cancer indications might be considered for oocyte cryopreservation, such as Turner's mosaics or endometriosis. Nevertheless, when asked if they would advise their daughter to cryopreserve oocytes, or even consider oocyte cryopreservation themselves, most women (and men) in the audience were positive about the technique. Despite the enthusiasm, the discussion emphasised that we still have an ethical imperative to gather data on the efficiency of oocyte cryopreservation in non-medical indications, and to follow up the offspring born to ensure that the technique does not affect the 'welfare' of the future child. Such discussion underlined the importance of our own ESHRE study, a prospective full data gathering with eventual use and success rates presented according to indication and patient age.

Speakers at the ESHRE precongress course at this year's ASRM annual meeting; from left, Siladitya Bhattacharya, Françoise Shenfield, Laura Rienzi and Cristina Magli.

Plans for Helsinki

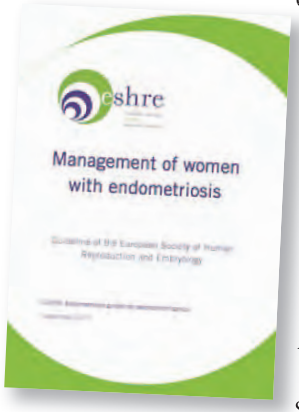
Our precongress course for this year's Annual Meeting, organised with the SIGs Early Pregnancy and Ethics & Law, is titled **What happens in utero lasts a lifetime: A multi-disciplinary approach to improving preconception and early pregnancy care**. Full details are on the ESHRE website and, with such multidisciplined interest, early registration is recommended.

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

From guideline to implementation in clinical practice

The EndoKey project

Our ESHRE guideline on the management of women with endometriosis aimed to improve endometriosis care in European hospitals by providing recommendations based on evidence and good clinical practice (there were 83 recommendations in total).[1]



Unfortunately, however, guideline development is not automatically followed by healthcare improvement in practice. We have thus felt a need to gain insight into the application of the new guideline in the management of women with endometriosis in everyday practice (ie, actual clinical care) and the potential barriers to guideline adherence. By measuring and monitoring actual care, 'quality indictors' can help to better implement the guideline in European hospitals.

The EndoKey group (led by Schleedoorn, Nelen, Dunselman and Vermeulen) have taken the first steps in the development of quality indicators by selecting a compact set of recommendations on which to focus, ie, 'key recommendations'. Using a basic RAND Delphi method, the group is now systematically selecting key recommendations from the ESHRE guideline with the support of an international expert panel of both patients and professionals.

Collaboration with the the European Society for Gynaecological Endoscopy

The Chair of the Endometriosis Guideline Development Group and the President of the European Society for Gynaecological Endoscopy (ESGE) have begun a project to develop a joint guideline on the surgical management of endometriosis. The goals of the project were discussed at two meetings last year, with representatives of ESHRE (Saridogan, Grimbizis, Vermeulen, Dunselman) and ESGE (De Wilde, Keckstein, Tanos, Ulrich). It was agreed that the aim should not be to rewrite existing guidelines (the ESHRE and German endometriosis guidelines) but to provide guidance on how endometriosis surgery should be performed. During the course of the project surgical techniques will be discussed in detail, making use of a video library of the most common surgical procedures based on recommendations of the ESHRE and German endometriosis guidelines. In the final version the video clips will be accompanied by written and spoken commentary. The first clip will cover the surgical management of ovarian endometriomas. The next meeting of the taskforce will be in Leuven on 9 April.

European Commission funds research on endometriosis

A multidisciplinary team of researchers from Germany, Scotland, Sweden, Argentina and Chile has received a EU Horizon 2020 grant for endometriosis research. The MOMENDO project will support an exchange programme to explore current concepts of disease aetiology, including work on adult stem cells, microRNAs, iron-induced inflammatory responses, and novel endocrine approaches. The aim is a deeper understanding of the molecular mechanisms behind the inflammatory pain associated with endometriosis and the persistent growth of lesions. By combining non-academic and clinical partners, the consortium plans to translate these findings into novel therapeutic approaches. For more information please contact martingotte@uni-muenster.de.

James Lind Alliance Endometriosis Priority Setting Partnership

A group of UK endometriosis researchers have established a James Lind Alliance (JLA) Priority Setting Partnership to conduct a national survey in Great Britain and Ireland to identify endometriosis research questions that are important to patients, their carers and professionals with clinical experience of endometriosis. The JLA is a non-profit organisation funded by the National Institute of Health Research (NIHR) in the UK. It provides a 'tried-and-tested', fair and rigorous process to help patients and clinicians work together to agree on the most important research questions in a particular area (in this case, endometriosis), in order to influence the prioritisation of future research in that area. The project has been formally endorsed by the World Endometriosis Research Foundation. For more information please contact andrew.horne@ed.ac.uk.

Look forward to 2016: mark your agenda!

The new year will start with a SIGEE Campus meeting in Istanbul in February (26-28 inclusive), a joint venture with the Turkish Society of Endometriosis and Adenomyosis. The meeting will debate and discuss controversies in the diagnosis and management of endometriosis and adenomyosis. Our activities will continue with our yearly precongress course in Helsinki (3 July) on the medical treatment options for endometriosis, ranging from basic, through translational to late preclinical and clinical subjects.

Andrew Horne
Co-ordinator SIG Endometriosis and Endometrium

1. See https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline/Guideline-on-the-management-of-women-with-endometriosis.aspx.

The safety of new technological developments

Founded in 2002, the SIG SQART has a long history of active participation in ESHRE and, with a new steering committee in place, has recently reaffirmed its continuing mission. SQART is involved in many aspects of ART and still contributes to SET policies and preventive measures for OHSS in an environment of fast developing technologies. On this fast lane to the future, SQART is present at the intersection of scientific design and clinical implementation - as is evident in the subjects of our upcoming events.

Back to the future of ART

Alongside the SIGs Ethics & Law and Stem Cells, we are organising two upcoming events that return to the future of ART. These will cover standard treatments such as ultrasound but will also move forward to innovative experimental treatments. We thus warmly invite you to our precongress course in Helsinki, which is organised with the SIG Stem Cells on 3 July and titled **ART in 2020: the next frontier**. All the topics featured - stem cell therapies, the manipulation of gametes, uterine transplantation - are all experimental but still attract much interest. And it's fair to say that, in our progress to overcome mitochondrial and other diseases, the use of nuclear transfer or 'next generation' gametes is no longer fiction.

Although such advances are scientific, they must still be considered from a safety and ethical point of view: they all SEEM okay, but are they really okay? So join us in Amsterdam for an ESHRE Campus course at the cutting edge of the future of ART: **Novel gamete manipulation technologies in ART: SEEM (safety, ethical, efficient, moral) okay?** on 22-23 September.

The SIG SQART is also in the process of organising a Campus course on oncofertility in women. Some central questions - when to preserve gametes or gonadal tissue and in which patients - are still a matter of debate. More details will be soon available on the ESHRE website.

To help us plan future SQART events, we'd be grateful if you could complete the questionnaire accessible on the ESHRE website (https://www.eshre.eu/sqart/questionnaire) and tell us your ideas, so that future SQART events will be best tailored to suit your needs. We hope to hear from you soon.

Arianna D'Angelo
Co-ordinator SIG SQART
Kelly Tilleman, Deputy

Answer our questionnaire via the QR above or SIG SQART page on the ESHRE website, and help us plan future events.

Guidelines for quality and safety

ESHRE began its investment in guidelines in 2009 with a manual for guideline development and recruitment of a research specialist. Five years later, the ESHRE guidelines programme is firmly established and has resulted in three published clinical guidelines - on the management of women with endometriosis and premature ovarian insufficiency, and on routine psychosocial care in infertility and assisted reproduction. An update of the revised guidelines for good practice in IVF laboratories has been completed.

More exciting projects are planned for 2016. First, a multidisciplinary guideline group is working on the development of a guideline on recurrent miscarriage (working title), which will include recommendations on the diagnosis of underlying conditions and on the various treatment options for couples after multiple miscarriages.

ESHRE will also focus more on the dissemination and implementation of its guidelines, whose final aim is acceptance in clinical practice and the improvement of care of patients with infertility. So this year more emphasis will be placed on the development of tools to help clinicians implement the ESHRE guidelines in their local practice, on the development of patient information, and on the evaluation of impact.

Finally this year a topic for the next ESHRE guideline must be selected. Do you have any idea of a subject in need of a European guideline? Do you have a strong opinion on a certain topic that should be addressed in an ESHRE guideline, a subject with high variability in care and/or high potential for improvement of care? Please contact nathalie@eshre.eu or the Co-ordinator of the appropriate SIG. Your idea may well be the start of a new exciting guideline project.

Nathalie Vermeulen
ESHRE Research Specialist

The SIG SQART steering committee at its business meeting in November. Left to right, Kelly Tilleman, Willianne Nelen, Ioana Rugescu, Zdravka Veleva, Arianna D'Angelo

Highlights of 2015 in reproductive genetics

The goal remains identifying gametes and embryos with development potential

Thirty-eight years after the first IVF baby, 'success' remains a major challenge in reproductive medicine, with two-thirds of IVF cycles still ending in failure. Some of the outstanding papers described below will likely be the basis of novel methodologies to select gametes and embryos with the best quality and developmental capacity. Their common theme is that they make use of combinations of new technologies in molecular, imaging and genetic analysis to study the human oocyte and embryo.

In the context of embryo selection for IVF, Capalbo et al investigated the microRNAs secreted into blastocyst culture media and identified some microRNAs differentially expressed in subsequently implanted versus non-implanted blastocysts, though further work is required to explore their use as biomarkers of implantation potential.[1]

Aneuploidy in early human development is still a hot topic in our field, particularly the search for predictive markers and a better understanding of the mechanisms behind chromosome abnormalities. One recent development in analysing the genetic content of embryos and predicting implantation potential is the use of blastocoel fluid as a source material. The prediction of aneuploidy was achieved by peptide detection and quantification in the blastocoel cavity of human preimplantation embryos.[2] This showed that it might be possible to identify aneuploid embryos based on the levels of GAPDH and the detection of histone H2A proteins. On the other hand, aCGH on amplified DNA from the blastocoel fluid indicated karyotypic discordance when compared to aCGH of the remaining ICM-TE sample. This study, although showing that the diagnostic accuracy of blastocoel fluid aCGH is unacceptable for clinical use, did suggest a mechanism that marginalises aneuploid nuclei into the blastocyst cavity.[3]

Another recent study supports the notion that embryo development is strongly influenced by maternal factors and may be determined even before major embryonic gene activation.[4] From this study it appears that the chromosomal status of an embryo may be predicted by a 12-gene transcriptomic signature. Furthermore, the study presents evidence for a correlation between the kinetics of early embryo development and gene expression that might be used to develop special algorithms for predicting development to the blastocyst stage or for time-lapse with chromosomal analysis to identify cell cycle and fragmentation parameters diagnostic of ploidy, in line with previously published work of others.

An alternative avenue has been explored by the group of Fragouli and Wells. In a recent study they identified an association between mitochondrial DNA, aneuploidy and the ability of an embryo to implant in the uterus.[5] The authors observed that the quantity of mtDNA in biopsied trophectoderm cells was significantly higher in blastocysts from older versus younger women, as well as in aneuploid versus euploid blastocysts, independent of age, while the mtDNA levels were lower in blastocysts capable of establishing a clinical pregnancy than in those failing to implant after transfer. The authors also established a mtDNA quantity threshold above which implantation failure was 100% and proposed that assessment of mtDNA could represent a novel biomarker of embryo viability, forming the basis of a simple and inexpensive clinical test with potential value for IVF treatment. Results from ensuing similar studies have also proved encouraging.[6]

The use of array technologies to detect and understand aneuploidy in embryos and gametes remains a major focus, and a study of aneuploidy by aCGH in pooled first and second PBs shows that meiotic separation errors in oocytes can effectively be detected in this way.[7] When employed in embryo selection this approach may increase live birth rate in a PGS versus control group of patients with repeated implantation failure or of advanced maternal age.

Overall, PGS with the use of comprehensive chromosome screening technology assists embryo selection, but results from several ongoing RCTs are still expected to clarify its use for different patient groups and embryo biopsy stages. In the meantime, several studies have focused on validating and applying next-generation sequencing (NGS) as a new platform, which has so far proved highly concordant with aCGH.[8] NGS may allow the simultaneous diagnosis of single gene disorders and aneuploidy and may have the potential to provide more detailed insight into other aspects of embryo viability.

From a mechanistic point of view, a striking new discovery was made studying chromosomal constitution and chromosome-specific recombination rate and distribution in single oocytes.[9] This not only supported data from trisomy screening showing that chromosome segregation in meiosis I is greatly affected by recombination, which subsequently affects segregation in meiosis II, but also that a majority exhibit equational separation of chromatids in meiosis I and reductional division at meiosis II, much different from all common mechanisms which prevail in meiosis of most eukaryotes. This study firmly establishes the

fact that meiotic errors significantly contribute to aneuploid conceptions, and enhances our understanding of the origin of aneuploidy and the chromosomal constitution of the oocyte and its corresponding polar bodies. The implications remain to be determined, but the knowledge is significant considering, for example, that transplantation of any of the products of female meiosis between oocytes has been proposed for treatment of mitochondrial disease. Complex aneuploidies of mitotic origin were also extensively investigated in another study, providing an additional explanation to the limitations of human fertility.[10]

The field of fertility genetics has also been yielding interesting results. For instance, McCoy et al recently published a genome-wide association study of aneuploidy risk in patients undergoing PGS.[11] They genotyped the embryos and compared them to the parental DNA using SNP microarrays, and identified the rs2305957 SNP as a polymorphism associated with high rates of embryonic mitotic errors. The polo-like kinase 4 (PLK4) gene, involved in cell cycle and cytoskeletal regulation, is tightly linked with this variant and was thus identified as a candidate gene involved in mitotic errors in preimplantation.

On the methodological front, several novel experimental approaches are revolutionising genetics research and are promising to shed light not only on the identification of novel genes, but also in the treatment of disease. One experimental approach to identify genes in female meiosis and fertility was reported by Pfender et al.[12] It involves the microinjection of small interfering RNAs into small follicle-enclosed mouse oocytes to block expression of distinct, still unknown meiotic genes during follicle growth and oocyte maturation. The assessment of the impact of this in vitro knockdown by quantitative live imaging of the oocytes helped identify a number of new genes implicated in meiosis and to provide new information on causes of chromosome segregation errors and risk factors of anaphase lagging in oogenesis.

Another of these exciting methods is RNA-guided genome editing for genetic research.[13] This method has also opened new perspectives to eliminate mutations, model human disease in primates, or prevent disease in transgenic mouse models. However, the safety, benefit and particularly the ethical and legal implications of germline editing still need to be assessed, as recently addressed by editorials in *Nature Medicine* and in meetings of concerned scientists.[14,15]

Certainly, for the time being the reproducibility and validity of all novel methods and studies must be more extensively tested, while the rapid developments in reproductive genetics promise new exciting findings in the near future - to improve assisted reproduction and understand the basics of gamete and embryo development and quality.

Georgia Kakorou, SIG Deputy, describes 'outstanding papers of the year'.

Future SIG activities

This year we are looking forward to two Campus workshops, **Oocyte maturation, from basics to clinic** to be held in March in Brussels, and **All about preconception, preimplantation and prenatal testing** in April in Maastricht, as already described in the previous issue of *Focus on Reproduction*. Finally, our precongress course in Helsinki will focus on **Genetics and epigenetics behind subfertility and reproductive system disease**. We hope to welcome you to this exciting course.

Georgia Kakourou
Deputy, SIG Reproductive Genetics

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POI guideline now approved and available

Looking back on 2015, we can feel very happy and a little proud about what has been achieved. First, an ESHRE guideline on the *Management of women with premature ovarian insufficiency* was published on the ESHRE website in December (https://www.eshre.eu/guideline/POI). This evidence-based guideline was written by the development group chaired by Lisa Webber and Melanie Davies (co-chair until December 2014). A summary paper for *Human Reproduction* and a patient version will be published in 2016. Also, a very well designed workshop on **Old and new in reproductive endocrinology** took place in Helsinki in April and our precongress course in Lisbon on **Recurrent implantation failure** was the best attended at last year's annual meeting!

STEERING COMMITTEE

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

Upcoming events

With two new crew members aboard, Peter Humaidan and George Lainas, our Steering Committee looks ahead to the year 2016 with high expectations. These will comprise a Campus workshop on 8-9 April in Istanbul on the **Multifaceted challenge of female reproductive ageing**, with focus on the physiology of the ageing process and the management of couples with age-related fertility decline.

In addition, a joint workshop with the SIG Reproductive Surgery has also been planned for Thessaloniki on 5-6 May on **Surgery in reproductive medicine: benefits and limits**. Topics will include PCOS, endometriosis, tubal disease and fibroids. Later the Annual Meeting in Helsinki in July (on mid-summer night) will feature a very attractive pre-congress course dedicated to **Managing the difficult IVF patient: facts and fiction**. This will offer participants an insight into working with the older IVF patient, the medically complicated, the fat and the thin, and the patient with a co-morbidity such as endometriosis and uterine cavity distortion.

This will also see the presentation of two large IVF trials on dosage and individualisation of ovarian stimulation. With the likelihood of new evidence, these trials may yet be the kick off for developing an ESHRE guideline on ovarian stimulation protocols for IVF/ICSI. It will be an extensive work package and the SIG RE is now considering a guideline group for OS-ART.

Frank Broekmans
Co-ordinator SIG Reproductive Endocrinology

ESHRE/FIGO meeting on ethics of human reproduction and health

A successful third joint meeting of the Ethics Committee of FIGO (International Federation of Gynecology and Obstetrics) and ESHRE's SIG Ethics & Law was held at last year's FIGO world conference in Vancouver in October. The meeting was jointly chaired by Veerle Provoost, Past Co-ordinator of the SIG Ethics & Law, and Bernard Dickens, chair of FIGO's Ethics Committee.

The plan was to have five presentations on topics of mutual interest: two from each society and a further one by Françoise Shenfield, who is active in both organisations. She was due to speak on the ethics of oocyte cryopreservation, the subject of an imminent report by the SIG Sociocultural aspects of infertility. However, due to illness she was unfortunately unable to join in.

The session therefore went ahead with four talks. For ESHRE, Wybo Dondorp, associate professor of Bioethics at Maastricht University, reviewed the ethical aspects of expanded universal carrier screening for recessive diseases, while Veerle Provoost discussed the findings and policy implications of qualitative research into couples' decisions on embryo disposition. For FIGO, presentations were given by Duru Shah, gynaecologist and past honorary professor of Obstetrics & Gynaecology in Mumbai on the ethical challenge of adolescent pregnancies and by Joanna Cain, professor of O&G at the University of Massachusetts, on the use and limits of conscientious objection in medical practice. The upside of the lower number of talks was more time for fruitful discussion with the audience and among the members of the panel.

STEERING COMMITTEE

Guido Pennings (BE), Co-ordinator
Guido De Wert (NL), Deputy
Lucy Frith (GB), Deputy
Veerle Provoost (BE)), Past Co-ordinator

Wybo Dondorp
Former Co-ordinator, SIG Ethics & Law

Almost 1000 guideline downloads since April

These are exciting and busy times for the SIG Psychology & Counselling. Our precongress course in Lisbon was on cross-cultural issues in infertility, the meaning of parenthood and the experience of infertility treatment. We learned more about how cultural characteristics can play an important role in shaping infertility both within and outside Europe.

We also found out more about the perception of fertility among mental health professionals. Indeed, an online survey of ESHRE members revealed that there is a positive perception of psychologists and counsellors in fertility care. However, there is also a lack of awareness about the different roles they perform, both with patients and their colleagues in an interdisciplinary context.

Guideline downloads

Our ESHRE guideline on *Routine psychosocial care in infertility and medically assisted reproduction - A guide for fertility staff* was published in April last year and has been attracting much attention, with 962 downloads of the document since then. The majority of downloads were by clinicians (30%), psychologists (17.3%) and embryologists (15.9%). The most frequent reasons for downloading were implementation or to learn more (64%).

We are quite satisfied to see how the guidelines have been disseminated so far and how professionals seem interested in knowing more about them and their implementation.

Campus meetings

We joined the SIG Endometriosis and Endometrium to organise our latest Campus meeting on **Sexual functioning in women dealing with infertility and/or endometriosis**. The meeting delivered an update on the interrelationship between sexual function, infertility and endometriosis, which encouraged discussion of important topics related to sexual health which are difficult to manage in clinical practice.

This year, as noted below, we are joining forces with four other ESHRE SIGs in the May Campus workshop on fertility preservation in boys. The meeting will have a strong emphasis on the psychological challenges for patients and their parents.

Our next precongress course, **Complex cases in infertility counselling: Discovering new territories, implementing new techniques and creating new conversations** to be held in Helsinki will consider new techniques for complex cases (with expected results) and how we can manage their arising legal, ethical, medical and psychosocial issues. We will also have the opportunity to learn more about sexual dysfunction in infertile couples and fertility assessment and counseling.

Juliana Pedro
Junior Deputy, SIG Psychology & Counselling

Five ESHRE SIGs join forces for fertility preservation Campus

Five Special Interest Groups of ESHRE (Andrology, Ethics & Law, Psychology & Counselling, Socio-cultural aspects of (in)fertility, and Stem Cells) have combined to design a multidisciplined Campus workshop on fertility preservation in boys. The workshop, titled **Future fertility for the male child and adolescent with cancer: best practice, research breakthroughs and current dilemmas**, will take place on 13-14 May this year at the Factory Hotel in Münster, Germany.

This important meeting will focus on clinical dilemmas in fertility preservation for pre-pubertal boys. Impressive breakthroughs have been made in the cure rate of childhood cancer but survivors may still face a devastating loss of fertility as a side effect of oncological therapies. Novel fertility preservation strategies targeting the regenerative potential of stem cells may be applicable, especially for boys whose testes contain spermatogonial stem cells.

This workshop brings together clinical and biomedical specialists from oncology, paediatrics, andrology and stem cell biology to provide an update and discuss the latest breakthroughs in research. The course will provide an update on current and future procedures for fertility preservation in boys with practical information on cryobanking immature testicular tissue.

There will also be discussion of the ethical, psychological and socio cultural issues associated with the availability of new treatment options, with a view to guidelines for best practice.

The organising SIGs say the workshop is relevant to a broad audience and brings together clinicians and basic researchers as well as social workers and ethicists to discuss this highly innovative and clinically relevant topic.

Registration and full programme details are on the ESHRE website.

Subtle pelvic abnormalities: SIG survey to assess impact

Following the Annual Meeting in Lisbon, we held a very well attended Campus workshop in Leuven in October. This was the last workshop following this frequently repeated programme and now for 2016 a totally renewed programme will be proposed in cooperation with Liege University. Thanks are due to Michelle Nisolle, Deputy of our SIG, and Stephan Gordts and his team who have been able to develop this advanced course (with work on cadavres) as a complement to the Leuven workshops.

Upcoming events

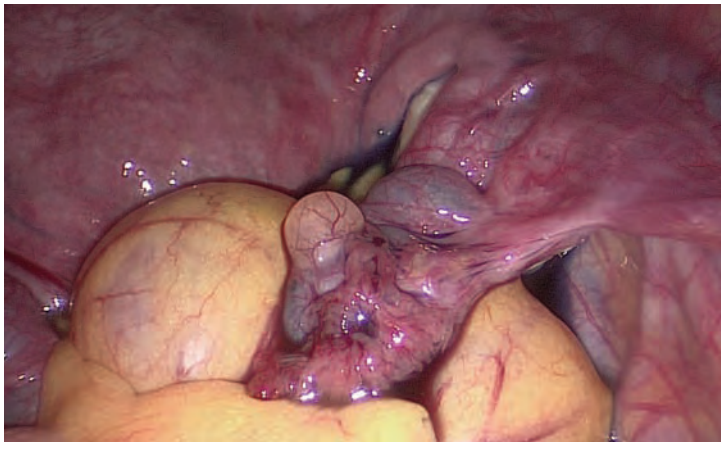
This month (21-22 January) we will be running our first meeting in Coventry on **When is surgery the answer to early pregnancy complications?** followed just a week later (28-30 January) by a workshop in Milan on **The impact of reproductive surgery on cross-talk between the embryo and the endometrium**.

These will be followed by our precongress course in Helsinki in July, which this year will be about the **Managmement of myomas in women wishing to preserve reproductive function**.

We have also agreed that our precongress course in Geneva in 2017 will be on the management of complications in reproductive surgery

In addition to these activities, we have made the assumption that a lot of subtle pelvic abnormalities (minimal endometriosis, minimal uterine pathology, subtle tubal lesions) are either not diagnosed or not treated, which may often prevent many patients from conceiving naturally. In the light of these assumptions the SIG RS is keen to launch a survey of the diagnosis and treatment of such abnormalities to assess their impact on fertility treatment and outcome. A proposal will be made to all interested members over the coming weeks, and we hope that a great number of reproductive surgeons will respond positively.

Antoine Watrelot
Co-ordinator SIG Reproductive Surgery



Subtle tubal lesion: hydatid of Morgani on patent tube. How do such abnormalities affect fertility treatment?

Updated guidelines on good laboratory practice nearing completion

Two major SIG Embryology activities are nearing completion – *The revised guidelines for good practice in IVF laboratories* and the digital *Atlas of embryology* – while other projects are in development.

Oocyte maturation: from basic to clinic, to be held in Brussels 3-5 March, will be one of two courses planned for 2016. An understanding of oocyte maturation is needed not just to improve the clinical efficiency of IVM, but also for a more objective and specific definition of oocyte quality in ART. The programme will cover the fundamental principles of oocyte maturation, plus the translational and clinical aspects of IVM, as well as its introduction into an ART programme.

We will also support the **Advanced training course for embryologists and paramedics** promoted by the Paramedical Group on 3-5 November in Gothenburg. The programme will cover specific and practical aspects of IVF, including culture media composition, quality control, and cryopreservation - with hands-on training. A significant part of the course will cover the use of statistics for correct data interpretation, study design, and manuscript preparation.

We are planning for early 2017 a third ESHRE Campus **From gametes to blastocysts – a continuous dialogue**, a course extremely well received in the past which will now be updated to include the latest developments in gamete and embryo research.

Giovanni Coticchio
Co-ordinator SIG Embryology

Eight years after assessing need and opportunities in developing countries, the first low cost 'Walking Egg' clinic opens in Ghana

The first Walking Egg IVF centre in Africa, November 2015.

The Arusha meeting of December 2007, jointly sponsored by ESHRE and the Genk Institute for Fertility Technology, brought together 37 experts of different origin to assess the problem of childlessness and infertility care in resource-poor countries. Medical, socio-cultural, ethical, economic and political issues on this topic were discussed.

The meeting was the opening initiative of ESHRE's Task Force for Developing countries and infertility and two important goals were set: first, to make infertility care in developing countries an open 'discussible' problem, and second, to develop methods to perform ART at a much lower cost. The latter would be achieved by simplifying ovarian stimulation protocols and modifying IVF procedures such that IVF treatment would be substantially cheaper.

A trial to examine the value and effectiveness of a new 'simplified' laboratory method began at the Genk Institute for Fertility Technology in 2011. The first results of our prospective study were presented at the 2013 ESHRE Annual Meeting in London, where results showed that fertilisation and embryo implantation rates were similar to those reported by high resource IVF programmes. The first baby was born on 17 November 2012.[1] With such reassuring results from this simplified IVF method, we next aimed to start similar studies in different centres in resource-poor countries.

Although demand for our project is immense, funding remains very difficult. International societies, NGOs and foundations show some interest, but this is where the story ends. All costs linked to the project are now covered by The Walking Egg non-profit organisation.[2]

In November the first Walking Egg centre in a resource-poor country was set-up in Accra, Ghana, with the support of the Pentecost Church. A team from Ghana attended a one-week training course in Genk in February 2015 and in November the first patients were treated in a new centre in Accra. Jonathan van Blerkom and a team from Genk were present in Accra for the ten-day set-up.

The first cohort of patients were treated with a combination of tamoxifen, low-dose hMG if needed, indomethacin, 5000 IU hCG and intravaginal progesterone in the luteal phase. Although ovarian response to tamoxifen was unexpectedly low, the

November 2015, Jonathan Van Blerkom, left, examining fertilised eggs from the first cohort of patients, and the clinic's first embryo transfer.

fertilisation rate of the eggs retrieved was very good and 12 embryo transfers could be performed. Results were not available at the time of writing.

Local clinicians and biologists have been trained to perform the different procedures, and results of this were very reassuring for both parties. This month, January 2016, a second Walking Egg centre will be set up in Nairobi, Kenya.

Willem Ombelet
Co-ordinator TF Developing countries and infertility

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2. Ombelet W. Is global access to infertility care realistic? The Walking Egg Project. Reprod Biomed Online 2014; 28: 267-272.

Trainees from Ghana and Nairobi, Kenya, meeting in Genk, February 2015.

PGD CONSORTIUM

Final testing for new online database system

After the successful launch of the online PGD database in Lisbon, the Steering Committee has now worked out final details and implemented some of the suggestions put forward by participants. Thus, following an initial test by Steering Committee members, the database is now ready for a second round of testing, to which all PGD Consortium members will be invited. Provided that no major problems are encountered, the database will finally be brought into use and PGD data can be entered both retrospectively and prospectively from then on.

Working groups

Our working group for monitoring new technologies in PGD, chaired by Martine DeRycke, has set up and recently sent out a second survey to investigate the take up rate and implementation of new technologies in ART and genetic diagnostic labs. As soon as all results have been collated, a manuscript will be prepared focusing on the comparison between the period covered by the first survey in 2013 and a comparable period in 2015 to provide insight into real-time trends in PGD or PGS.

The working group on HLA, chaired by Jan Traeger-Synodinos, has received input from 15 centres reporting on more than 750 PGD-HLA cycles. This dataset will be a valuable source of information for evaluating the clinical utility of HLA-PGD, and to investigate those aspects of PGD cycles which influence a positive outcome (birth of a genetically suitable donor-baby) and clinical outcomes of bone marrow transplant from PGD-selected donors. Data are now being cleaned and the results will be presented in Helsinki.

Upcoming events

PGD and PGS are procedures at the crossroad of clinical genetics and reproductive medicine. There can be no successful collaboration without cross fertilisation. Building on this idea, we have joined forces with the European Society of Human Genetics in organising a Campus course titled **All about preconception, preimplantation and prenatal genetic testing**, to be held in Maastricht, the Netherlands, from 13-15 April 2016. Information on the programme, speakers, registration and accommodation is availableon the ESHRE website.

A new chair will take over my role in the Steering Committee in Helsinki. As a result, there will be a vacancy for a committee member and I would like to invite all Consortium members who feel they can contribute to the importance and scientific prosperity of the Consortium to come forward and send their nomination to ESHRE's Science Officer, Veerle Goossens.

Edith Coonen
Chair PGD Consortium

The rush to publish

- Medical journal or TV news?
- Peer review or public interest?


Communiqués de presse

Imprimer

Paris-Lyon, 17 septembre 2015

Première spermatogénèse humaine in vitro

Obtenir des spermatozoïdes humains complets in vitro à partir de prélèvements effectués chez des hommes infertiles : c'est la première mondiale réalisée par Kallistem. Cette start-up issue de l'Institut de génomique fonctionnelle de Lyon (CNRS/Inra/Ecole normale supérieure de Lyon/Université Claude Bernard Lyon 1) a développé une technologie de thérapie cellulaire permettant la différenciation des cellules souches germinales[1] afin de produire, hors du corps, des spermatozoïdes morphologiquement normaux. Leur

French startup, government lab claim development of in-vitro human sperm

There were two eye-catching developments in reproductive science last year which were each apparently reported in the popular press before peer review in a medical journal. First, the birth of the world's first 'stem cell baby' was described in exclusive detail in *Time* magazine in May following the oocyte transfer of mitochondria from the mother's 'egg precursor cells'. A few weeks later a French start-up company working with a government lab in Lyon publicly presented a method for creating human sperm in vitro. This followed publication of a patent application in June (also announced by press release) for a process of in vitro spermatogenesis from male germinal tissue 'in a bioreactor'.[1] At a press conference in Lyon in September the researchers said (according to press reports) that the method took 20 years to refine, and may yet take several years before the quality of the sperm is confirmed. The process involved development of a bioreactor using a viscous fluid made partly of substances found in mushrooms or in crustacean shells resembling the fluid of seminferous tubules.

> "Nous attendons avec impatience une publication scientifique validée par les pairs.
>
> *Le Monde 17 September 2015*

As our report on page 12 indicates, the first details of energising oocytes with mitochondria from oogonial stem cells have now been published and, apparently, exposed to peer review. The published paper, which reports 'global patient experience' in two series of poor prognosis IVF patients in two treatment centres, was received by an open-access journal on 28 July and accepted for publication on 7 August; the journal has no formal impact factor (just a self calculated 'unofficial' IF of 1.0).

The in vitro spermatogenesis research is yet to be peer reviewed and, while the sperm cells are said to appear normal, it is not known whether they are viable. A press release issued on 17 September was accompanied by 37 images illustrating several stages of the process. Most experts asked by journalists to comment on the press claims were cautious, and non-committal before publication of any data. The French daily *Le Monde* quoted a French clinician saying: 'Nous attendons avec impatience une publication scientifique validée par les pairs.'

Press reports on both developments no doubt were a reflection of public interest. These were indeed attractive stories, both likely to stir public interest and each a step forward in reproductive science with important public health implications. But one wonders why the researchers took their findings first to the press and not to peer review.

What both processes have in common, of course, is commercialisation, the one from a French start-up company called Kallistem, the other from a US organisation called OvaScience, and publicity (what the earnest promise of marketing would call 'raising awareness') will inevitably have some ill-defined spin-offs.

For example, Kallistem announced in a press release in May last year that 'it aims to raise funds to accelerate its plans for growth and is also looking for partners for its expansion into the US'. The announcement seemed nothing more than an appeal for partners to take on the technology under licence. OvaScience explained in a press release in late September that it expected to miss its 2015 target of 1000 cycles but would continue 'to enhance its commercial operations'. There is more than a suspicion that these press initiatives - despite their public interest - are driven more by commerce than by science, and are more for investors than for clinicians.

Most scientific developments reported in the press are, however, the result of press releases. For example, all the major journals (except the *New England Journal of Medicine* but including *Human Reproduction*) have their own well oiled press operations, with press releases issued under embargo with frequent regularity - even several every week by *The Lancet* or *JAMA*. Their aim, of course, is to promote the journal title, the importance of the work, and ultimately the impact factor.

And ESHRE too, like most other learned societies, has a very active press programme at its annual meeting in

which abstracts with news and scientific value are selected for press release. The press programme, ESHRE agrees, presents its members and their work as scientifically progressive, clinically helpful and ethically responsible.

Most of these press releases, and especially those issued by the medical journals, are based on scientific papers which have passed the test of peer review to some extent, either for inclusion in a publication or at a congress.

At the other end of this communications continuum lies the journalist (and the boss), bombarded by a daily avalanche of 'news' via Twitter, e-mail, telephone informant and . . . press release. A specialist reporter on a top London newspaper will receive more than 50 'tips' a day for stories, and all must compete with each other for the limited space available.

Most news editors will defend their choice of health stories more on the grounds of public interest than of scientific validity. They, therefore, claim to be the best judge of public interest. If it gets in the paper, gets on the TV news, it *must* be in the public interest. So who could resist a sperm-in-the-lab story, or the first stem-cell baby? Yet is it right that such apparently important developments in reproductive science, with such huge implications, are made public without any evidence for professional assessment, without the opportunity for legitimate public scrutiny?

Contrast this approach to publicity accompanying the first live birth following uterine transplantation, which was descibed in *The Lancet* in October 2014 in a detailed report from the Gothenburg group.[2] Principal investigator Mats Brännström had made it clear throughout the 15 years of this programme that case details (always anonymous) would only be described in a scientific paper subject to peer review; and in this case the press release came from *The Lancet* (not the investigators), and the press conference in Gothenburg (plus YouTube video) came only after the *Lancet* publication.

The press, of course, doesn't always get it right, even with a press release to guide them. And a press release will always inhibit that most prized of journalists' trophies, the exclusive. Indeed, the first word in the headline of *Time* magazine's report on the first egg precursor cell baby was 'Exclusive'.

But usually the press does get it right, and certainly the press usually has the best idea of what will interest the public and what's in the public interest. The two are not mutually inclusive, however, and an initial test of peer review may well help mark the distinction between these two commonly confused priorities.

Simon Brown
Focus on Reproduction

1. See https://data.epo.org/publication-server/pdf-document?pn=2886644&ki=A1&cc=EP
2. Brännström M, Johanneson L, Bokström N, et al. Livebirth after uterus transplantation. Lancet 2014; 385: 2352-2353.

'The press doesn't always get it right'


Daily Mail
Good Health
Why snacking could be GOOD for your waistline
IVF AND A LINK TO OVARIAN CANCER
Women who need IVF treatment are a third more likely to develop the disease, reveals major UK study
So Wills, why DO they call you Royal Highness?

A press release issued by the ASRM during its anual meeting in October alerted journalists to a large registry study based on the HFEA database. The study cross-linked all women having ART in Britain between 1991 and 2010 (n = 255,786) with the UK's national cancer registries. The abstract added to the press release noted that with an average 8.8 years follow-up the increased risk of developing ovarian cancer after ART was 1.37 (standard Incidence ratio), although no added risk was found with increasing number of ART cycles. Increasing risk was also found with decreasing parity and female factor infertility (though not male factor). In their conclusions the investigators said that the results 'suggest that this increase is at least partially mediated by patient factors such as low parity and endometriosis', and that certain results (no increased risk with male factor infertility or increasing number of cycles) 'argue against an association with ART itself'. The study's principal investigator Alastair Sutcliffe was even quoted by the *Daily Mail* as saying he was 'convinced IVF itself was not at fault'. The *Mail*'s headline above is not inaccurate ('link', not cause) but the link *is* statistical, and not yet biological or causative.


Journal of Fertilization: In Vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology
ISSN: 2375-4508
Open Access
Research Article
The AUGMENT℠ Treatment: Physician Reported Outcomes of the Initial Global Patient Experience
Open Access

The report of 'global patient experience' using a proprietary technique of energising oocytes with mitochondria was published in August in the open access Journal of Fertilization: In Vitro - IVF Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology.

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