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The IUI revival in unexplained infertility

- Highlights from Geneva
- ESHRE news
- The practicalities of trophectoderm biopsy

// SEPTEMBER 2017

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SCIENCE MOVING
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CHAIRMAN'S INTRODUCTION

The blue skies shining over Geneva ushered in a new wave of members and participants. Yet again, congress numbers have broken new records with 10,397 participants from 116 countries. Of the 1725 abstracts received, 52% were from outside Europe, a remarkable figure that reflects the increasing visibility of the ESHRE Annual Meeting. Our recent membership survey told us how important networking has become as a raison-d'etre for attendance. It was a wonderful occasion to interact with so many national societies and individual members. From the Opening Ceremony to the last event on Wednesday afternoon, attendance was at an all-time high.

Recent interaction and feedback from our Junior Deputies in February gave a useful insight into the aspirations and wishes of our young ESHRE members. In particular, the use of social media and more accessible and easily digestible information was high on their list. As a result, a working group on social media has been actioned to support this initiative. Our Twitter ambassadors in Geneva did a great job, so many thanks to 'the group of five'.

The ESHRE travelling fellowships seem to be popular, with a rapid uptake of applications - and the first round of awards was made at the end of May. Congratulations to those who were successful and, to everyone else, please think about applying. It's all about building a clear area of study for three or six months to improve skills in a well regarded laboratory or clinical centre. The Executive Committee is keen to continue and support this grant process.

The Special Interest Groups (SIGs) will expanded to 14 with the inclusion of Nursing & Midwifery and Fertility Preservation groups. We welcome them both and the added opportunity for ESHRE members to become engaged with a SIG, as Deputy or Junior Deputy, and learn how ESHRE works.

The Executive Committee will have a more complex and growing agenda over the next two years. We welcome the five new ExCo members who joined us in Geneva. The strategy meeting held over two days in June clearly identified areas for development and reconfiguration. As a result, a one-day meeting will be held in September to action the points and construct a roadmap for future direction. Ongoing collaboration with our international partners will consolidate the shared areas of common interest likely to benefit from multiagency working. It is a rewarding atmosphere to engage with WHO, ASRM, IFFS, ICMART, FIGO and EBCOG on a continuing basis.

But without your participation ESHRE would not be the dynamic entity it is now, so thank you all for your support. If you want to do more, get in touch and give us your idea.

Roy Farquharson
ESHRE Chairman 2017-2019

// SEPTEMBER 2017

Invited scientific programme now in place; abstract submissions for free communication must be with ESHRE by 1 February 2018

EVEN BEFORE the final curtain went down on yet another successful Annual Meeting in Geneva, planning was well ahead for our next appointment. Barcelona 2018 promises to deliver a great blend of outstanding science in a tried and true meeting venue, opportunities for networking, and a flavour of the local Catalan culture. And let's not forget that 2018 will mark the 40th anniversary of the birth of Louise Brown, the world's first IVF baby. As our report on page 19 indicates, the world total of IVF births is now put at more than 7 million, enough to populate a small country and a remarkable achievement in such a relatively short time.

The 34th Annual Meeting of ESHRE will be held at the CCIB, a well connected and expansive venue just a short subway ride from the city centre but surrounded by several hotels for those who prefer to stay close to the heart of science.

As the meeting programme takes its final shape, it will be a true privilege to hear some of the most distinguished speakers scheduled to address the most pressing themes in reproduction today. It would be a long read to list all outstanding invited contributors to the programme, which is already available on the ESHRE website (https://www.eshre.eu/Annual-Meeting/Barcelona-2018/Programme.aspx).

To start the meeting you can choose from no fewer than 17 precongress courses on Sunday, with topics of great interest and relevance, from endometriosis to early pregnancy management and to a reflection on surrogacy.

The main programme will start with our traditional two keynote lectures, the first based on the most downloaded recent paper from *Human Reproduction*, to be followed as an invited speaker by Professor Katsuhiko Hayashi, whose group in Japan was the first

DIARY DATES FOR 2018

ESHRE's 2018 Annual Meeting will be held at the Centre de Convencions Internacional de Barcelona (CCIB) from Sunday 1 July to Wednesday 4 July. The CCIB is an architecturally stunning congress centre located in the newly developed Diagonal Mar district, close by the sea.

ESHRE warns that www.eshre.eu and www.eshre2018.eu are the only official websites. Our official housing agency is Mondial & Cititravel Congresos, S.L. Beware of fake agencies and websites offering services linked to the Annual Meeting for (mostly) registration and accommodation.

to achieve the complete derivation of oocytes in the lab from stem cells, and whose research is now bringing our understanding of germline development and oocyte biology to a new level. What an appropriate way to celebrate the 20 years anniversary of the derivation of the first human stem cell lines, by looking ahead to the future!

The oocyte will also take centre stage in the powerful lecture of Melina Schuh, who applies cutting-edge imaging and molecular techniques to unravel the intricacies of maternal age, oocyte aneuploidy and gene expression. Chromothripsis, a genomic phenomenon just recently discovered, will also be discussed by Drs Kloosterman and Pellestor in what promises to be an exciting and forward-looking session.

True to the mission of ESHRE to improve clinical practice, several important lectures will present an update on long-term follow-up of treatments, such as the development of children born after ICSI or PGD by Ulla-Britt Wennerholm and Julie Nekkebroeck, as well as an important and candid reflection on mistakes in the IVF lab, and how best to prevent them.

In vitro models of implantation continue to be a hot topic after recent reports suggesting the ability of human embryos to self-organise to a certain extent, and Miguel Ramalho-Santos and Magdalena Zernicka-Goetz review these recent developments.

The local organising committee is now working to make sure that Barcelona in 2018 will be a successful and engaging event, so come along, enjoy the science, and enjoy our beautiful city.

Rita Vassena
On behalf of the local organising committee

Keynote lecture: The full cycle of germline development in the lab

Katsuhiko Hayashi will present one of next year's two opening keynote lectures - on 'oocytes from stem cells and back'.

The Japanese stem cell biologist Katsuhiko Hayashi will present one of the two opening keynote lectures in Barcelona. Last year his group was the first to use pluripotent stem cells to reconstitute the full female germline cycle in a mouse model, saying that the work - in what has become known as in vitro gametogenesis, or IVG - 'will provide a platform for elucidating the molecular mechanisms underlying totipotency and the production of oocytes of other mammalian species in culture'. The group's work was published as a letter to *Nature* describing a series of studies which, via the generation of mature mouse oocytes in culture from embryonic stem cells and from iPS cells, culminated in the transfer of lab-created embryos and the birth of healthy mouse pups. The maturation took place entirely (and remarkably) in a laboratory dish, suggesting that 'the platform', as Hayashi described it in *Nature*, might one day be applicable in humans.

IUI, oocyte number and ESTEEM take centre stage

- More than 10,000 take part in ESHRE's 2017 Annual Meeting in Geneva
- New work and reviews presented in 295 oral presentations and 814 posters

WHERE WILL IT ALL END? Well over 10,000 registered for this year's Annual Meeting in Geneva, another attendance record, beating the previous high of 10,088 recorded in Lisbon in 2015. There's already speculation that an attendance of 12,000 cannot be far away . . .

Such bursting-at-the-seams pressure meant that this year's opening keynote lectures were delivered to the biggest audience ever known in reproductive medicine, almost 4000 gathered in a hall with 3400 seats and many standing at the back.

The keynote lecture they heard - based on the most downloaded paper from *Human Reproduction* following online publication between January 2015 and June 2016 - proved a tour de force of translational medicine from the distinguished and prolific Spanish clinical researcher Carlos Simón. The paper behind his keynote lecture in Geneva was a pilot study of bone marrow-derived stem cells used as therapy in the treatment of Asherman's syndrome and endometrial atrophy. Simón's group in Valencia had already shown that CD133+ bone marrow-derived stem cells could be effective in the reconstitution of the human endometrium, in these two incurable pathologies. Now,

Carlos Simón at this year's opening keynote lecture: stem cell therapy in Asherman's syndrome.

2017 HONORARY MEMBERSHIPS

Honorary membership of ESHRE was awarded to Switzerland's Marc Germond, pictured right after receiving his award, and to Rob Norman from Australia, who, left, received his award from Chairman Kersti Lundin and Chairman Elect Roy Farquharson. Germond was one of the early members of ESHRE and an organiser of ESHRE's first Annual Meeting in Switzerland, while Norman will be well known to ESHRE members for his work in PCOS - including the Rotterdam consensus of 2003.

Simón reported that the same application of cell therapy in a cohort of 16 patients had been shown to increase the volume and duration of menses over three months, as well as the thickness of the endometrium while decreasing intrauterine adhesion scores. The resumption of menstruation occurred in 15 of the 16 patients, and several pregnancies were achieved spontaneously and through ART - with so far one baby born.

This was a massive undertaking, with Simón disclosing that around 50 million CD133+ bone marrow-derived stem cells had been collected from each patient. 'So far,' he said, 'we've only been able to treat the symptoms of Asherman's syndrome. Now we're looking at a cure.'

It was also standing-room only for one of the first free communication sessions of the meeting, this one mainly on IUI protocols in unexplained infertility. This would prove to be one of the important sessions of the congress, a step back to the future with clomiphene citrate taking a first-line role in IUI stimulation, and IUI itself proving three-times more effective than expectant management.

The opening two reports of the session indeed made a strong case for IUI itself, and in contradiction to the recommendations of NICE, which, on the basis of limited evidence, had recommended in 2013 two years of expectant management to be followed by IVF. Indeed, said investigator Cindy Farquhar, this controversial recommendation was the very basis of her New Zealand trial, which compared three cycles of IUI (with clomiphene citrate) with three cycles of expectant management on cumulative LBRs. Dr Farquhar, from the University of Auckland, said that the NICE recommendations were based on just two trials in unexplained infertility, one of which included IUI without stimulation. Results of the study, which had randomised 201 patients with unexplained infertility to IUI or expectant management, showed that the former was associated with a three-fold greater live birth rate than the latter (31% vs 9%). 'IUI with clomiphene,' said Farquhar with a little understatement, 'may be offered to couples with unexplained infertility as a safe and effective treatment.'

This too was the conclusion reached by another RCT, this from the Netherlands, whose presenter, Monique Mochtar from the Amsterdam Medical Centre, even went so far as to recommend IUI with clomiphene stimulation as first choice in unexplained infertility – less invasive, less expensive and just as effective as FSH. The study, performed in 24 fertility centres in the Netherlands, randomised 369 women to IUI with FSH and 369 women to IUI with

IUI as a treatment for unexplained infertility was an important theme of this congress. Two randomised trials, one from New Zealand, reported by Cindy Farquhar, left, and the other from the Netherlands, reported by Monique Mochtar, each reached persuasive conclusions that stimulated IUI with clomiphene citrate should now be first-line therapy in such cases.

The everyday case for fertility preservation

Richard Anderson: The first population-based results of the effect of cancer treatment on pregnancy.

For the first time, a large population study has quantified the chance of pregnancy after treatment for cancer diagnosed in girls and women aged 39 or under. This landmark study, which linked all cancers diagnosed in Scotland between 1981 and 2012 to subsequent pregnancy, found that the cancer survivors were 38% less likely to achieve a pregnancy than women in the general population. This detrimental effect on pregnancy (though not necessarily on fertility) was evident in almost all types of cancer diagnosed.

'This analysis provides the first robust, population-based evidence of the effect of cancer and its treatment on subsequent pregnancy across the full reproductive age range,' said presenter Richard Anderson from the MRC Centre for Reproductive Health at the University of Edinburgh, UK.

The study, which cross-linked 23,201 female cancer survivors from the Scottish Cancer Registry with hospital discharge records, revealed 6627 pregnancies among the cancer survivors when nearly 11,000 would have been expected in a comparable matched control group from the general population.

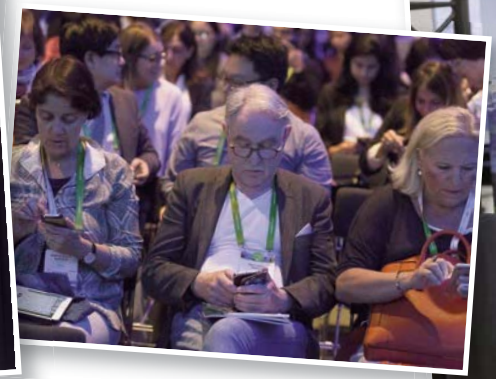
For women who had not been pregnant before their cancer diagnosis, 20.6% of the cancer survivors achieved a first pregnancy after diagnosis (2114 first pregnancies in 10,271 women), compared with 38.7% in the control group. Thus, women with cancer were about half as likely to achieve a first pregnancy after diagnosis as were controls.

Anderson described fertility preservation services in all parts of the world, including the USA and Europe, as 'very variable'. 'Oocyte and embryo freezing are regarded as established,' he said, 'but ovarian tissue cryopreservation is still considered experimental, even though it is still the only option we have for prepubertal girls.'

clomiphene. Results showed that 31% (113 women) had an ongoing pregnancy following IUI-FSH and 26% (97 women) an ongoing pregnancy following IUI-CC. Results also showed that five women (1%) had a multiple pregnancy following IUI-FSH and eight (2%) a multiple pregnancy following IUI-CC – again, a statistically non-significant difference.

A follow-up on these two trial reports by UK journalists suggested that NICE was ready to change its recommendations with the publication of these two trials. Roy Homburg, on page 26 of this issue, explores the background to these controversies in unexplained infertility. Similarly, Ben Cohlen in an invited session on IUI in Geneva reported that the NICE guidelines 'have not been well received in the UK and have caused much apprehension among gynecologists', with apparently only 4% of UK clinics discontinuing IUI. Doctors believe in IUI, said Cohlen, patients want it, and the evidence (so far) 'partly supports it'.

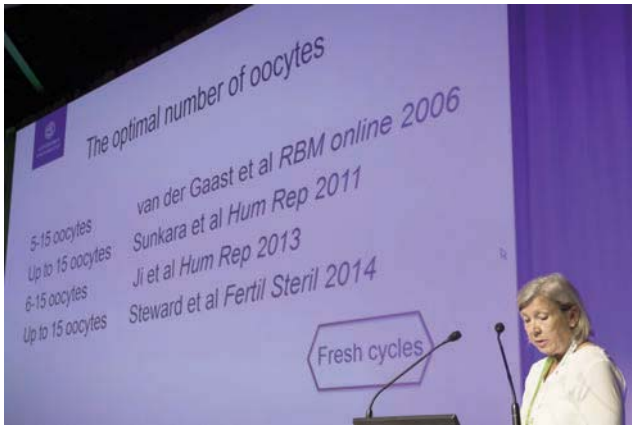
Another ongoing discussion in ART is response to stimulation as reflected in the number of eggs collected - and this too was a feature of several oral and poster communications in Geneva. A large study reported last year from the VUB in Brussels found evidence that cumulative live birth rates increase significantly with the number of oocytes retrieved. This association was not evident in the initial fresh cycle of treatment, where birth rates were comparable among high and normal responders. However, when outcome was assessed cumulatively, high responders (producing more than 15 oocytes for collection) demonstrated a significantly higher birth rate



than poor responders (0–3 oocytes), but also higher than those with normal (10-15 oocytes) ovarian response. Now, a European multicentre study reported in Geneva of nearly 15,000 women also found that cumulative LBRs rose continuously with the number of oocytes retrieved. Nikolaos Polyzos, of Dexeus University Hospital in Barcelona and the VUB Brussels, presenting the results confirmed the single-centre conclusion that cumulative LBRs are dependent on response to stimulation and that stimulation 'is unlikely to have a detrimental effect on oocyte or embryo quality'. Efficient cryopreservation, he added, is the key for these high cumulative LBRs, and the mean optimal number of oocytes for maximum fresh LBRs is 13 (7-20).

An explanation for this trend was found in a poster presented by Christos Venetis and colleagues from New South Wales, Australia, showing that a higher number of eggs retrieved in an IVF cycle is independently associated with more euploid embryos available for transfer. The number of euploid embryos identified by PGS from each of 724 cycles analysed was correlated with the number of oocytes retrieved in that cycle. This analysis showed, first, that the number of euploid embryos per cycle was negatively associated with female age, and second, that the number of oocytes retrieved was positively associated with the number of euploid embryos generated. Thus, to produce one and two euploid embryos respectively, five and 14 oocytes would be required at age 34, while 10 and 24 oocytes would be required at age 38. This result, like that of Polyzos, is not too far away from the data-crunching of Sunkara et al in 2011, which suggested that birth rate in IVF is directly related to the number of eggs retrieved (ie, birth rates rose according to the number of eggs retrieved, but levelled out after 20 eggs). The study reported that around 15 eggs were needed to maximise the chance of delivery in a first fresh cycle.

Venetis, like Anders Nyboe Andersen in an invited session noted that, while stimulation dose might be individualised to maximise cumulative outcome, there still remains the need to balance oocyte yield with safety. The Polyzos study found that OHSS rates began to increase (from 0.26%) with 10-15 oocytes and reached 2.96% by 25 oocytes collected.



Oocyte number collected at IVF was a recurring theme at this congress, with opinion moving back towards higher totals, particularly with respect to cumulative live birth rates. Both Nicholas Polyzos, lower left, from the Brussels group and Christos Venetis, right, from the University of New South Wales found evidence that more might be better.

However, a huge registry study from Denmark - 30,000 women followed-up from 2002 - found that cumulative LBR did not increase with more than 15 aspirated oocytes, although the number of oocytes in the first cycle did predict outcome in later cycles. It's not yet all one-way traffic, but there does seem a shift in the wind in favour of quantity over quality.

This was a not a congress to persuade the doubtful that PGS works - or at least works in increasing the probability of a live birth. Yet PGS - or as new ICMART nomenclature will now describe it, preimplantational genetic testing for aneuploidy, or PGT-A - still has a compelling attraction. A debate organised by the Paramedical Group was for many the most entertaining of the meeting, with Rome embryologist Laura Rienzi pitched against the perennial antagonist Sjoerd Repping on 'PGS for all'. Before the debate, few in the packed audience would agree with the motion - and, despite the cheerleaders' persuasive and committed presentations, that was still the verdict afterwards.

What, however, was striking in both presentations was the acceptance that PGS would not and could not improve live birth rates. Thus, the principal 'benefit' of 20 years of promotion seems now to have been superseded by other 'secondary' advantages. For

Rienzi, these were a minimised risk of miscarriage, a reduced time to pregnancy, and a more efficient programme of transfers, For Repping, as ever, the PGS numbers simply didn't add up.

And so it proved with the much anticipated presentation of results from the ESHRE-sponsored ESTEEM trial, this protracted RCT of polar body analysis by array CGH as a comprehensive test of aneuploidy. Karen Sermon, co-ordinator of the trial following the retirement of its instigator Joep Geraedts, said that the trial's first primary outcome question was whether full chromosome analysis of both polar bodies would increase the likelihood of a live birth within one year in women of an older maternal age – and the answer to that question was unequivocally 'no'. Among the 205 patients allocated to aneuploidy testing there were 41 with at least one live birth; and among the 191 randomised to no intervention there were 42.

So what both Repping and Rienzi accepted as a given in their debate seems now carved in stone by the ESTEEM trial - that PGS will not increase the chance of delivery. But it was also clear from the small print of Sermon's presentation that there were far fewer transfers in the screening group (178 vs 270), suggesting that aneuploidy testing did at least make for more efficient treatment. The bare details of the data also showed that the miscarriage rate in the PB group

Rome to the fore in PGS: Laura Rienzi defended PGS in a lively debate on PGS for all, while Francesco Fiorentino exntended his work on the viability of mosaic embryos.

was substantially lower than in the no-intervention group. These were important positive findings - as echoed by Rienzi in her case for PGS for all. But in everyday practice, would they be enough in the patient's view to compensate for no benefit in delivery rate?

Of course, other questions remain, and opinion was divided among those in the room listening to the results. There was discussion on both strict interpretation and wider implications - and particularly on the question of implantation rate. Clearly, there's much work yet to be done but no-one present was in any doubt that completion of the

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

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

Basic Science Award for oral presentation
João Pedro Alves Lopes (Spain) - Gradient system for testicular organoids generation – a novel system to model germ to somatic cell association in vitro (O-016)
Clinical Science Award for oral presentation
Heleen Zandstra (The Netherlands) - Weight and waist circumference of IVF children at the age of 9 years still affected by embryo culture medium (O-033)
Basic Science Award for poster presentation
Ellen Casser (Germany) - ART media act as modifiers that substantially influence embryo survival (P-217)
Clinical Science Award for poster presentation
Paula Piomboni (Italy) - Gene polymorphic variants in taste receptors (TAS) genes and male fertility: a possible correlation (P-035)
The Fertility Society of Australia Exchange Award
Mina Popovic (Belgium) - Comprehensive comparison of inner cell mass and trophectoderm reveals the complex nature of chromosomal mosaicism in human embryos (O-181)
The Nurses Award
Sarah Bailey (United Kingdom) - Hope for the best …. But prepare for the worst (O-148)
The ART Laboratory Award
Sofie Ellegiers (Belgium) - A time-lapse incubator is a superior incubator for excellent quality blastocyst embryo development compared to a conventional incubator (O-092)

The new language of infertility

Like success rates and cycle numbers, the language of ART continues to grow. An initial ICMART glossary of terminology in 2006 contained 53 terms; by the first revision in 2009 the list had risen to 87; and now in a further revision presented in Geneva 283 terms were included in the glossary. This time, said Fernando Zegers-Hochschild presenting the results on behalf of ICMART, the update was in the hands of five working groups, and their deliberations and revisions will not be without comment.

Gone are PGD and PGS, to be replaced by the all-embracing 'preimplantation genetic testing' - for aneuploidy (PGT-A), for monogenic diseases (PGT-M) and for chromosomal structural rearrangements (PGT-SR), new definitions said to more accurately reflect the broad applications.

Also apparently consigned to history is 'IVF' itself, now defined as either CIVI (conventional in vitro insemination) or ICSI. Similarly, the confusing terminology of sperm concentration is simplified to 'hypospermia' (low volume of ejaculate below the lower reference limit) and oligozoospermia (low concentration of spermatozoa in the ejaculate below the lower reference limit).

Also redefined is the term 'infertility', which now may be either a disease (characterised by failure to conceive after 12 months) or the result of 'an impairment of a person's capacity to reproduce either as an individual or with his/her partner'. Diagnosis, therefore, need not be clinical, but may simply recognise an inability in one person.

● Since Geneva the definitions have been published: Zegers-Hochschild F, et al. Human Reproduction 2017: doi:10.1093/humrep/dex234.

ESTEEM trial was a monumental work of diligence, determination and discipline. And ESTEEM may yet - like the Amsterdam trial of 2007 - become a landmark on this long and winding road of PGS.

One footnote to the PGS presentations was data from Francesco Fiorentino extending his already acknowledged work in embryonic mosaicism. In 2015 Fiorentino's group in Rome had in a letter to the *New England Journal of Medicine* described six healthy deliveries in a small series of 18 women for whom embryo screening had found no euploid embryos. Up to this point mosaic embryos were not transferred in IVF because they (like all other aneuploid embryos) were considered abnormal. Even in their *NEJM* letter, the Rome investigators noted that 'it is reasonable to assume that mosaicism reduces the likelihood of success of IVF'.

However, here in Geneva Fiorentino had extended the work to conclude that success or failure following the transfer of a mosaic embryo depends on the extent of the mosaicism and aneuploidy in the embryo. The study included 73 women for whom embryo screening following IVF had found no chromosomally normal embryos for transfer. Screening had, however, identified mosaic embryos in each of these patients, which were then offered for transfer. Results of the study showed that pregnancy and delivery were indeed possible. However, the transfers of mosaic embryos with a high percentage of chromosomally abnormal cells (≥50%) resulted in a live birth rate of 16.7%, with a miscarriage rate of 10%. In contrast, mosaic embryos with a lower aneuploidy percentage (<50%) resulted in a higher live birth rate of 39.5%, with miscarriage occurring in just 7.0% of the transfers. The difference between the two delivery rates was statistically significant, suggesting, said Fiorentino, that 'priority for transfer should be given to mosaic embryos with low levels of aneuploidy'.

For the first time the WHO had its own session at an ESHRE Annual Meeting, with Richard Kennedy, president of IFFS, setting out the global status of ART. The picture - as we can also see from data described in detail on page 19 - was not far different from the ICMART scene described in Geneva by David Adamson, but Kennedy, using recent figures from the World Bank, did emphasise that fertility rates were in decline in most regions of the world, including Africa. However, according to WHO, infertility remains among the ten most common moderate and severe disabilities in low and middle income countries. As for ART, Kennedy showed very recent data suggesting that rates of ART intervention were now relatively static in most regions, except Europe and Japan. The latter, as Adamson would report, is now the world's most active *recorded* country in ART, at least until China's registry numbers are published.

World data also show - albeit belatedly - that egg donation continues its steady increase in usage, a trend likely to accelerate with uptake of vitrification. Data on outcomes from vitrifid oocytes are scarce, with registry figures barely able to keep pace with practice. But one group - IVI - does have huge experience of egg donation with cryopreserved oocytes, which 'represents a large proportion of all ART cycles in IVI clinics,' according to Marcela Calonge from IVI Santiago de Chile. And this substantial - and probably unique - database has been analysed for all possibly predictive factors for successful outcome. The model included more than 120,000 vitrified donor oocytes compared with slightly fewer fresh oocytes. The model was designed to consider multiple variables, but especially number of donated oocytes. The analysis confirmed that, more than any other variable, embryo quality was key to prediction, but the key to embryo quality was the number of oocytes retrieved. And this too was important in predicting oocyte survival, fertilisation and embryo development - and so yet again a recurrence of a recurring theme at ESHRE 2017.

Simon Brown
Focus on Reproduction

The psychological implications of modern ART were well represented in Geneva. Mathilde Brewaeys reported that children in single-mother-by-choice families do just as well as those in two-parent families, while Mariana Martins, with evidence from a large population study, said that ART does not increase the risk of divorce.

Annual Assembly of Members

Membership at a record high, record congress attendance

ESHRE's Annual Assembly of Members took place at the Palexpo, Geneva, on 4 July 2017 at 18.00. The minutes of the meeting are recorded below. Matters arising and their approval will take place at next year's Annual Assembly in Barcelona.

1. Minutes of the last meeting held in Helsinki

- The minutes of the 2016 Annual Assembly of Members (AAM), having been circulated to all members in Focus on Reproduction (September 2016), were approved.

2. There were no matters arising.

3. Membership of the Society

- Membership of the Society (as at 29 June 2017) stands at 7015, a substantial increase on last year's figure of 6714 (December) and an all-time record membership. European members account for almost two-thirds of the total. The top European membership countries are UK (482 members), Italy (437), Spain (326), Germany (298), Netherlands (287) and Belgium (272). The USA is represented by 328 members, and India 469 (now ESHRE's second largest national membership).
- The Chairman reported that disciplines most prominently represented among members (according to SIG membership) are embryology and reproductive endocrinology, which together represent 60% of total membership.

4. Society activities

Annual meetings

- Last year's Annual Meeting in Helsinki attracted 9711 participants. Feedback, said the Chairman, was generally positive about both the organisation and scientific programme.
- Annual Meeting attendance by the time of the AAM in Geneva was already at an all-time record with a total of 10,397 registered (which included 2017 exhibitors and 26 press).
- From a total of 1725 abstracts submitted, 234 had been selected for oral presentation and 802 for poster. The greatest number were in embryology (343), female infertility (246), andrology (203) and reproductive endocrinology (198). The majority (48%) were submitted from Europe, but there were high representations from Asia (32%) and the Americas (12%). 'Asia is rising rapidly,' said the Chairman.
- Next year's event will be at the Centre de Convencions Internacional de Barcelona (CCIB), from 1-4 July, with 17 precongress courses organised by the Special Interest Groups and exchange partners. The invited programme is already available online.
- The Annual Meeting of 2019 will be held in Vienna, Austria, from 23-26 June.

Educational activities

- The Chairman reported that 14 Campus courses had been held in 2016 and five already in 2017 (with ten still to take place).
- The Chairman also announced that e-Campus, the Society's e-learning platform available to members via the website, has now got 579 videos available (which so far have been played almost 6000 times). She added that the very successful ESHRE Atlas of Human Embryology is now on a very user-friendly and interactive platform, and is freely accessible to members.
- A pilot run of ESHRE's 'Fertility on Tour' project in April attracted 70 very enthusiastic participants in Barcelona. The project, as a series of similar meetings, aims to broaden understanding of fertility (and ESHRE) among university students.

Data collection

- The Chairman praised the work of the European IVF Monitoring (EIM) and PGD Consortium. The EIM group, under the chairmanship of Carlos Calhaz-Jorge, has been collecting data retrospectively since 1997 from around 30 European countries and is now monitoring more than 700,000 ART cycles each year; this represents a cumulative total of more than 1.46 million babies born since the EIM began its work.
- Data collected for 2013 have now been submitted for publication in *Human Reproduction*. Preliminary data for 2014, the first to be submitted with a new online data collection system, were presented in Geneva. Data collection for 2015 has a deadline of 31 October 2017.
- Data reported for 2013 (from 1169 reporting clinics) indicate that the number of frozen cycles has reached that of fresh cycles (154,712 FER vs 144,299 fresh), with FER pregnancy rates rising from 14.1% in 1997 to 27% in 2013. The majority of transfers are with two embryos, while SET continues to rise (representing more than 30% of all cycles in 2013). Multiple delivery rates continue to decline, while pregnancy rates increase (in 2013 to 30% from 26% in 1997).

- PGD Consortium Data XIII (for 2010) has now been published and Data XIV-XV (2011-2012) submitted for publication. Data for 2013, 2014 and 2015 were collected in summary form during 2016 and are 'almost ready for submission'. The summary data mark the interim phase between former retrospective data collection and the new online prospective system with which the first data are now being added to the database.
- The PGD Consortium will mark its 20th anniversary with a celebration Campus meeting in Brussels on 8-9 December.

ESTEEM trial

- The ESHRE-sponsored Study into The Evaluation of oocyte Euploidy by Microarray analysis (ESTEEM) was completed earlier in the year by eight European centres The trial had two primary aims: to estimate the likelihood of having no euploid embryos in future ART cycles and to improve live birth rates in women of advanced maternal age.
- First results of the study were reported in Geneva, with delivery rates comparable in the intervention and non-intervention arms of this randomised trial. Secondary outcome results suggested that the intervention may avoid unnecessary embryo transfers and decrease miscarriage rates. The Chairman said the results will be published 'very soon'.

ESHRE research grants

- The Chairman explained that ESHRE will award two grants in 2017, one of 50,000 euro and one of 150,000 euro. Applicants for these grants were asked to focus on the theme of 'endometrial receptivity'. ESHRE received 40 proposals for the smaller award, and 51 proposals for the larger. The award of 50,000 euro was won by Paola Vigano of the Ospedale San Raffaele in Milan for work on 'uterine fluid exosomes as a "liquid biopsy" for depicting personalized endometrial receptivity'; the award of 150,000 was made to Guiying Nie of Monash University, Australia, and Vrije Universiteit Brussel in Belgium for research on a new mechanism of endometrial receptivity establishment and its clinical significance.
- A pilot project with the ReproUnion group of clinics in Denmark and Sweden aims to provide fellowship funding for a number of clinical and basic science trainees working in fertility. A three-month fellowship is for 5000 euro and six-month for 8000 euro. The first round of applications has been completed, with four grants from 54 applications approved.
- A second round of applications is now under way.

Guidelines

- The Chairman reported that guidelines are becoming an increasingly important activity of ESHRE. Two were published in 2015, *Routine psychosocial care in infertility medically assisted reproduction* and *Management of women with premature ovarian insufficiency*. The ESHRE guideline on *Recurrent pregnancy loss* is scheduled for publication later this year.
- ESHRE is also collaborating with other societies in the development of guidelines - notably on key performance indicators for ART, on the surgical management of endometriosis, and on Turner syndrome.
- ESHRE guidelines in development are on ART in patients with viral disease, female oncofertility, updated PGD and PGS,

Roy Farquharson becomes the new Chairman of ESHRE. The Executive Committee 2017-2019 now comprises: Roy Farquharson (GB, Chairman), Cristina Magli (IT, Chairman Elect), Basak Balaban (TR), Thomas Ebner (AT), Mariette Goddijn (NL), Borut Kovacic (SI), Nicholas Macklon (GB), Anja Pinborg (DK), Karen Sermon (BE), Thomas Strowitzki (DE), Snežana Vidaković (RS), Rita Vassena (ES), Kersti Lundin (SE, Past Chairman), Cecilia Westin (SE, Paramedical Group), Estratios Kolibianakis (GR, SIG Committee)

ovarian stimulation in ART, and, as an international collaboration, PCOS.
- All ESHRE guidelines are developed according to an established methodology and are published as a full version, in summary format in *Human Reproduction*, and as a lay version. They are freely available to everyone. They may also be produced as pocket guidelines and as an app.

ESHRE accreditation and certification

- ESHRE certification is of two types: for individuals as a reflection of their expertise and competence; and for centres as a mark of their quality of service and training. Thus, the objectives of ESHRE certification are to improve safety and quality in clinical practice and to improve training. 'Accreditation and certification are becoming a big part of what we're doing,' said the Chairman.
- Individual certification is now available to ESHRE members in embryology, reproductive endoscopic surgery, and fertility nursing. In preparation is an ESHRE-EBCOG European Diploma for Reproductive Medicine
- The cumulative total of certified clinical embryologists is 1344 (with 729 certified at the senior level). Interest remains high, with 169 clinical and 104 senior embryologists accepted for 2017 certification (27% non-European).
- Certification for reproductive endoscopic surgeons (ECRES), introduced in 2013, is on two levels, level 1 (bachelor) and level 2 (master), and assesses both practical and theoretical skills. Currently, there are 24 certified at the primary level (although 42 passed the examination at last year's Annual Meeting, only 24 fulfilled the other requirements). There were 30 primary and six master applicants for Geneva.
- The first examination for nurse and midwife certification took place in Lisbon in 2015, and there are now 66 certified; 18 applicants were accepted for 2017.

Hans Evers, Editor-in-Chief of Human Reproduction, reviewed progress of the four ESHRE journals.

- Thirteen centres have so far been accredited under ESHRE's joint programme for accreditation of subspecialist training programmes with the European Board and College of Obstetrics and Gynaecology (EBCOG).
- ESHRE is trialling an E-exam project in India which, if successful, will allow 50 participants to take the embryology certification exam in New Delhi in parallel with the exam in Barcelona on 30 June 2018.

Surveys and audits

- A membership survey performed this year recommended higher visibility of the Society, greater incentives for membership, more networking opportunities, greater activity on social media, and more hands-on activities.
- A meeting with SIG Junior Deputies echoed these findings, with an emphasis on hands-on training, more expert contact, a higher profile to posters at the Annual Meeting, travel grants, and more benefits from membership.
- Alongside Fertility Europe, ESHRE presented a survey for the European Parliament on regulation and reimbursement policy in 28 member states.
- At the EU level ESHRE is a stakeholder with DG Sante and EDQM (European Directorate for the Quality of Medicines at Council of Europe), working with developments for the Tissue & Cell Directives, protection of donors, and harmonisation within ART regulation.
- ESHRE is now formally considering its strategic future, with consideration of membership, finances, organisation and management, scope (European or global, scientific or policy) and levels of autonomy.

Special Interest Groups

- A new SIG for Fertility Preservation was announced in 2017, co-ordinated by Richard Anderson (GB). It was also announced that the Paramedical Group would be disbanded over the next two years and its members devolved to the SIGs, notably SIG Embryology, SIG Andrology or the new SIG for Nursing & Midwifery.

Committees

- The affairs of ESHRE are now in the hands of an Executive Committee and nine further committees: Finance, Publications, Communications, SIGs, Scientific, Research Grant, European Affairs, Certification & Clinical Management, and Ethics. There is also a new working group on use of social media.

5. ESHRE journals

- Speaking on behalf of the 'HR Team', Hans Evers, Editor-in-Chief of *Human Reproduction*, said that this had been 'an extremely successful' year, adding: 'The way the journals are progressing is unique in reproductive medicine.' He reported that the editorial teams of the four ESHRE journals are supplemented by six statistics/methods editors, 134 associate editors, 4500 peer reviewers, and 14,000 authors. Their common task is to ensure 'good science and clear writing', reflected in three questions: Is it new? Is it true? Do I care?
- Evers reported that from 1 January 2017 *Human Reproduction* has joined the leading journals in the field to require prospective registration of every RCT submitted for publication.
- He added that the rate of *HR* 'pre-review' rejections had risen to 36% in the past decade, with time to decision now down to 3.6 days.
- Submissions to *HR* are stable, with new submissions at about 1500 per year. Reviewing time for new submissions to a first decision is now down to 21 days. Overall rejection rate rose from 73% in 2015 to 77% in 2016.
- The latest impact factors ranked *Human Reproduction Update* and *Human Reproduction* as the top two journals in the categories of Obstetrics & Gynaecology and Reproductive Biology, with *MHR* fourth in the latter category. The three ESHRE titles, *HR Update*, *H*R and *MHR*, recorded impact factors of 11.7, 5.0 and 3.6 respectively, the first two record highs. Downloads from *HR* reached an 'amazing' 3.5 million in 2016.
- Evers reported that several recent innovations, notably short alerts and editor's highlights via the website, had proved popular.
- ESHRE's new open access journal, *HR Open*, launched in 2017 and has attracted manuscripts from spontaneous submission, ESHRE pages, cascade from *HR*, and commissions.

6. Paramedical group

- Helen Kendrew, Chair of the Paramedical Board, reported that historically paramedical members comprise nurses, midwives, 'lab technicians' (the largest group), counsellors and psychologists, and clinical embryologists up to BSc level. Some of these descriptions, said Helen, were no longer appropriate, prompting a rethink on the composition and modernisation of the group. 'The world has changed,' she said.
- The group's training and precongress courses, as well as Geneva paramedical sessions, were all well attended. Also progressing with enthusiasm was the certification course for nurses and midwives.

7. Financial report

- Bruno Van den Eede, ESHRE's managing director, presented the balance sheet (income and expenditure) for 2016 and the budget for 2017. Income in 2016 (6,496,320 euro) was ahead of expenditure (5,219,478 euro), leaving a favourable balance of 1,276,842 euro. A budget similarly constructed to 2016 - to provide a positive balance - has been set for 2017.

Income	31/12/2015	31/12/2016	budget 2017
	€ 6.362.608,13	€ 6.496.320,79	€ 6.404.750,00

Expenditures	31/12/2015	31/12/2016	budget 2017
	€ 5.516.613,99	€ 5.219.478,11	€ 5.858.388,15

Result	31/12/2015	31/12/2016	budget 2017
	€ 845.994,14	€ 1.276.842,68	€ 546.361,85

Income in 2016 (€6,496,320) was ahead of expenditure (€5,219,478), leaving a favourable accounts balance of €1,276,842. The source differential of ESHRE's income (above) and expenditure is shown in the charts below.

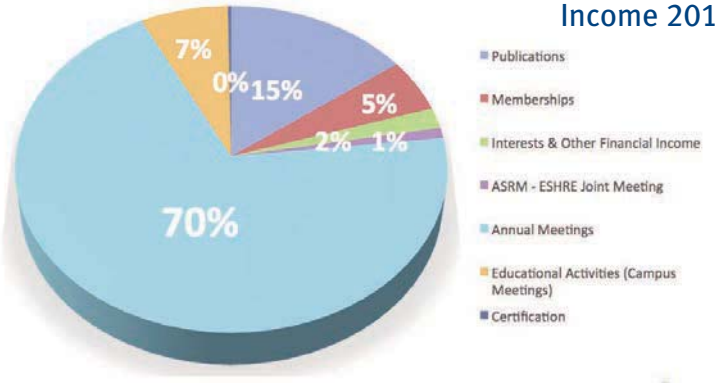
- The Annual Meeting continues to provide the Society's greatest source of income (70%) and expenditure (41%). Educational activities are the major source of SIG expenditure.
- The financial report for the year ending 31 December 2016 and the budget for 2017 were approved by the members.
- The Chairman took this opportunity to praise the dedication of Bruno, whose career with ESHRE now spans 30 years.

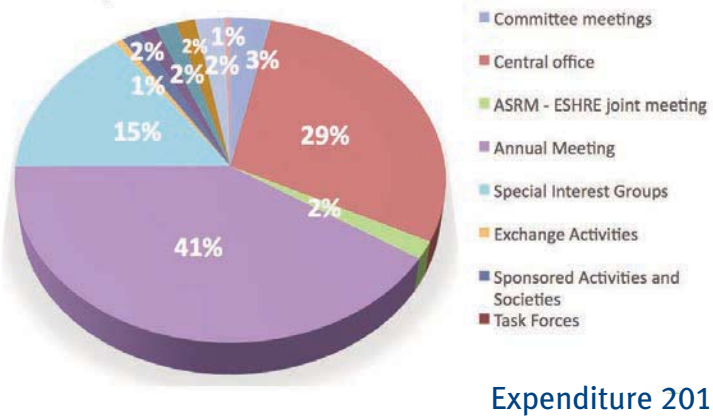
8. Executive Committee

- Nominal changes to the membership of the Executive Committee were unanimously approved by the membership. They were:
- Kersti Lundin (SE) stepped down as Chairman to become immediate Past Chairman, Roy Farquharson (GB) became the new Chairman of ESHRE, and Cristina Magli (IT) the new Chairman Elect. In accepting the nomination, Farquharson said that his major challenge as Chairman was to address 'the complexity and increasing size of ESHRE'.
- Stepping down from the Executive Committee after two two-year terms in office were Petra De Sutter (BE), Georg Griesinger (DE), Grigoris Grimbizis (GR), Tatjana Motrenko (ME), Andres Salumets (EE), Helen Kendrew (GB) and Juha Tapanainen (FI, as Past Chairman). All were thanked for their tireless work and commitment.
- Continuing for a second two-year term as members of the Executive Committee were Mariette Goddijn (NL), Nick Macklon (GB), Basak Balaban (TR), Borut Kovacic (SI), and Rita Vassena (ES).
- New members, whose nominations were ratified by the meeting, were Thomas Ebner (AT), Anja Pinborg (DK), Karen Sermon (BE), Thomas Strowitzki (DE), and Snežana Vidaković (RS). Estratios Kolibianakis (GR) joins the Executive Committee as an ex-officio member (as Chair of the SIG Committee) and Cecilia Westin (SE) as paramedical group representative.

Bruno Van den Eede, whose 30-year dedication in the management of ESHRE was praised by the Chairman.

Income 2016





Expenditure 2016

9. Election of honorary members for 2018

- The two nominees proposed by the Executive Committee for honorary membership in 2018 were Dr Pedro Barri from the Universitari Dexeus in Barcelona and Dr Ursula Eichenlaub-Ritter, Professor of Cell Biology at the University of Bielefeld, Germany. Both nominations were ratified by the AAM.

10. Any other business

- Søren Ziebe, Professor of Clinical Embryology at Rigshospitalet, Copenhagen, urged ESHRE to give greater attention to the prevention of infertility, and not just to its treatment. His comment was met with applause from the membership.

● The next Annual Assembly will be on 3 July 2018 at the Centre de Convencions Internacional de Barcelona at 18.00.

More record impact factors for the ESHRE journals

Human Reproduction Update achieves the highest ever impact factor in O&G

Two of ESHRE's three leading journals, *Human Reproduction* and *Human Reproduction Update*, have each increased their impact factors in the citation categories of Reproductive Biology and O&G, the former from 4.621 to 5.020 and the latter from 11.194 to 11.748, in the latest journal analysis (for 2016). Both titles are now firmly established at the head of the Reproductive Biology category, while *Human Reproduction Update* also leads the O&G category by a substantial margin, with the highest recorded impact factor ever in both categories.

ESHRE's other print title *Molecular Human Reproduction* confirmed its high-ranking status in the category of Reproductive Biology with an impact factor of 3.585, thus placing all three ESHRE journals within the top four of this category.

Only last year did *Human Reproduction*'s editor-in-chief Hans Evers make an impact factor of 5 his next stated ambition - and this has now been achieved in just 12 months.

Among other journals in the field, *Fertility and Sterility* fell slightly from 4.426 to 4.373, while *Reproductive Biomedicine Online* rose from 2.796 to 3.249. The biggest mover in the O&G category was *BJOG*, which saw its impact factor rise from 3.943 to 5.051.

Reproductive biology

Title	Total cites	2015 Imp Factor	2016 Imp Factor
Human Reproduction Update	7768	11.194	11.748
Human Reproduction	29721	4.621	5.024
Fertility & Sterility	33096	4.426	4.373
Molecular Human Reprod	5130	3.943	3.585
Biol Reprod	21861	3.471	3.432
Reprod Biomed Online	5775	2.796	3.249
Reproduction	8072	3.184	3.100
Am J Reprod Immunol	4317	2.916	3.013
Reprod Biol Endocrinol	3755		2.849
J Reprod Immunol	2615	2.85	2.798

Obstetrics and gynaecology

Title	Total cites	2015 Imp Factor	2016 Imp Factor
Human Reproduction Update	7768	10.194	11.748
Am J Obstet Gynecol	39185	4.681	5.574
Obstet Gynecol	32073	5.175	5.426
BJOG	15315	3.943	5.051
Human Reproduction	29721	4.621	5.024
Gynecol Oncol	22924	4.198	4.959
Ultrasound Obstet Gynecol	11611	4.197	4.710
Fertility & Sterility	33096	4.426	4.373
Pregnancy Hypertension	527		3.930
Molecular Human Reprod	5130	3.943	3.585

Coming to a university near you

An initiative to present a basic understanding of infertility and its treatment - and indeed the work of ESHRE - to young students was tested as a pilot exercise in April at the Universitat Autonoma de Barcelona (UAB), Spain, and attracted more than 70 enthusiastic participants. The three-hour programme of 'Fertility on Tour' comprised four presentations - on the history of assisted reproduction (by Anna Veiga, embryologist for Spain's first IVF baby), the 'myths' about fertility (Rita Vassena), current techniques in treatment (Francesca Vidal) and ethical considerations in assisted reproduction (Josep Santaló). ESHRE's aim now is to present similar seminars as a series of 'Fertility on Tour' awareness events for students at other universities in Europe. The programme left time for the audience to ask questions and talk at length with the speakers.

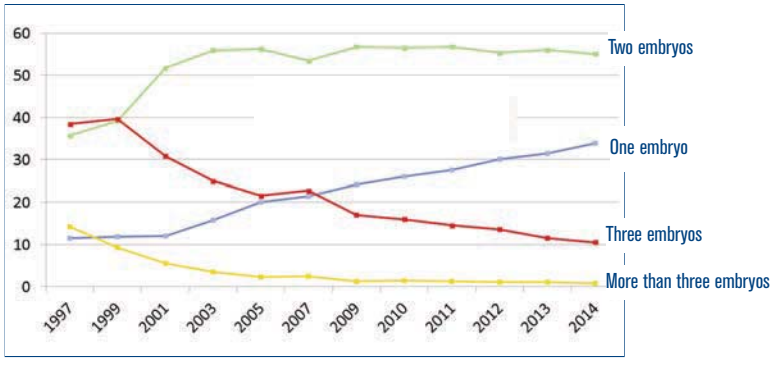
Spain now Europe's most active country in ART

- Preliminary results reported for 2014
- Pregnancy rates steady at around 28%
- Big increase in frozen embryo transfers
- 8 million cycles monitored since EIM formation

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

THE NEXT INSTALMENT of data from ESHRE's European IVF Monitoring (EIM) Consortium - preliminary results of activity in 2014 - shows a slow increase in the number of cycles reported (though lacking data from the UK), a steady record of success in IVF and ICSI, and a slight increase in pregnancy rate in frozen transfers and egg donation.

Carlos Calhaz-Jorge, chairman of the EIM Consortium, said there had been an increase in total numbers of treatment cycles of 3% from 2013, a rise mainly attributed to enhanced registry requirements in Spain and Russia. As a result, Spain was the most active European country in ART (with almost 110,000 cycles reported), followed by Russia (95,000 cycles) and France (90,000 cycles). Mainly because of its particularly wide use in Spain, frozen embryo replacements and egg donation cycles were also seen to increase significantly, egg donation up 33% on the previous year and FER up 15%. EIM estimated that in 2014 almost 6% of all IVF/ICSI cycles were freeze-all.



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

The report covered a total of 707,171 treatment cycles performed in 2014 and 146,232 babies born - representing around 80% of all European treatments, and thus the largest and most accurate snapshot of ART in Europe.

The data collection and monitoring of ESHRE's EIM Consortium have grown more complex with the progress of ART. IUI was added to the techniques monitored in 2002, while present data collections must include PGD, IVM, and frozen oocyte replacements. Data for 2014 were submitted from EIM members via a new online data collection system which is considered simpler than the previous time-consuming paper version. The current requirement is based on eight data modules comprising ten pages and 20 tables.

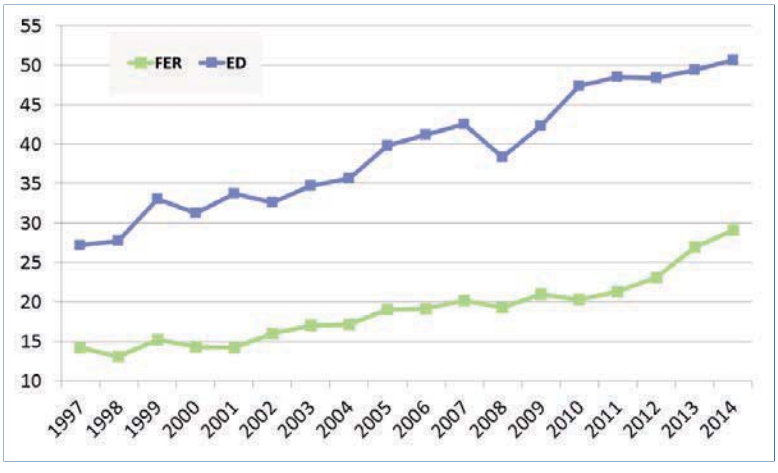
'Numbers are going up every year,' said Calhaz-Jorge, noting that the total number of cycles submitted to the Consortium for 2014 increased by 3% over the previous year, meaning that the Consortium has monitored a cumulative total of almost 8 million cycles since its formation in 1997 and 1.45 million children born.

EIM is now in its 20th year and among the trends identified over this period Calhaz-Jorge noted an increase in SET (from 11% in 1997 to almost 35% in 2014), a major decrease in triplet rates (from 3.8 in 1999 to 0.5% in 2014), improving success rates from frozen embryo transfers, but a general stabilisation of

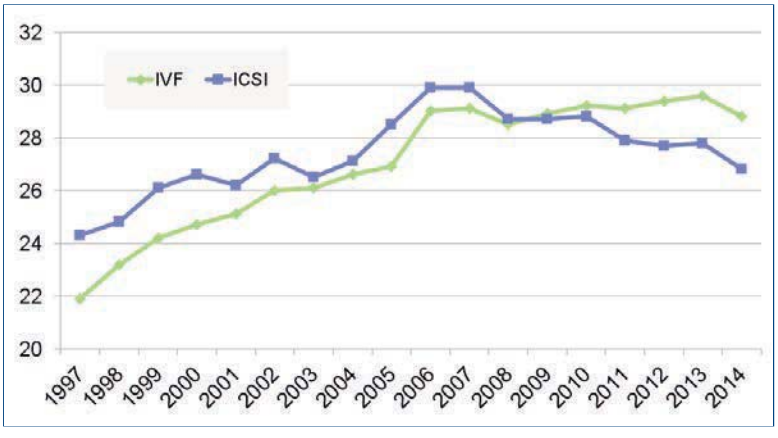
80% OF EUROPEAN CYCLES NOW MONITORED

ESHRE's EIM Consortium is now in its 20th year and has reached the remarkable data milestone of more than 8 million cycles monitored and 1.454 million babies recorded. In 2014 alone the Consortium's coverage was derived from 36 countries, 1184 treatment centres, 707,171 cycles monitored (without the UK), and 146,232 babies born. 'Numbers are going up every year,' said EIM chairman Calhaz-Jorge, noting that the total number of cycles submitted for 2014 increased by 3% over 2013. The number of egg donation treatments increased by 33% over 2013 (to 52,950).

Steering committee of the EIM Consortium pictured in Geneva. From left, Edgar Mocanu, Tatjana Motrenko representing ESHRE's ExCo, former Chairman Markus Kupka, Christine Wyns, Karin Erb, Jesper Smeenk, Jacques de Mouzon, Chairman Elect Christian de Geyter, Giulia Scaravelli, Chairman Carlos Calhaz-Jorge, and ESHRE Science Manager Veerle Goossens.



% pregnancy rates per thawing and per ET with FER and egg donation.



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

pregnancy rates in IVF and ICSI (after a steady rise to 2005). Also stable is the number of two-embryo transfers (at around 55% of all ETs); the increase in SETs seems to be from the decline in three-embryo and higher ETs, said Calhaz-Jorge.

The distribution of IVF and ICSI remains much in favour of ICSI, despite EIM evidence in 2014 of a slightly higher pregnancy rate per aspiration from IVF (28.9%) than from ICSI (26.8%). Nationally, Macedonia recorded the highest pregnancy rate per aspiration (53.1), though local results were, as always, extremely varied.

Similarly, Denmark, Belgium and Czech Republic had the greatest provision of ART in 2014, with more than 2500 cycles of IVF/ICSI per million population. Active countries such as France, Netherlands and UK were each below 1000 cycles per million. A health economics report in 2002 put the 'global need' for ART' at 1500 cycles per million.

The highest ART pregnancy and delivery rates are now seen in egg donation, either fresh or as embryo transfers from cryopreserved oocytes. Pregnancy rates (per ET) from frozen donor eggs (49%) are higher than from frozen embryos and around the same as from fresh donor eggs (51%).

'Generally, success rates seem to have stabilised, although outcome in egg donation and with use of frozen embryos is still moving upwards,' said Calhaz-Jorge. 'The biggest upwards movement, however, is from treatments with frozen eggs, which have been revolutionised by the widespread introduction of vitrification.'

Among the complications of treatment OHSS remains the most frequent, at a rate of 0.3%.

World IVF baby total now put at 7 million

● China now thought to be the world's most active ART country, with estimated 800,000 annual cycles

David Adamson presented global data on behalf of ICMART.

Preliminary global data (for 2013) presented in Geneva by David Adamson on behalf of ICMART show that the estimated world total of IVF babies has now reached 7 million. Reported cycles for 2013 rose by 10% from 2012 to a new total of more than 1.5 million - and growth, said Adamson, is still 'very rapid'. 'We are now recording around two-thirds of global activity,' he added, noting that the task remains 'very difficult' because of the growth and ever increasing complexity of treatments.

Japan remains the world's officially most active country (with 368,627 cycles recorded for 2013) but Adamson made it clear that China is now likely to set the pace with an estimated 800,000 cycles annually.

Almost three-quarters of global activity (excluding China) is now performed in just ten countries of Europe, the Americas and Australia, with Europe responsible for around 50%. Data are missing or patchy from some Asian countries and the Middle East, though 12 African countries through the ANARA network registry, said Adamsom, are now contributing.

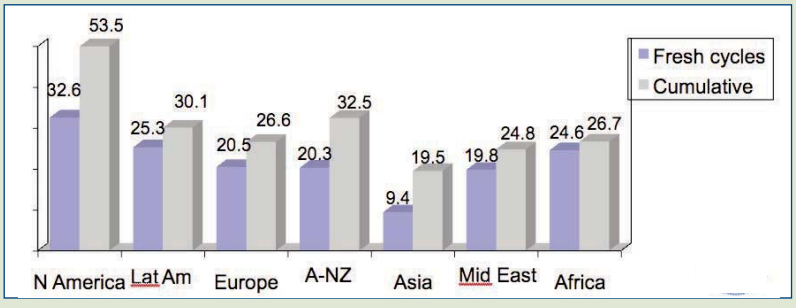
The world data, as in Europe, show ICSI (607,000 cycles) still hugely favoured over IVF (275,000 cycles) for fertilisation, with no sign of the trend reversing. The use of ICSI was reported to be 100% in the Middle East (represented by data from Egypt), 85% in Latin America, and 75% in North America.

Delivery rate remains steady at around 20%. There was, however, a substantial increase in the number of freeze-thaw cycles (up 17.3% over 2012), with a slightly higher delivery rate of 22%. The global trend over the past ten years shows a clear but steady increase in the number of 'thawed' cycles and a decline in fresh. Thus, cumulative delivery rates (per aspiration) were as expected higher than fresh, but substantially so in North America (53.5% vs 32.6%).

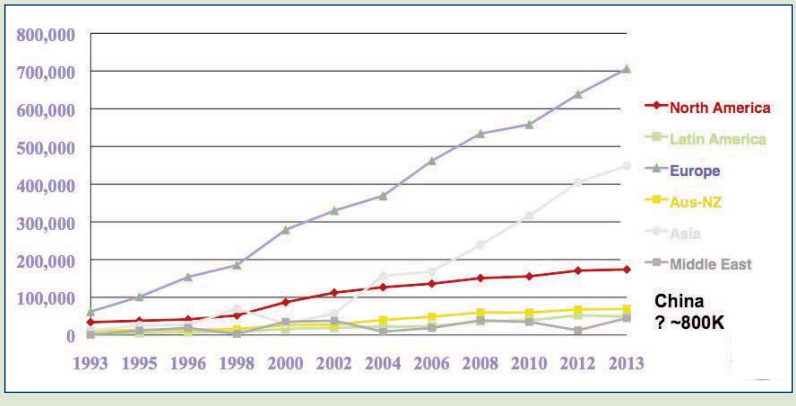
The proportional transfer of one or two embryos was in 2013 at or above 80% in North America, Europe, Asia and Australia/New Zealand (where the proportion was 100%), with a marked changing global trend from 1998.

Estimating the full picture from the recorded data, Adamson projected 2.4 million cycles performed in the year, up to 530,000 babies born and an overall cumulative delivery rate of 27.4%.

Notably, more than one-quarter of the women treated in 2013 were over the age of 40 and the mean number of transferred embryos was 1.81. Freeze-all protocols were 'an issue' for registry analysis, which in the European EIM data for 2014 accounted for around 6% of all reported cycles.



Fresh and cumulative delivery rates (per aspiration) by region 2013.



Growth of ART cycles per region 1993-2013.

Gene editing corrects mutation in human embryos

Report said to have taken germline editing 'further than ever before' in humans

An international group of scientists led by Shoukhrat Mitalipov of Oregon Health and Science University, USA (pictured left), has successfully changed the DNA of a large number of one-cell human embryos with the CRISPR-Cas9 gene-editing technique.[1] The researchers targeted a mutation in a gene called MYBPC3 known to cause hypertrophic cardiomyopathy, the leading cause of sudden death in young athletes.

According to the report, eggs were fertilised for the experiment using the donor sperm of men carrying this dominant mutation. The genetic correction was applied at the same time as the eggs were fertilised and before embryonic development. The report makes clear that the fertilised eggs were never intended for transfer.

There have been earlier reports – from China - of germline editing in human embryos, but these experiments appear to have been compromised by editing errors and mosaic response. The latest experiments are said to have 'significantly reduced mosaicism' and to have taken germline editing in humans further than ever before.

The widely publicised report on germline editing from the US National Academies of Science, Engineering, and Medicine in February - and summarised by Robin Lovell-Badge at an invited session of this year's Annual Meeting in Geneva - gave cautious support for the CRISPR-Cas9 technique, but subject to strict oversight and only in research.

Commenting on behalf of ESHRE's SIG Stem Cells, Cristina Eguizabal describes the report as 'a major milestone in the field of gene editing' and adds: 'Importantly, the researchers addressed several steps to improve the precision , but these results have to be confirmed by other laboratories.

'To date, the CRISPR-Cas9 technology used in embryos and pluripotent stem cells has frequently generated mosaics by repairing the mutation in some cells but also by introducing a high rate of unwanted genetic changes (known as off-target mutations) or extra mutations in the targeted gene (non-homologous repair).

'However, Mitalipov's team considerably improved on previous efforts by injecting the CRISPR-Cas9 components together with the patient sperm directly into normal MII oocytes. Until now, the Cas9 complex has been injected directly into the zygote. Remarkably, they now found high efficiency of homologous-repair, no evidence of off-target genetic changes, and only a single mosaic generated in an experiment involving 58 human embryos.

'Interestingly, and in contrast to human

Sperm counts: 'The canary in the coalmine'

It's rare for a paper from *Human Reproduction Update* to make the headlines. But that was the case this summer when a huge systematic review found 'a significant decline in sperm counts between 1973 and 2011'.[1] The finding also came with a public health warning, that such declines might be considered as 'the canary in the coalmine', with catastrophic implications beyond fertility for male health.

The meta-analysis included more than 40,000 men whose semen samples were screened in 244 studies within the study period. Declines in sperm concentration and total sperm count fell significantly - 'driven by a 50–60% decline among men unselected by fertility from North America, Europe, Australia and New Zealand'. The decline in sperm concentration was put at -1.4% per year and in total sperm count at -1.6% per year. These findings, the authors report, remained unchanged after controlling for such variables as age, abstinence, method of collection and methods of screening. Moreover, there was no sign of any levelling off when analyses were restricted to studies with sample collection in 1996–2011.

The results were so significant that the authors said research on the cause of the decline was 'urgently needed'. The findings imply 'that an increasing proportion of men have sperm counts below any given threshold for sub-fertility or infertility'. Sperm concentration below 40 million/ml, they add, is 'particularly concerning'.

They further add that this decline in sperm count is consistent with other male health indicators, such as cryptorchidism, testicular tumours and testosterone levels.

1. Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. Hum Reprod Update 2017; doi:10.1093/humupd/dmx022

pluripotent stem cells, the authors demonstrate that the genetic repair preferentially relied on the wild-type maternal copy of the gene and not on the template introduced for repair by the researchers.

'This may suggest that the DNA repair mechanism in early embryos differs from that in stem cells. However, in this case only one gene copy needed to be targeted for editing (heterozygous mutation), while in several other diseases both the maternal and paternal gene copy will be mutated (homozygous mutation). In this situation, no wild-type allele is available as template, hence further adjustments to the technique will be required for the genetic repair to rely on the use of the introduced template.

'Investigating applicability for targeting other gene mutations, increasing efficiency of homology-directed repair, abolishing mosaicism and defining with certainty whether off-target effects do occur in such contexts will now be imperative for future clinical applications. Moreover, correcting a gene mutation in the oocyte may pose more challenges than found in the sperm.

'However, this medical breakthrough is undoubtedly an immense step forward, launching an exciting, yet controversial era in medicine.'

The study reported in *Nature* thus represents a significant improvement in efficiency and accuracy over previous efforts. Of the 58 human embryos fertilised with sperm carrying the MYBPC3 mutation, 42 were successfully edited to contain two normal copies of the MYBPC3 gene.

The CRISPR-Cas9 technology has already been described as relatively straightforward and efficient to use, and emphasis will inevitably shift from technique to ethical considerations, and particularly any off-target effects or enhancement of any traits. Nevertheless, a commentary in *Nature* said the study 'is paving the way . . . that might lead to CRISPR–Cas9 reaching the clinic in the future. Until then, embryo genetic testing during IVF remains the standard way to prevent the transmission of inherited diseases in human embryos.'

1. Ma H, Marti-Gutierrez N, Park S-W, et al. Correction of a pathogenic gene mutation in human embryos. Nature 2017; doi: 10.1038/nature23305.

Three in four women starting fertility treatment will deliver in five years

● Large population study provides basis for reliable long-term prediction at the outset of treatment

Three in four women starting fertility treatment will have a baby within five years, whether as a result of the treatment or following natural conception. The results have emerged from a large cohort study analysing the birth records of almost 20,000 women having fertility treatment in Denmark between 2007 and 2010. The majority of these women (57%) had their baby as a result of the treatment, but a significant proportion (14%) conceived spontaneously without treatment. More than half (57%) gave birth within two years.

Results showed that within five years 65% of women aged 35 years and under had had a baby because of treatment, 49% of women aged 40 and under, and 16% of women over 40.[1] Additionally, in these same three age groups 16%, 11% and 10% delivered after natural conception, yielding total five-year birth rates of 80%, 60% and 26%.

The study - as so many in Denmark are - was a cross-link between the national ART registry and the medical birth registry. Treatments comprised ART - of which three fresh cycles are generously reimbursed in Denmark - and IUI, first-line in unexplained infertility and also reimbursed.

Results also showed as expected that female age was the most important factor to predict outcome, with total live birth rates declining over five years from 80% in under 35s to 26% in women over 40.

Looking at specific treatments, 35% of women starting with IUI delivered within five years, 24% after switching to ART, and 17% after natural conception. Similarly, 53% had delivered within five years of starting ART, and 11% delivered after natural conception. The investigators thus concluded that 'IUI may be a feasible first-line option' for couples with idiopathic or mild male factor infertility.

More generally, the results provide a realistic prognosis of success for all couples embarking on fertility treatment, with age-stratified outcomes. 'Infertility patients have two key questions,' first author Sara Malchau said when preliminary results were reported last year in Helsinki. 'What are our chances of having a baby, and when will it happen. These results help us provide realistic information based on their age and chance of natural conception.'

Malchau added: 'Overall, chances of a live birth are good, but successful treatment takes time. Couples will often need several treatment cycles. And even though the greatest chance of conception is following treatment, there is still a reasonable chance of spontaneous conception.'

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First author Sara Malchau: 'Infertility patients have two key questions. What are our chances of having a baby, and when will it happen.'

Online data collection up and running

20 years of the PGD Consortium to be marked in December

With one of the major mission statements of the Consortium to collect data on PGD/PGS services, we have worked hard to catch up with our annual collections. Data collections XIV and XV (over 2011-12) have been combined in one manuscript, which has been accepted for publication. The main trend observed is the increased application of array technology at the cost of FISH in PGS cycles (up from 4 to 20%) and in PGD cycles for chromosomal abnormalities (from 6 to 13%). Biopsy at the blastocyst stage was still limited in 2011-2012.

Data collections XIV-XV are the last datasets collected via the Filemaker Pro system. This database developed in 1997 by Céline Moutou has served the Consortium for over 15 years and yielded publications of 14 retrospective datasets plus an overview of the first 10 years. The system was quite user-friendly, but is no longer fit for purpose. PGD/PGS services have evolved quickly over recent years and we found an increasing amount of inconsistent and incomplete data, which made curation quite labour intensive. Thus, as the Filemaker Pro database was stopped and a new one still in development, we agreed to report summary data for 2013-2015 to minimise workload and still capture overall data. A manuscript with these summary data is foreseen at the end of 2017.

As a supplement to these summary data and with the intention to monitor trends on various PGD/PGS aspects, an additional survey was conducted. Data were collected from ESHRE PGD Consortium members at the end of 2013 using questionnaires and a second data collection was carried out two years later. A clear tendency from these data is that the uptake of new genome-wide genetic testing technologies accompanied a switch to trophectoderm biopsy and vitrification and this trend is most advanced with PGS.

The current PGD Consortium Steering Committee includes, from left, Filipa Carvalho, Veerle Goossens (ESHRE science manager), Carmen Rubio, Céline Moutou, Edith Coonen (Past Chair), Martine De Rycke (Chair), Madelon Meyer-Hoogeveen and Georgia Kakourou (Chair SIG Reproductive Genetics).

Online data collection

Finally, a new online platform was launched last June, permitting prospective data collection. The system differs from the cycle-based Filemaker Pro database as the central module is 'analysis' with links to modules of oocyte retrieval, biopsy, transfer and follow-up. These links are flexible and allow for instance to combine two cohorts of retrieved oocytes with one biopsy event, which is then linked to analysis, cryopreservation and outcome of each transferred embryo. Overall feedback on the database has been quite positive. A number of small problems have already been solved, others may take some time.

The next challenging step is designing a powerful query module for annual data reporting and specific research questions. The Steering Committee asked members to submit data on the new platform from 2016 onwards; they are very aware that data submission remains a lot of work and wish to thank all centres for their engagement. We hope the new online platform will also attract new members to join the Consortium; they are most welcome.

The 20th anniversary of the founding of the PGD Consortium will be marked by a Campus symposium in December

Educational activities

Another major mission statement of the Consortium is education. Last December, an interactive webinar on trophectoderm biopsy was hosted by Georgia Kokkali in which over 300 participants took part. As this was a very successful webinar, we intend to put the theory into practice and organise next year a hands-on Campus event for trophectoderm biopsy and vitrification in collaboration with the SIG Embryology. Another hands-on Campus event would focus on SNP array for monogenic disorders, including handling de novo mutations. And another ESHRE Campus organised by the SIG Reproductive Genetics on **Current approaches in genetics and reproduction** is planned for

Geneva PGD Consortium report: trends in biopsy, technique and outcome

Data collection by the ESHRE PGD Consortium has undergone a complete revision during the past few years. This has not just been marked by progress from a manual record to a new more efficient online platform, but also the introduction of prospective data collection.

The Consortium's Chair, Martine De Rycke, explained in Geneva that all data collection from 1997 (when the Consortium was founded) to 2012 was retrospective and based on cycles; this met the original aims to survey the availability and application of PGD for different conditions. From this year, however, with the introduction of the new online system, data collection is prospective and based on analysis, not cycles. So far, said Martine, 46 of the Consortium's 121 members had used the new database.

This hiatus in the Consortium's data collection meant that the traditional annual reports were replaced by summary data (for 2013-15) and findings from a member survey designed to track trends as new technologies were introduced.

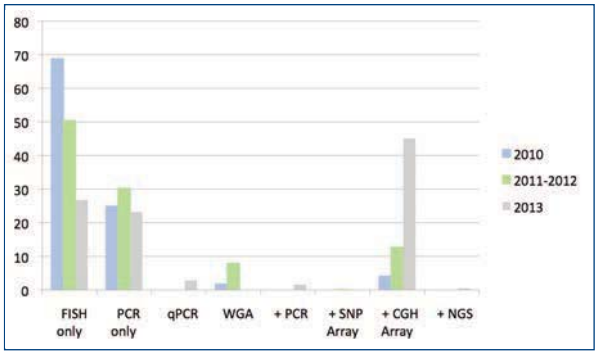
The annual and summary data showed that by 2015 almost all centres were performing their biopsies by laser and the majority (by 2013) at the cleavage stage (70%) for PGD and PGS. Most biopsies performed at the blastocyst stage in 2013 were for PGS.

How was the testing done? The use of PCR for cases of PGD for monogenic disorders was quite constant until 2015, but for chromosomal aberrations there was a decline in FISH between 2013 and 2015 (from 27% to 12%) and an increase in array CGH - and in 2015 a very slight introduction of NGS. Testing for aneuploidy was dominated by array CGH throughout this time, with just a moderate (10%) use of qPCR and NGS in 2015.

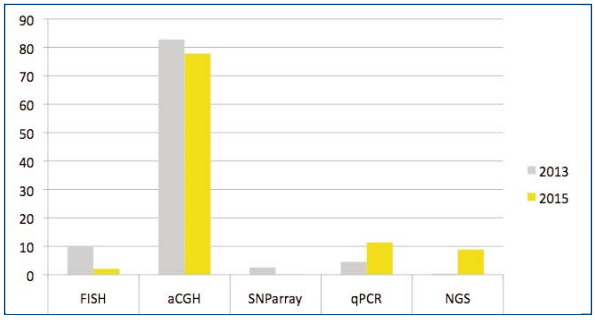
Martine De Rycke presenting her Consortium review in Geneva.

The available data also show that nearly all PGD/PGS cases were successfully biopsied and diagnosed in 2010 through to 2013, with just around 30% transferrable and 20% transferred, yielding a delivery rate (per ET) of about 25% in 2010-12 and 36% in 2013. This improved outcome was also observed in the summary data of 2014-2015. The switch to blastocyst biopsy and concurrent uptake of genome-wide testing is likely to account for an improvement from 2013 onwards.

A report on the data collections for 2011 (collection XIV) and for 2012 (collection XV) has now been accepted for publication.



Analysis method of all Consortium cycles 2011-2013. The majority of the array CGH techniques were for PGS.



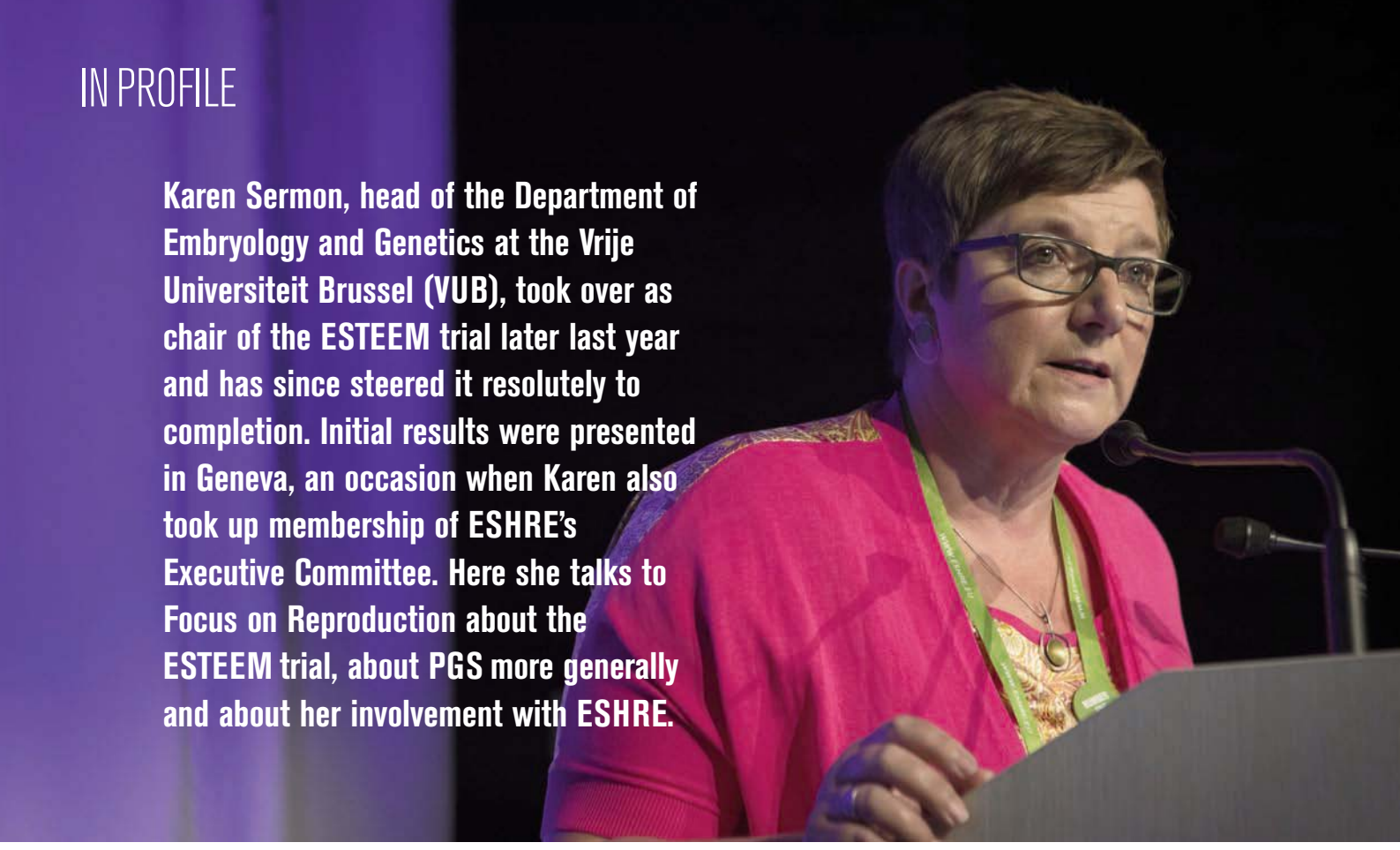
PGS analysis methods 2013-2015.

26-28 April 2018 in Sofia. This will concentrate on the latest technical developments in PGD and PGS, as well as embryo selection and child follow-up.

With respect to forthcoming educational activities in 2017, a very special event on **PGD and PGS: past, present and future** will take place in Brussels on 8-9 December and has been organised as a celebration of 20 years of the PGD Consortium. Speakers invited (see ESHRE website) have a longstanding expertise in the field, so we will look back to the early days from the perspectives of counselling, biopsy and technologies and ahead to what the future holds for PGD and PGS. We hope to meet friends from many centres during this wonderful occasion.

Martine De Rycke
Chair PGD Consortium

● Georgia Kokkali comments on troubleshooting questions raised by her TE biopsy webinar on page 40.



Karen Sermon, head of the Department of Embryology and Genetics at the Vrije Universiteit Brussel (VUB), took over as chair of the ESTEEM trial later last year and has since steered it resolutely to completion. Initial results were presented in Geneva, an occasion when Karen also took up membership of ESHRE's Executive Committee. Here she talks to Focus on Reproduction about the ESTEEM trial, about PGS more generally and about her involvement with ESHRE.

Held in high ESTEEM

'When you have a cohort of embryos, there's no way you can improve them.'

FoR: Karen, you're Head of the Department of Embryology and Genetics at the Vrije Universiteit Brussel - VUB - and I gather it's here where you also did your training?
KS: Yes, when I started thinking about medical school I wanted to be a gynaecologist. But then, while I was in medical school my grandfather died of cancer and that made me change my mind to think more about research. So at the end of my medical training at the VUB I still wanted to go into research and spoke to Inge Liebaers, and there too was her husband André Van Steirteghem and the prospect of reproductive genetics. After my PhD, I went into the clinic and did a lot of hands-on PGD - and because we had embryos from PGD cycles available for research André suggested we start using these embryos for embryonic stem cell lines carrying natural monogenic diseases. So stem cells have become one of my other side lines.

And today do you do any hands-on work?
It's all research - stem cells and still work on chromosomal abnormalities in embryos.

So it's a big lab that you have at the VUB?
No it's not huge, but there are several labs with overlapping interests. The PGD clinic is a collaboration between the Centre for Medical Genetics and the Centre for Reproductive Medicine at the UZ Brussel, which is the university hospital of the VUB. The programme is big - and I work very closely with them. But we are independent - we belong to the university.

What's your main work now?
Mostly stem cells, but there's still a core of embryology. In this last stretch of my career I'd like to go back to embryology.

You were Co-ordinator of ESHRE's Special Interest Group for stem cells from 2010 so had a chance to look at it from a distance. Don't you think progress has been somewhat disappointing?
No, no. I think it's getting there. We already have success stories in macular degeneration, diabetes, spinal cord injury.

So you are optimistic that stem cells really will provide a cure for many diseases?
Yes. The thing is, when using embryonic stem cells or iPSCs for regenerative medicine you need perfect differentiation protocols. You need to be able to make useful cells from your stem cells. And now we are moving towards those protocols which are very efficient, high yielding, and safe, with specific differentiation.

But I guess your recent thoughts have been in embryology and completion of the ESTEEM trial, for which you were

chair of the steering committee. What were your thoughts about the results?
I think they were completely in line with expectations. When you have a cohort of embryos, there's no way you can improve them. One of them might become a baby - so you can transfer them one by one or try to figure out a selection method. And of course there are other important considerations - about the uterus, for example.

Unlike the 2007 Amsterdam trial, ESTEEM didn't show harm from aneuploidy testing.
I think this may be because we chose to remove polar bodies and not embryonic cells. Polar bodies are a by-product, expendable.

Are you saying that there might have been an adverse effect with removing a cell?
Well, when we started PGD we believed that the biopsy would not harm the embryo - the best ones will survive anyway. But PGS is different. These are infertile couples.

And progress in PGD? It's 20 years now since ESHRE formed the PGD Consortium.
Yes, again much progress - in both PGD and PGS. I still have my PGD notebooks from the beginning and it's remarkable how we dared to make a diagnosis on the information we had. That's why in Brussels we removed two cells, to validate the diagnosis. But when you look at how accurate the diagnosis has become now . . .

And today there's really no monogenic disease you can't test for?
That's true, so long as you know what the gene is. There are still many diseases where we haven't identified the gene.

I suppose one could say that PGS has got nowhere in 20 years. As you just said, you can't improve the quality of an egg or an embryo. If it's normal and healthy it will probably implant and become a pregnancy; if it's not, it will fail to implant or miscarry. And that's taken 20 years to understand?
I think many people have understood that from the beginning, but it's taken 20 years to prove it. It is what it is. There are people, especially in the US, for whom this is a business.

So ESTEEM won't be the last word in PGS?
No, because everyone is now looking at the secondary outcomes. They're moving to the secondary measures - miscarriage rate, useless transfers, implantation rate. These may be good reasons to do PGS, but we should know for whom. ESTEEM was strictly in advanced maternal age, so we shouldn't extend the results to implantation failure.

But do you think clinics will still promote PGS on the back of delivery rates?
Yes. We didn't have the full implantation rates in Geneva, but it was clear that they were better in the PGS group. And it's implantation rates that clinics show on their websites.

So clinics are making an assumption that improved implantation rate means improved pregnancy rate?
No, they're not directly making that assumption, but I think they don't discourage their patients from making it.

So despite ESTEEM, I'm sure it's a debate that's not yet over. Something a bit more certain is that you have just become a member of ESHRE's Executive Committee. You've always worked with ESHRE?
Yes, I've always been involved with ESHRE. I was a founder member of the PGD Consortium and was its chair from 1998 to 2006. And I've also been co-ordinator of the Stem Cell and Reproductive Genetics SIGs. So it was no surprise to be asked about the ExCo, indeed a great honour, because I'm now the only representative of Belgium.

Where do you see the Society now? Membership at an all-time high, more than 10,000 at the Annual Meeting, financially strong. It seems remarkably successful?
When I look around I see a lot of mature members. So where I think the Society should really invest is in attracting young people, young scientists, because people like me all started when we were very young. I was fresh out of medical school the first time I came to an ESHRE meeting, and I miss that a little bit now. I know ESHRE is trying to attract young people again, and I think that's right.

How can ESHRE do that? There's no magic bullet.
It's a big challenge. Travel grants are important, because many young scientists don't have the financial means to attend workshops and the bigger meetings. Many tell me that they don't feel comfortable at a big meeting. But we have to recognise that ESHRE is now a big and successful society. Attracting young members is just one of many priorities which demand an adaptable management structure. It's not like some huge tanker which can't change direction. But we do have to think more like a big business now, to deal properly with the budgets and with the members.

PROUST QUESTIONNAIRE*

- **What's your idea of perfect happiness?**
Sitting down after a long walk and a first sip of that tasty Belgian beer

- **Your greatest fear?**
To lose my home, husband and family

- **What's the trait you most deplore in yourself?**
Laziness

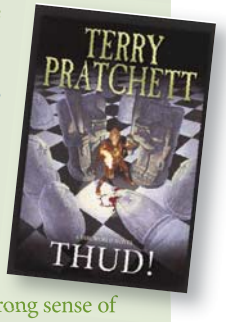
- **And in others?**
Rudeness trying to pass for honesty

- **Which living person do you most admire?**
Michelle Obama

- **What's your greatest extravagance?**
The jacuzzi in my garden

- **Which words do you most overuse?**
'But', as if making an excuse for what I say

- **What is your favorite pastime?**
Reading fantasy and science fiction



- **The last novel you read?**
Thud! by Terry Pratchett

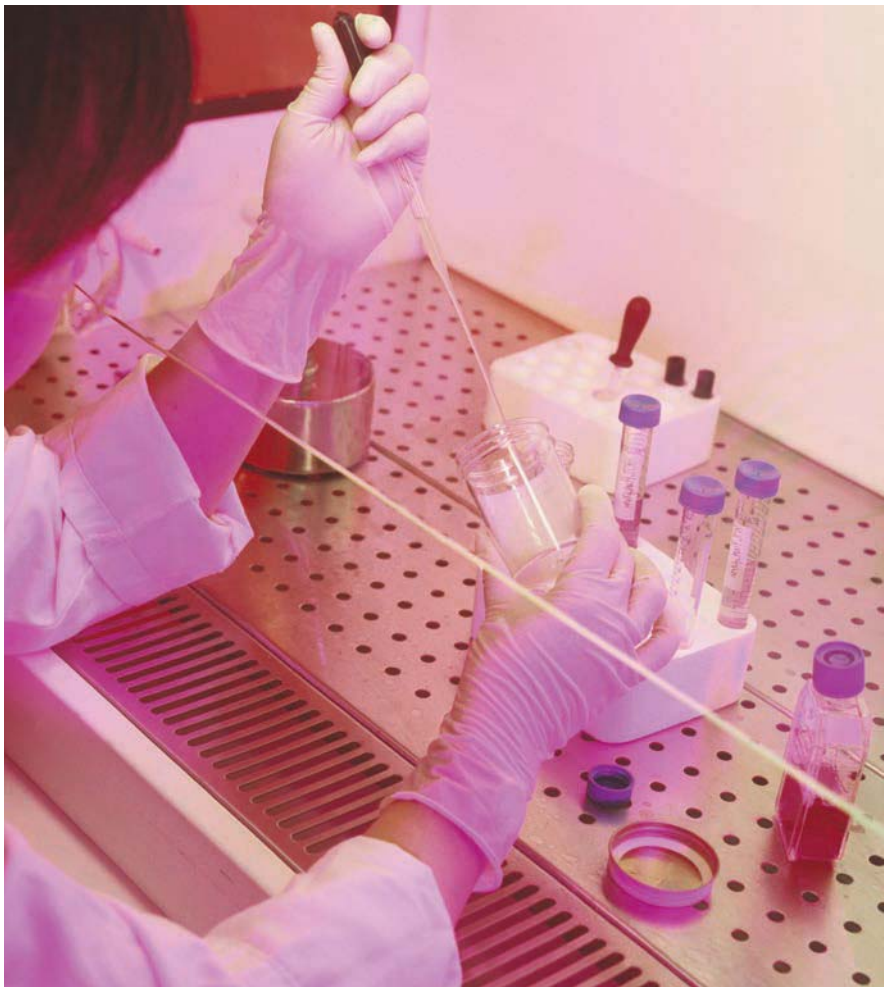
- **And the last film you saw?**
Whiskey Tango Foxtrot with Tina Fey, one of those combative women with a strong sense of humour I admire so much

- **If not Belgium, where would you prefer to live?**
My skin doesn't agree with the sun, and I get depressed with the rain, so Belgium it is

- **Where did you spend your latest vacation?**
The Scottish Highlands

- **Champagne or Belgian beer?**
A tough one, but Belgian beer in the end

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



Unexplained infertility

Diagnostic dilemmas and debatable decisions

As many as one-third of couples receive no clear explanation for their infertility - and their course of treatment is similarly far from clear. Roy Homburg makes a strong case for IUI with ovarian stimulation as first-line treatment in couples with a favourable prognosis. Yet this approach was rejected in the NICE guidelines of 2013, in favour of expectant management and IVF. That view has been challenged, most recentley by new data presented in Geneva at ESHRE 2017.

Treating infertility can be a very rewarding but sometimes very frustrating exercise. It is probably more worrying for the infertile couple to be told that we do not know the cause of their problem than actually identifying the problem. However, the term 'unexplained' or idiopathic infertility is not only an admission that we do not know the cause of the infertility but also that the couple may not be infertile at all.

The most acceptable definition of this situation is one to three years of attempting conception when routine tests for ovulation, tubal patency and sperm quality are all normal. These tests are far from fool-proof, however, and are but rough guides to fertility competence; the number of spontaneously conceived pregnancies following even two years of unexplained infertility bear witness to this fact. A diagnostic laparoscopy would arguably improve the chances of making an accurate diagnosis, but few are the clinics that include it as a routine procedure.

Expectant management, a euphemism for doing nothing, may frequently be successful but, depending on cultural differences, few couples when told that no intervention is necessary will be content with this judgement, especially after a year or more of unprotected regular intercourse. Thus, the idea of restricting an expectant approach to couples with less than two years' infertility and a female partner under the age of 35, especially those with a previous pregnancy, would seem to be the most sensible approach. Conversely, couples with more than three years' infertility and with a female partner of over the age of 35 years would demand intervention.

Up to 30% of all couples presenting with infertility after one year will be 'diagnosed' with 'unexplained infertility'. The number of interventions (or lack of intervention) proposed to solve the problem for these couples is large. But in my view, this basically comes down to three options: expectant management, IUI with mild gonadotrophin or clomiphene citrate (CC) stimulation of ovulation, or IVF/ICSI.

IUI, CC or gonadotrophin stimulation

as individual treatments are little more effective than expectant management. Even the combination of CC stimulation and IUI so far reported has produced disappointing results but a presentation at this year's ESHRE Annual Meeting disputes this.[1] In a large randomised study of 738 couples with an unfavourable prognosis, four cycles of IUI + FSH did not prove superior to four cycles of IUI + CC, with 31% and 26% ongoing pregnancies respectively.

For couples arriving one way or another at the stage of IVF, should we be doing conventional IVF or ICSI? Although ICSI understandably reduces the rate of total failed fertilisation compared with conventional IVF, there is no evidence that 'blanket' ICSI improves pregnancy or live birth rates.

When the female partner is ovulating and the sperm is apparently normal, the choice of IUI with ovarian stimulation seems completely paradoxical. The thinking behind ovarian stimulation to produce more than one ovulation and selecting the most progressively motile sperm from a washed sample is that hormonal stimulation, as well as increasing the number of ovulations, may also improve the uterine environment and endometrial receptivity. In addition, the selection of the best sperm introduced nearer the egg would seem to shorten the sperms' journey and negate any problems with the cervical mucous. Personally, I suspect that the ability to time insemination more accurately than with normal sexual intercourse accounts not a little for any success.

When to intervene?

A vexing question is at what stage should we intervene. My own temptation has always been that one year of unexplained infertility is enough. However, and not for the first time, personal experience is not always in agreement with the literature. The sensible approach is to classify the individual case particularly according to the duration of infertility and the age of the female partner before deciding on the approach to treatment. For example, for those with less than two years' infertility and a female partner under the age of 35, there is apparently a similar chance of pregnancy with or without IUI or IVF.[2,3] Indeed, when comparing results in those couples with a favourable prognosis, intervention within six months after finalising the work-up produced the same number of ongoing pregnancies within both six and 12 months as expectant management.[4] For those with a poorer prognosis (more than three years' infertility and over 35 years old) one cycle of IVF with elective single embryo transfer produced the same number of ongoing pregnancies (24%) as three cycles of IUI with controlled ovarian hyperstimulation (21%).[5]

Roy Homburg: 'The obvious conclusions would seem to be that we are over-using IVF to treat unexplained infertility'

First-line treatment?

The evidence available so far on the best first-line management for couples with unexplained subfertility is inconsistent, controversial and differs considerably in the study design. Because of the clinical heterogeneity among existing trials, the effectiveness of IVF remains inconclusive.

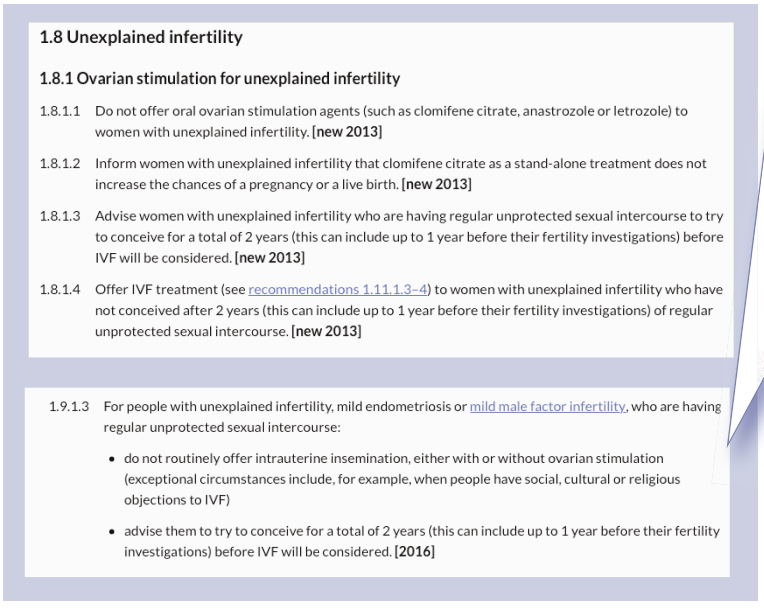
Our own study randomised more than 200 couples with unexplained infertility to receive up to three cycles of IUI with mild gonadotrophin stimulation or one cycle of IVF.[6] There was no significant difference between the live birth rate with IUI + COH (28.7%) and IVF (33.9%).

An ad hoc cost analysis using per protocol results revealed that per live birth the cost ratio of IUI/IVF (1:1.3) was higher for one cycle of IVF than for three cycles of IUI. Notably, there were 17 live births following spontaneous conception in between cycles, again emphasising the frailty of the label of unexplained infertility.

These results were preceded by a massive RCT from the Netherlands demonstrating that in couples with an unfavourable prognosis three cycles of IVF-SET, six cycles of IVF in so-called modified natural cycles and six cycles of IUI-COH all gave a similar rate of live birth (52%, 43% and 47% respectively), with no difference in multiple birth rates.[7]

The reported outcome of live births or ongoing pregnancies from IUI + ovarian stimulation described here, ranging from 27% to 47%, would seem to challenge the National Institute for Health and Care Excellence (NICE) guidelines in the UK, whose recommendation, unchanged since 2012, was that failed expectant management for up to two years should be treated directly by IVF. By completely excluding IUI, NICE was denying up to 47% of unexplained infertility couples a live birth from a treatment that is less invasive, less complicated and less expensive than IVF. Indeed, in one study the cost necessary to achieve one additional healthy child using IVF-SET compared with IUI-COH was €43,375.[8]

Fortunately, in surveys performed in the UK only 16% of practitioners recommend IVF as first-line treatment and 96% of fertility clinics continued to offer IUI - despite the NICE recommendations.[9,10] Unfortunately, however, many funding groups in the UK immediately jumped on the bandwagon following the NICE decision, cancelling funding for IUI and



1.8 Unexplained infertility

1.8.1 Ovarian stimulation for unexplained infertility

1.8.1.1 Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole or letrozole) to women with unexplained infertility. **[new 2013]**

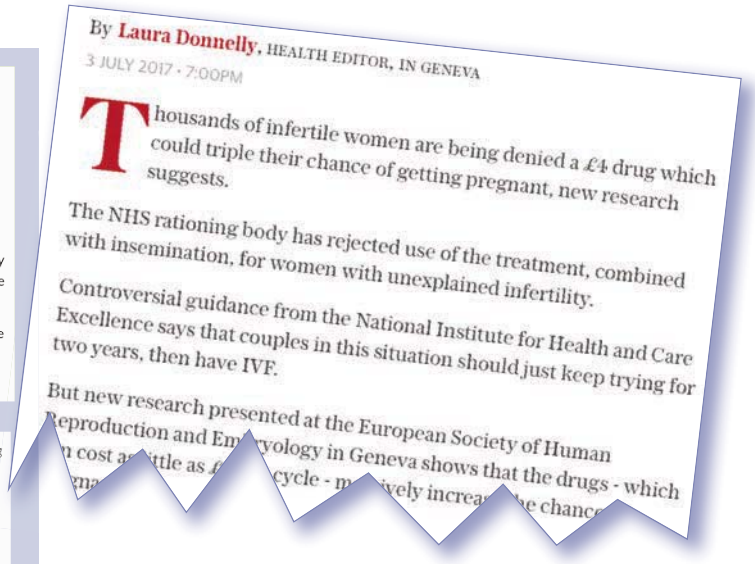
1.8.1.2 Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. **[new 2013]**

1.8.1.3 Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[new 2013]**

1.8.1.4 Offer IVF treatment (see recommendations 1.11.1.3–4) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. **[new 2013]**

1.9.1.3 For people with unexplained infertility, mild endometriosis or mild male factor infertility, who are having regular unprotected sexual intercourse:

- do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF)
- advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. **[2016]**



By **Laura Donnelly**, HEALTH EDITOR, IN GENEVA

3 JULY 2017 • 7:00PM

Thousands of infertile women are being denied a £4 drug which could triple their chance of getting pregnant, new research suggests.

The NHS rationing body has rejected use of the treatment, combined with insemination, for women with unexplained infertility.

Controversial guidance from the National Institute for Health and Care Excellence says that couples in this situation should just keep trying for two years, then have IVF.

But new research presented at the European Society of Human Reproduction and Em[bryo]logy in Geneva shows that the drugs - which [can] cost a[s] little as £[4] [per] cycle - m[ore] effectively increa[se] the chanc[es]

The NICE guidelines of 2013 advised that first-line treatment for unexplained infertility should be expectant management for two years followed by IVF. IUI was not recommended. UK journalists covering ESHRE's Annual Meeting this year followed up data presented by Farquhar et al (that LBRs were three times higher with IUI than with expectant management) and were told by the NICE press office that NICE planned to update their guidance in light of this latest research. 'This new paper will be considered as part of that update,' NICE told the Daily Telegraph (above).

forcing many patients to pay for treatments which were previously funded by the NHS. The alternative to paying for IUI is to proceed directly to IVF/ICSI, which may be described by some as using a sledge hammer to crack a nut.

The final nail in the coffin for the NICE guideline recommendations must surely be the randomised controlled trial presented by Cindy Farquhar at ESHRE this year. In this trial 201 couples with 3-4 years unexplained infertility were randomised to receive three cycles of IUI or expectant management. The bottom line was a live birth rate of 31% with IUI and 9% with expectant management, a three-fold difference in outcome.

The obvious conclusions would seem to be that we are over-using IVF to treat unexplained infertility. With correctly selected patients from those who failed to conceive with expectant management, IUI with ovarian stimulation is more cost effective and less invasive than IVF.

Professor Roy Homburg is Head of Research, Homerton Fertility Centre, Homerton University Hospital in London.

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● ESHRE will host a Campus workshop on the evidence base for IUI on 23-25 November in Antwerp.

'Capri, c'est fini . . . ' (pas encore)

ESHRE workshops on the island of Capri have been held annually since 1986. Subjects are always topical and controversial, and publication of proceedings always well cited. Hans Evers looks back over their history.

Capri, c'est fini,
Et dire que c'était la ville
De mon premier amour.
Capri, c'est fini,
Je ne crois pas
Que j'y retournerai un jour.

Hervé Vilard is a French singer who became instantaneously famous with his first song *Capri c'est fini* in 1965. The record has sold 3.3 million copies and as a live performer Vilard has announced at the last count (2017) Capri to be fini for 13,523 times. And he is still going strong. As does Capri.

So it's no wonder that Pier Giorgio Crosignani in 1985 arranged to organise ESHRE's first Capri workshop on the island of Augustus, Tiberius, Suetonius, Limoncello, Friedrich Alfred Krupp, Emil von Behring, Axel Munthe and Maxim Gorky.

His idea was to bring a group of experts together in a remote, inaccessible spot (sober lodgings, simple meals), and – over two days – discuss controversial clinical issues in a bid to reach consensus, formulate clinical guidance and publish the results in the Society's journal, *Human Reproduction*. Please remember that Gene Glass had coined the term 'meta-analysis' only a few years before.

Pier Giorgio Crosignani, Chairman of ESHRE from 1989 to 1991 and instigator of the Capri workshops.

Since 1995, for logistic reasons, two back-to-back meetings have been organised, leading to the production of two series of manuscripts, one always in the area of contraception-menopause, the other in fertility-reproduction.

The ESHRE Capri workshop group adopted a rigorous working strategy: extended abstracts were prepared (and evaluated by all participants) well before the meeting; critical appraisal of the most robust scientific information was presented and discussed at the meeting; high quality clinical guidance manuscripts were published in the ESHRE journal – later the ESHRE journals – under the collaborative authorship of the 'ESHRE Capri Workshop Group', a brand name meanwhile recognised and well appreciated by the scientific community.

The meetings have always been supported by generous unrestricted educational grants from pharmaceutical companies, first Schering, later Ferring. More recently IBSA has agreed to sponsor both events.

Over the years, the ESHRE Capri workshop has published 17 papers in *Human Reproduction* and 25 in *Human Reproduction Update*. In 2017, ESHRE

Continued over page

A new SIG for nurses and midwives

With plans in place to disband the Paramedical Group in 2019 and devolve its interests to the SIGs, ESHRE has announced the formation of a new SIG for nursing and midwifery. The SIG will be open to all ESHRE members who have an interest in nursing and midwifery in reproductive medicine. Other ESHRE SIGs, notably Embryology, Andrology and SQART, are likely to provide popular interests for paramedics.

The new SIG will provide education in the form of Campus and precongress courses and will have a close working relationship with the ESHRE Nurse and Midwifery Certification committee.

In addition, the SIG Nursing & Midwifery hopes to stimulate discussion between all nurses and midwives working in the field and promote research to provide evidence for treatments and care carried out in daily clinical practice.

We are looking for a junior member to join the SIG Nursing & Midwifery. If you are a nurse or midwife under 35 and have been an ESHRE member for two years then please send us a message to info@eshre.eu.

Co-ordinator of the Steering Committee will be Eline Dancet, a fertility midwife now working as a post-doc in Leuven and Amsterdam, with Annick Gerril and Valerie Blanchet De Mouzon as Deputies. All have been active in the Paramedical Board, whose new Chair, Cecilia Westin, will represent all paramedics on the ESHRE Executive Committee from 2017 to 2019.

After a successful congress for the Paramedical Group, whose debate on PGS was thought the highlight of Geneva by many, Past Chair Helen Kendrew presents the Nurses Award to Sarah Bailey for her presentation on recurrent miscarriage.

ESHRE Capri workshops Continued from previous page

announced that the latest Impact Factor for *Human Reproduction* had risen to 5.020 and acknowledged the contribution of the Capri papers to the journal's successes. All papers received excellent citation scores; the most frequently cited are listed in the box below.

Invitations to participants in the meeting are based on their academic expertise, and the group is supplemented by the (past) ESHRE chairmen, who from 2011 have also held their semi-annual business meeting in Capri between the two workshops.

The composition, structure and functions of the ESHRE Capri Workshop committees are as follows:

- The Programme Committee is charged with identification of the most urgent scientific topics to be discussed, selection of the two annual titles, selection of the expert speakers, preparation and publication of the two manuscripts, and diffusion of the new information after the meeting. The committee consists of the immediate Past Chairman of ESHRE, David Albertini (New York), David Baird (Edinburgh), Siladythia Bhattacharya (Aberdeen), Pier Giorgio Crosignani (Milano), Hans Evers (Maastricht), Anna Glasier (Edinburgh), Carlo La Vecchia (Milano), and Edgardo Somigliana (Milano). Two of the members are replaced every third year.
- The Budget Committee is charged with the preparation of the annual budget, the logistics of the workshop, and the invitation of speakers selected by the Programme Committee. This committee consists of Pier Giorgio Crosignani (Milano), Hans Evers (Maastricht), David Baird (Edinburgh), Anna Glasier (Edinburgh), and Edgardo Somigliana (Milano). One of the members is replaced every second year.

We hope to be able to sing the praise of the meeting as long and as frequently as Hervé Vilard has repeated that Capri is fini.

Capri workshop paper	Journal, year	n citations
Fertility and aging	Human Reproduction Update 2005	471
Multiple gestation	Human Reproduction 2000	279
Intrauterine insemination	Hum Reprod Update 2009	170
Diagnostic tests	Hum Reprod 2000	169
Nutrition and reproduction in women	Hum Reprod Update 2006	149
Intrauterine devices and systems	Hum Reprod Update 2008	139

Timelapse and morphokinetics highlight Geneva

Steering committee changes

As reported in the previous *FoR*, we said farewell and thank you to Maria José De los Santos as Past Co-ordinator and to Sophie Debrock as Deputy after many years of dedicated hard work. Giovanni Coticchio has now passed on the Co-ordinator's duties to me, Susanna Apter, although he continues to contribute significantly as Past Co-ordinator. We are happy that our former Junior Deputy, Debbie Montjean, has been appointed Deputy together with our new Deputy, Ioannis Sfontouris. Our new Junior Deputy is Mónica Marques. Roger Sturmey continues his outstanding work as our Basic Science Officer.

Especially noteworthy in the constitution of the Steering Committee is the enlargement of the committee for the upcoming two years. It has been decided by the ExCo of ESHRE that the Paramedical Group will dissolve in 2019. Many members of this group have a significant interest in embryology and we hope they will feel that the SIGE is a natural new home for them. To ensure a seamless transition, two present deputies from the paramedics, Leonie Van Den Hoven and Yves Guns, will also join the SIGE Steering Committee. We are certain this development will further strengthen our special interest group in the future.

Annual Meeting in Geneva

SIGE participation in the 33rd ESHRE Annual Meeting in Geneva started on Sunday with our preongress course on **Cellular and molecular biology for clinical embryologists**. Presentations were a reminder of how important key concepts of cellular and molecular biology influence gamete function and embryo development, through cell gamete interaction, cycle regulation, genetics and epigenetics, and biochemistry. It was a great start to the meeting, allowing us not only to learn from the remarkable speakers we were fortunate to attract, but also to network with them.

Timelapse technology and morphokinetics were the highlight of this year's oral presentations, although cryopreservation, embryo chromosomal/genetic status, and embryo culture conditions were also among a range of other subjects well represented. 'Novel ideas in embryology' as presented at the meeting were summarised in our *FoR* blog (https://focusonreproduction.eu/). Briefly, embryo morphology, mitochondrial/nuclear DNA ratio and kinetics were correlated to mosaicism/ploidy, implantation potential and sex ratio, respectively. There were also studies demonstrating the potential use of genomic analysis combined with timelapse to improve embryo selection. However, it was concluded that algorithms for timelapse and embryo selection still need to be improved.

The last session of selected oral communications on Tuesday considered some future non-invasive methodologies for embryo selection, such as media lipidomics. There was also given a very interesting lecture on the future use of artificial intelligence with mathematical variables for embryo grading and selection. On vitrification, semi-automated and conventional systems seem to have similar results for blastocysts, while embryos vitrified on day 6 have a lower live birth rate than those vitrified on day 5. Embryology sessions had a vast number of participants, which prompted dynamic discussion. Most of the talks from our sessions are available online (see 'Searchable programme with abstracts and webcasts' at https://www.eshre2017.eu/Programme.aspx).

Upcoming Campus events

We are pleased to remind you that in 2017 SIGE will host two more Campus courses. The first, **From gametes to blastocyst - a continuous dialogue**, is a popular course that has been arranged several times before. This time it will be held in Edinburgh on 12-14 October. It is organised in collaboration with the SIG Reproductive Genetics, with local input from Chris Barratt, Scott Nelson, and Siladitya Bhattacharya.

The second course, **Reproductive medicine between science and commercialization**, is organised together with Borut Kovačič, Veljko Vlaisavljević and other Slovenian colleagues. It is held in Ljubljana on 30 November-2 December. The course objective is to discuss safe and effective means to develop and introduce new laboratory and clinical methods.

As the new Co-ordinator of SIGE, I wish the new committee members a warm welcome and hope that we together can produce interesting and useful courses, workshops and consensus documents for our members. The SIGE has achieved a lot under the guidance of Giovanni Coticchio. I believe there are many important advances still to be done, and I look forward to completing at least a few of them during the next two years.

Susanna Apter
Co-ordinator SIG Embryology

Defining the limits of science and commercialisation

Geneva precongress course on transgenderism well received

Willianne Nelen stood down from the Steering Committee as Past Co-ordinator having participated in the SIG for many years. The steering committee sincerely thanks her for enthusiasm and managerial qualities, which undoubtedly will have a lasting impression on the current team. Arianna D'Angelo will now become past-coordinator and Kelly Tilleman the new SQART Co-ordinator. Alessandra Alteri was elected as Junior Deputy, and Zdravaka Veleva and Ioana Rugescu as Deputies. With Augusto Enrico Semprini as International Advisor and Daniela Nogueira as Basic Science Officer, the SIG SQART is ready for another two years of quality governance.

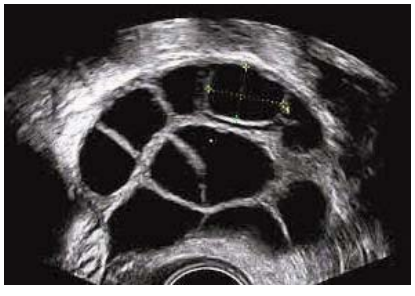
STEERING COMMITTEE

Kelly Tilleman (BE), Co-ordinator
Zdravaka Veleva (FI), Deputy
Ioana Rugescu (RO), Deputy
Alessandra Alteri (IT), Junior Deputy
Arianna D'Angelo (GB), Past Co-ordinator
Daniela Nogueira (FR), Basic Science Officer
Augusto Semprini (IT), International Officer

Precongress course Geneva

Our precongress course in collaboration with the SIGs Psychology & Counseling, Ethics & Law and Global and Socio-cultural Aspects of Infertility on **Transgenderism and reproduction: State of the art in fertility options for transgender and people with sex reassignment** was well received in Geneva. Transgender people are a very small patient group in our fertility centres, but nonetheless require a very specific patient-tailored approach. We learned in detail how cross-hormone therapy has a tremendous effect on fertility, so information on fertility preservation and future family building strategies are necessary for people seeking treatments. Terminology will be important: 'her ovaries', for example, or 'his sperm' are traditional gender-specific terms. A more gender-affirming or gender-neutral communication might be preferred by many patients. Training in communication for all caregivers could bring a more balanced and gender-friendly language to the consultation.

Access to care for this specific group was another theme of the course. Not all European countries allow fertility preservation or ART for transgenders.



Ultrasound in ART and early pregnancy. A theoretical Campus course in November with hands-on training.

Although huge steps have been made, we are not there yet. PDFs of the course presentations are now available on the ESHRE website - where you might also read our congress blog.

Upcoming events 2017

Our course in Cardiff on **Ultrasound in ART and early pregnancy: a blended training approach** will take place on 16-17 November 2017 and has been organised in collaboration with the SIGs Endometriosis & Endometrial Disorders, Implantation and Early Pregnancy, the Paramedical Group and the British Society of Gynaecological Imaging. This is not only a theoretical course, but will also provide practical hands-on training in ultrasound. The course will focus on controlled ovarian stimulation, the endometrium and implantation, ovarian and adnexal pathologies, interventional ultrasound, and the quality and safety aspects of ultrasound.

A week later - on 30 November-2 December in Ljubljana, Slovenia - we are considering **Reproductive medicine between science and commercialization**, a Campus meeting organised in collaboration with the SIG Embryology. The course will certainly be provocative and hope to draw the line where science in ART ends and commercialisation begins. Yes, we do have experimental and innovative ART treatments, because it's science which drives ART. But scientific research is expensive and trying to find funding from sources other than governments has shifted much research to the commercial sector. It is important to distinguish between experimental, innovative and established treatments in daily practice; compliance, regulation and transparency are key factors in this, and all will be discussed in Ljubljana.

Upcoming events 2018

Because of its huge success in Paris in 2016, our Campus course on female fertility preservation **Taking care for the future fertility of women cancer survivors** will be repeated in Tbilisi, Georgia, on 3-5 May 2018. We have enhanced the 2016 programme with more recent information, and the programme can be found on the ESHRE education web pages.

Together with the SIG Embryology we are now in the process of composing a Campus course on ICSI and micromanipulation which will take their basic principles to a higher level. Keep an eye on the ESHRE website for more details.

Work is also in progress for a Campus course on quality management, a back to SQART basics course,

which also involves risk management and trouble shooting. QM is also change management, people management and financial management. - and all will be covered to take your QM skills to the next level.

Guideline development

We are pleased to report that guideline proposals on **Ultrasound in ART** (an initiative of the SIGs SQART, Endometriosis & Endometrial disorders, Implantation and Early Pregnancy) have now been submitted to ESHRE's ExCo and were approved in Geneva. The guideline development group is now being formed. SIG SQART is also involved in proposals for a ESHRE guideline on female oncofertility care and fertility preservation in women and girls.

Kelly Tilleman
Co-ordinator on behalf of the SIG SQART

ESHRE extends stakeholder role in Euro tissue and cell project

The ART team responsible for Euro-GTPII: from left, Francesco Lombardo, Iona Rugescu, Martine Nijs, Kelly Tilleman, Guergoi Nikolov, Veerle Provoost, Nathalie Vermeulen, Zdravaka Veleva, Rita Piteira (project coordination).

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ESHRE is an important stakeholder in several EU projects and as such has the opportunity to participate at the highest level in order to defend the interests of the ART sector.

One such project is the Euro-GTPII programme (www.goodtissuepractices.eu), which aims to establish good practice standards as applied to the preparation process of tissues and cells and to procedures of patient follow-up. The aim is safe and effective implementation and evaluation.

Euro-GTPII gives continuity to the first Euro-GTP project, which developed European Good Tissue Practices for activities carried out in tissue establishments. The third (2017) guide on safety and quality of tissues and cells, which includes ART, is now freely downloadable from https://register.edqm.eu/freepub. Just provide your e-mail address and download from under the subheading 'organs, tissues and cells'.

Also available under the same heading are other relevant documents developed by the Council of Europe. This information can also be found on the ESHRE web pages of SQART.

The third 2017 guide includes recommendations applicable to ART centres.

This guide to quality and safety of tissues and cells for human application is an extensive 300+ page document which includes recommendations considered to be 'minimum standards' in aligning the principles set out in the various EU Tissue & Cell Directives. This third edition of the guide is the result of exceptional efforts and extensive discussions of which ESHRE was a part.

What is the status of current work in Euro-GTPII project? The generic tool to assess novelty and risks is now quite far into its development. The purpose of the meeting in Geneva was to put an ART topping on this generic tool. Several ART experts contributed to a lively discussion, which resulted in a broad consensus.

It was also decided that by the end of the year, ESHRE members would be invited to test the tool. This exercise will not only make the tool known to the ART community, but will undoubtedly provide us with valuable feedback on the uniformity of its use.

Watch out for the e-mail later this year. Your participation and opinion will be highly appreciated and much needed!

Kelly Tilleman

Ovarian stimulation guidelines moving ahead

More than 500 took part in our precongress course in Geneva on **Ovarian stimulation: individualizationa and beyond . . .** Discussion was active and lively but, as the course title implies, went beyond the simple concept of individualisation. The pros and cons of FSH dose tailoring were expertly debated, as well as the role of ovarian reserve markers in predicting IVF outcomes. Nick Macklon, former co-ordinator of the SIG RE and a current active member, presented an elegant, novel and comprehensive view of ovarian physiology, thus offering a rich background for fully understanding many other hot topics. Among them, available data on the possible adjuvant effects of co-medications were extensively analysed and discussed. Of paramount and topical importance, the cost efficiency and patient acceptability of different protocols were also considered.

Excellent interaction with an audience from multiple countries highlighted geographical differences in terms of equality and accessibility. Based on the reports collected by ESHRE Central Office, educational needs were fulfilled, and we hope that a new awareness of the management of women having ovarian stimulation for IVF will be readily translated into daily clinical practice.

From the beginning: the distinguished list of SIG RE co-ordinators.

Steve Franks 1991-1995
Bart Fauser 1995-2001
Basil Tarlatzis 2001-2004
Nick Macklon 2004-2008
Adam Balen 2008-2011
Georg Griesinger 2011-2013
Stratis Kolibianakis 2013-2015
Frank Broekmans 2015-2017
Daniela Romualdi 2017-2019

Below, ovarian stimulation guideline development group in Geneva.

Guidelines

We are thus proud to be actively involved in building the ESHRE guideline on ovarian stimulation for IVF/ICSI. In addition, our group is cooperating with the Australian Centre for Research Excellence in Polycystic Ovary Syndrome and the ASRM in the development of the international comprehensive guideline on PCOS. A critical final phase of both projects took place in Geneva.

Steering Committee changes

The selection process for a new Junior Deputy was carried out by evaluation of very high-level candidates. As a result, a fresh and enthusiastic member was introduced to the team: Julia Bosdou, MD, PhD, who is currently an Ob/Gyn resident at the Aristotle University of Thessaloniki. Our former Junior Deputy, Georgios Lainas, has moved up to become Deputy and will continue his much appreciated activities in the SIG. Efstratios Kolibianakis stepped down as Past Co-ordinator, and has now become Chair of the ESHRE SIG committee.

After being Deputy, I had the privilege of becoming the first female Co-ordinator of the SIG RE, following in the steps of so many distinguished figures in the field of reproductive endocrinology. We have benefited enormously from the work of Frank Broekmans, who has masterfully guided us towards the implementation of guidelines and many educational activities. He will continue to help build the future of the SIG RE in his role of Past Co-ordinator for the next two years. Finally, we are lucky to count on the support of our eminent international advisor, Roy Homburg, and of our basic science officer, Jenny Visser.

Forthcoming activities

By the time this issue of FoR is published, our Vienna Campus meeting (15-16 September) will be about to take place. The event, **The more the merrier? The impact of adjuvant treatments on pregnancy potential in IVF**, aims to evaluate traditional and novel adjuvant therapies in the context of modern fertility treatment. A variety of ancillary procedures and treatments, ranging from immuno-modulators to endometrial scratch to Chinese medicine, will be discussed within the context of efficacy and safety.

A Campus meeting on **The luteal phase: the neglected part of assisted reproduction?** will be held in Hamburg on 25-26 May 2018, organised by Georg Griesinger, with many other projects on the go. Please keep an eye on our SIG page on the ESHRE website.

Daniela Romualdi
Co-ordinator SIG Reproductive Endocrinology

Praise for congress's new poster sessions

Our precongress course in Geneva proved a very productive reflection on fertility awareness and the role it might have on preventing infertility. The syllabus attracted a huge number of participants - and a wide range of professionals (psychologists, counsellors, physicians, nurses, midwives, etc). The meeting's success was underlined by the quality of speakers and the discussion.

We were really happy with ESHRE's decision to have poster sessions formally included in the main programme. We had two poster sessions, which included discussions of the best eight posters and gave everyone an opportunity to discuss them in more detail - and to contact and share experiences with the authors. The sessions were really productive and interesting. Thanks to all those who attended.

Psychology and Counselling studies in the media

For the first time that we remember, two oral communication studies were selected for press release. The first, conducted by our new SIG Co-ordinator Mariana Martins, had found that 'fertility treatment does not increase the risk of divorce'. The second, conducted by Mathilde Brewaeys from the Netherlands, found that 'children in single-mother-by-choice families do just as well as those in two-parent families. You can watch the video interviews at our Facebook page.

STEERING COMMITTEE

Mariana Martins (PT), Co-ordinator
Juliana Pedro (PT), Deputy
Giuliana Baccino (ES), Deputy
Yoon Frederiksen (DK), Junior Deputy
Brennan Peterson (UAE), International Advisor
Sofia Gameiro (GB), Past Co-ordinator

New Steering Committee

We can also report that a new Steering Committee was announced at the Annual Meeting. Mariana Martins will be the Co-ordinator and Sofia Gameiro Past Co-ordinator. Giuliana Baccino will be Deputy (second term) and Juliana Pedro (first term). The Junior Deputy selected was Yoon Frederiksen from Denmark. Brennan Peterson will be the International Advisor.

Upcoming events

We will host two Campus workshops over the next year, the first in Barcelona in January 2018 on the medical, psychological and ethical considerations of egg donation. The second is a basic training course and it will address the theme of communication and providing information to patients. The programme will be available soon.

Keep an eye out for news on Facebook (@ESHREPsychologyandCounselling) and Twitter (@ESHRE_SIG_psy)! And we hope to see you again at one of next events.

Juliana Pedro
Deputy SIG Psychology & Counselling

Upcoming training events

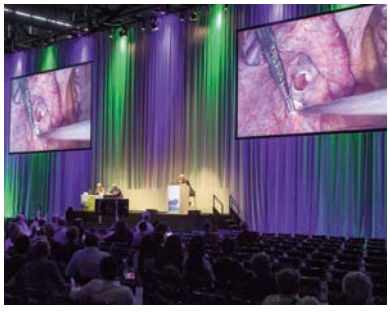
Our precongress course in Geneva on 'complications of reproductive surgery' focused on operative hysteroscopy, transvaginal laparoscopy, myomectomy, endometriosis and operative laparoscoy. The course attracted around 60 participants, who were very active during the discussion.

Our next Campus workshop - on tubal pathologies and their implication in infertility - will be held in Bucharest on 22-23 September. On 22-24 November 2017 (and in April 2018) we will repeat our biannual workshop in Leuven on endoscopy in reproductive medicine, with an emphasis on suturing, gynecological echography and live surgery practice. A course of laparoscopy on cadavers in Liège, Belgium, is being considered for 2018. This type of teaching is unique and allows real dissection without bleeding. Also being considered for 2018 is a workshop on eutopic and ectopic implantation.

Michelle Nisolle
Co-ordinator SIG Reproductive Surgery

STEERING COMMITTEE

Michelle Nisolle (BE), Co-ordinator
Maribel Acien (ES), Deputy
Razvan Vladimir Socolov (RO), Deputy
Linda Tébache (BE), Junior Deputy
Antoine Watrelot (FR), Past Co-ordinator



Live surgery and surgical training in Geneva.

From basic science to clinical application

Geneva: stem cells to the fore

With the contribution of several leading experts, our precongress course **At the crossroad between human embryology and embryonic stem cells: Lessons from molecular and morphological analysis** was especially well attended and received. The course covered a rich variety of topics, including the influence of embryo parameters and culture environment on human embryonic stem cell derivation, novel tools for investigating the epigenome and lineage commitment in in vitro versus in vivo human embryos, and the genomic (in)stability of hESCs. It was a pleasure to see the motivation and enthusiasm for sharing new ideas.

Presentations with a focus on stem cells were often at the forefront of the main programme, notably the Human Reproduction keynote lecture from Carlos Simón presenting a pilot clinical trial using autologous cell therapy with CD133+ bone marrow-derived stem cells for treating refractory Asherman's syndrome and endometrial atrophy. His colleague Xavier Santamaria described further stem cell treatments for endometrial pathologies, and both studies represent a major step forward for stem cell therapies in the treatment of female infertility.

In the stem cell-dedicated session, Jose Medrano gave an overview of past and ongoing research into the in vitro generation of stem cell-derived gametes, from mouse models to human. Heidi Mertes discussed the ethical concerns this raised. Certainly, comprehensive research and safety assessment is imperative before any clinical applications.

Finally, five young and ambitious junior researchers presented their data during the Stem Cell selected abstracts session. They covered a variety of interesting topics, including novel markers of naive and primed pluripotency, the effect of Wnt inhibition on the differentiation potential of hESCs, the role of the post inner cell mass intermediate for determining embryonic stem cell fate, the characterisation of a novel mitochondrial protein involved in pluripotency, and finally a report on two live births following stem cell ovarian auto-transplantation. This session underlined the place of fundamental and clinically translational stem cell research within ESHRE.

Future events

Our precongress course for the 2018 Annual Meeting in Barcelona will be on **Stem cell therapies in clinical applications: Progress and challenges**. Awareness of the clinical potential of stem cell therapies in human reproduction is rapidly increasing, as clearly evident in Geneva - which is why our next precongress course will consider several topics relating to the clinical application of stem cells. These will include clinical grade stem cell banking and HLA typing, while the current status of spermatogonial and ovarian stem cell banking and transplantation will also be covered. We will also debate the recent clinical trials of endometrial and other stem cells in female and male infertility. Finally, we will consider the possible use of human pluripotent stem cells, with a focus on the treatment of diabetes and blindness.

We are also delighted to announce our upcoming Campus course on **In vitro modelling: from embryo to gametes**, which will be held in Bilbao on 20-21 September 2018. We are pleased and excited to be host to several pioneers and experts in 3D modelling, artificial human blastocysts, preimplantation embryo imaging, novel in vitro implantation, and epigenetics of human primordial germ cells. These are the most trending topics in the fields of early development and gametogenesis, and will certainly contribute to the future of reproductive science and medicine.

Changes to the Steering Committee

In Geneva we announced a number of changes to the co-ordination of the SIG Stem Cells. Time flies, and after two years as Co-ordinator Björn Heindryckx has now stepped down and I would like to thank him for all his efforts and enthusiasm. I will now take on the position of Co-ordinator and am very enthusiastic to lead this dynamic and fantastic group of stem cell fans! Rita Vassena will also step down from her Past Co-ordinator role and I would like to thank her too for all her input and hard work. Susana Chuva de Sousa Lopes will continue in her role as Deputy for the next two years, while our past Junior Deputy, Mieke Geens, will step up as Deputy. Thus, a new Junior Deputy has been selected; Mina Popovic is a PhD student at the Ghent University Hospital, working in the Ghent Fertility and Stem Cell Team. Her research is on genomic instability during early human development, working with both human embryos and human embryonic stem cells. Last but not least, Sarita Panula will continue as Basic Science Officer for one more year. As most of our deputies are basic researchers in the stem cell field, we would like to take on a more clinically oriented officer. So, if you have a special interest in the translation of stem cells, please follow up our announcements and apply. We foresee plenty of exciting activity and a great atmosphere in our SIG. And we look forward to seeing you in Barcelona and in Bilbao in 2018! All aboard for stem cells in Spain!

Cristina Eguizabal
Co-ordinator SIG Stem Cells

First activities from a new beginning

It is very exciting for us that ESHRE now has a specific SIG dedicated to the rapidly growing field of fertility preservation. In the past ESHRE has supported task forces in both male and female fertility preservation, but a recognition of how much this is now part of our work in reproductive medicine has led to the formation of this SIG. Our remit is broad, covering fertility preservation in both males and females, for both medical and non-medical interventions, and we hope it will appeal to a very broad cross-section of the ESHRE membership and reflect their clinical, laboratory, basic science and ethical interests.

As a new SIG, we did not have a precongress course this year, but the field was in fact very well represented in Geneva, with a full day on transgender fertility preservation prompting discussion of its complex and very specific issues. Ovarian tissue replacement was also shown as one of the live surgery presentations: a video of this is being prepared and will be available on the website shortly.

Future plans

Geneva saw our first business meeting, which allowed an introduction of the co-ordinators, discussion of our remit, and future activities. One of these activities is the ongoing collection of data on fertility preservation by ESHRE; Françoise Shenfield, who is leading the work, gave a short presentation on this, and we will be able to support this very important activity.

The International Society for Fertility Preservation has its biannual meeting in Vienna in November, and as a result we will not be organising a Campus this year. Our first course will be in March 2018 in Amsterdam, held jointly with the SIG Andrology and 'Growsperm' Consortium and focusing on fertility preservation in the male, including the remarkable scientific developments in the production of male gametes in vitro.

Our precongress course in Barcelona is designed to highlight key points in the fertility preservation journey, from assessment of its need in cancer patients, through the patient's clinical journey, laboratory procedures, and assessment of the effectiveness of current strategies. Specific issues relating to fertility preservation in transgender men and women, and a critical review of the current status of social egg-freezing will round off a full and, we hope, very stimulating day.

We will also be organising a Campus workshop on key current issues in female fertility preservation in the second half of 2018: precise date and programme are still to be finalised.

We hope that the SIG Fertility Preservation will attract a broad membership from ESHRE's diverse base. To make sure you hear about our activities as soon as possible, please check your ESHRE membership web page and sign up for 'fertility preservation' as one of your key SIG memberships. We look forward to seeing you all in future meetings.

Richard Anderson
Co-ordinator SIG Fertility Preservation

Plans to continue cryopreservation data collection

Many activities remain for 2017 and plans continue for 2018. In collaboration with the SIGs Ethics & Law and Safety & Quality in ART, our precongress course in Geneva considered the fertility and parental intentions of transsexuals. It was a wonderfully stimulating day, with two of many highlight presentations: the endocrinological burden on fertility during cross-hormonal therapy by Petra De Sutter, and helping transgender adolescents consider their reproductive future from Gary Butler. The first was about the facts, completed by Rodriguez Wallberg's presentation on 'To keep or not to keep' (gonads and gametes) , and the second about the sensitive approach to adolescents facing this turmoil at an age when questions about the self are already very frequent. Finally, Guido Pennings gave us his usual clear dissection of the ethical issues involved, while Françoise Shenfield summarised the complex and rapidly changing legal approach in Europe, where the trend now is to increasingly not include surgery prior to the official change of gender.

Future activities

In October Françoise Shenfield will attend a meeting in Edinburgh with the SIG Fertility Preservation Co-

Continued over page

The biology of mitochondrial DNA and scope for future clinical application

In the past few years there has been a remarkable burst of knowledge on the role of mitochondria in early human development, fertility and reproduction. Our precongress course in Geneva, **Mitochondria in human reproduction and ART**, was organised in anticipation of further advances in the years to come. The course aimed to give an overview of current knowledge, combining basic science with clinical application.

The first session was focused on the role of mitochondria in male and female fertility, discussing reactive oxygen species (ROS) in oocyte ageing and the role of mitochondria in sperm quality. Carla Tatone described the relevance of reduced expression of mitochondrial and cytoplasmic sirtuins (NAD-dependent protein deacetylases) in ageing and on elevated ROS. She reported on the potential beneficial effect of nutritional supplementations, like coenzyme Q10, to counteract follicle depletion and support mitochondrial activity during ageing, eg, by activation of SIRT1 and SIRT3. She finally concluded that increased SIRT1 activity may not only ameliorate fertility in ageing but can also be beneficial in PCOS, diabetes, endometriosis, and xenobiotic stress.

The second speaker, Joao Ramalho-Santos, presented a critical review of methods to monitor mitochondrial quality in spermatogenesis and sperm. Thus, he focused on strategies of proteome analysis and the relative value and pitfalls in using different fluorescent probes in assessment of mitochondrial function and sperm quality. While overall activity analyzed by probes such as Mitotraker related to sperm number, there appeared to be much heterogeneity within sperm populations. Furthermore, he presented data on toxicologic effects of environmental pollutants like polychlorinated biphenyls (PCBs) and endocrine disrupting chemicals on sperm that can affect viability, motility and mitochondrial membrane potential, and exhibit non-genomic effects.

In the second session, speakers focused on the impact of mtDNA on health and development, from two different angles. Anna Victoria Lechuga-Vieco presented the high impact research done in her laboratory on the intriguing notion that different mtDNA genomes do not 'function' equally in different nuclear genome backgrounds. She showed how, using mouse models, her group found significant differences in the levels of mitochondrial functionality in mice with the same nuclear genome and different mtDNAs. These differences were reflected in the phenotype of the mouse, with striking differences in the way the mice aged, and the rates of tumour formation.

The second speaker, Hubert Smeets, gave a talk from the perspective of more classical mtDNA mutations as known in mtDNA disease. His presentation included a comprehensive overview of the impact of mtDNA variants with known pathogenic effect and information on the strategies to identify mutations in patients (mtDNA analysis by NGS, candidate gene analysis by Sanger sequencing, nuclear mitochondrial gene analysis by whole exome

SIG Global and socio-cultural aspects Continued from previous page

ordinator Richard Anderson, on continuing oocyte and ovarian tissue freezing data collection from European clinics (with first findings published in HR Open in March), and a possible collaboration from Australia, Japan, India and the US through the ASRM.

She will also take part in a meeting at the Council of Europe to celebrate the 30th anniversary of the Oviedo Convention in Biomedicine, at which the Executive Committee and members of the Ethics Committee will represent ESHRE. This will take place in Strasbourg, 24th and 25th October, and all members interested in ethics and politics are welcome.

Next year we look forward to a Campus meeting on egg donation titled **Egg donation: medical, psychological and ethical considerations**. This will take place in Barcelona on 26-27 January 2018 and will feature cross-border movements of patients and donors, recruitment of donors, donor anonymity and identifiability. The course will be organised with the SIGs Psychology & Counselling and Ethics & Law.

Our precongress course in Barcelona will be on **Surrogacy: a gift with consequences**. The aim is to present reflections from a socio-anthropological and legal perspective, with a presentation from our new Deputy Virginie Rozee.

Willem Ombelet, Co-ordinator SIG GSCAIF
Virginie Rozee, Deputy
Françoise Shenfield, Past Co-ordinator

sequencing) and to establish their potential pathogenic effect. He additionally discussed the recurrence risk (low) and frequency (23.5%) of de novo mutations and the possible mechanisms involved, with information on how mtDNA mutations segregate through the germline, into the embryo, and later in adult tissue.

The afternoon sessions provided a more clinically oriented approach to mitochondrial disease. Session 3 discussed latest developments in the treatment and prevention of transmission of mitochondrial disease. The first speaker, Michal Minczuk, described the latest experimental approaches to the design and application of engineered mitochondrially-targeted zinc finger nucleases (ZFN), showing how such technology allows discrimination between mtDNA haplotypes. Reducing the mutant mitochondrial DNA produces a shift in the heteroplasmic ratio, increasing the proportion of wild type mtDNA molecules in the cell. Sequential treatment with mtZFN can produce greater total heteroplasmy shifts, and the subsequent enrichment of wild-type mtDNA can rescue pathological phenotypes in heteroplasmic cells. This may provide therapeutic intervention in some mitochondrial diseases. The discussion that followed also touched on other approaches, such as the use of transcription activator–like effector nucleases (TALENs) and CRISPR-Cas9 technology.

The next speaker, Julie Steffann, described the reproductive options for couples at risk of transmitting mtDNA mutations to their offspring and the feasibility and current experience of PGD or prenatal diagnosis to assess mitochondrial mutant load either in cells sampled from early embryos or in fetal tissue. Current experience, chance of success and limitations associated with these procedures (risk of no embryo transfer in PGD, ideal embryo biopsy stage, risk of termination following PND, residual risk of symptoms with heteroplasmic embryo/fetus and inapplicability for homoplasmic mutated patients) were discussed.

Currently for PGD a 2-blastomere biopsy of cleavage-stage embryos at the 8-cell stage is the recommended approach, and amniotic cell sampling should be preferred for PND, as results from CVS have shown evidence of mutant load intraplacental heterogeneity.

The day was nicely closed with session 4, where speakers discussed the role of mitochondria in ART. Dagan Wells gave an update on mtDNA assessment in oocytes and embryos - with respect to mtDNA content and female age, aneuploidy or embryo implantation potential, - and on the conflicting data between published studies. Following a thorough discussion on the advantages and risks of the so far selected approaches, he presented the latest data, supporting the strong link between mtDNA quantity, age and aneuploidy risk - all suggesting a threshold of mtDNA content above which implantation of a euploid blastocyst may not occur. Wells concluded that mtDNA quantity may serve as an independent biomarker for the prediction of euploid blastocyst implantation potential, although randomised trials are needed to assess the true clinical utility of mtDNA.

The last speaker of the day, Joanna Poulton, focused on the importance of mtDNA quality and the stages of development that are affected by mitochondrial quality (eg, very important for placental function and postnatally) and also touched on the reproductive options for carriers of mtDNA diseases (natural conception, PGD and mitochondrial replacement). A very important point was the definition of mitophagy (autophagy of mitochondria that shows a burst in the very early stages, concomitant with a decrease in mtDNA copy number). The speaker discussed the potential of driving mitophagy against defective mitochondria as a way to improve PGD or MRT and reduce transmission of mtDNA disease.

New Steering Committee

Major alterations to the current format of our SIG's Steering Committee were announced in Geneva. Our Past Co-ordinator Ursula Eichenlaub-Ritter has stepped down to be superseded by Claudia Spits. Georgia Kakourou as former Deputy has been elected as the new Co-ordinator. Tania Milachich, our former Deputy, and Signe Altmae, our Junior Deputy, have each stepped down. Thus, following the election procedure, we announced two new deputies for the Steering Committee, Francesco Fiorentino and Antonio Capalbo, as well as our Junior Deputy Filippo Zambelli. Professor Stephane Viville remains our basic science officer. The new group will get together shortly and we all look forward to great co-operation for the organisation of exciting new activities that you will hopefully all enjoy.

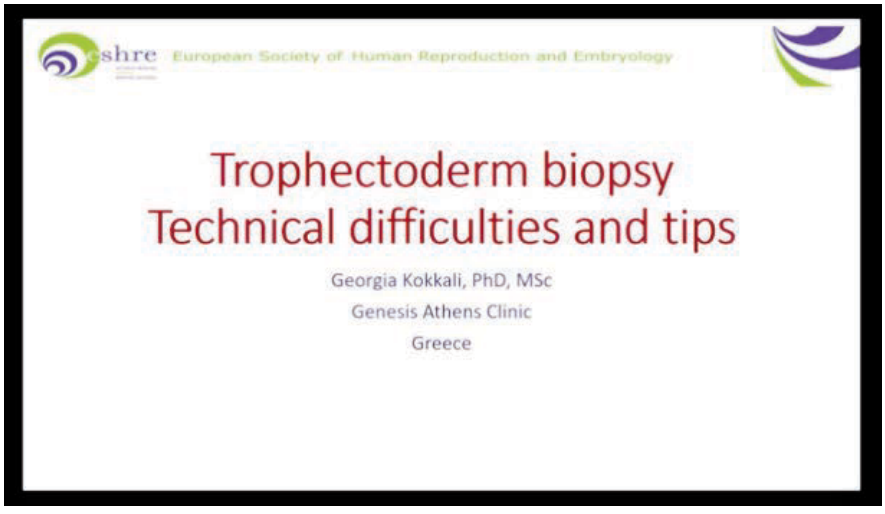
Upcoming events

Our next event for 2017 is the Campus **From gametes to blastocyst - a continuous dialogue** organised by the SIGs Embryology and Reproductive Genetics, which will take place on 12-14 October in Edinburgh.

For 2018 we are also involved in a meeting on **Current approaches in genetics and reproduction** that will take place in Sofia, Bulgaria, run by our former deputy, Tania Milachich. The course focuses on practical aspects, an update on latest developments and current best practices - and, with consideration of the latest genetic issues and controversies in ART, will generate fruitful discussion on methods (technical topics), result interpretation and counselling. The Campus allows those interested to submit abstracts, which may be presented as a short oral communication or poster. We hope to welcome many of you!

Georgia Kakourou, Co-ordinator
Signe Altmae, Ursula Eichenlaub-Ritter and Claudia Spits on behalf of the SIG Reproductive Genetics

Troubleshooting in trophectoderm biopsy: Do's and don'ts from an ESHRE webinar



A webinar on trophectoderm biopsy posted by the PGD Consortium and presented by Georgia Kokkali of the Genesis Athens Clinic, Greece, proved extremely popular, with more questions raised than could be answered at the time. Georgia now responds to those queries, with troubleshooting answers and practical advice.

Blastocyst trophectoderm (TE) biopsy using micromanipulation methods was first reported by Dokras and colleagues in 1990,[1] although not in the context of clinical application. The development of non-contact lasers has now greatly facilitated TE biopsy, first to make a hole in the zona pellucida and secondly to excise TE cells.[2] Blastocyst stage biopsy strategy has been an important breakthrough for PGD/PGS. The first pregnancies and live births following TE biopsy and PGD on fresh cycle blastocysts were reported in 2005;[3,4] successful application on frozen-thawed blastocysts was reported in 2009.[5]

In recent years, several preclinical and clinical studies recognised its value and IVF centres are increasingly implementing TE biopsy in their clinical practice for PGD/PGS. Blastocyst-stage biopsy has many advantages for increased predictive value: less traumatic for the embryos,[6] non-compromised implantation potential,[7] and an adequate number of biopsied cells for molecular analysis,[8,9] which may increase reliability and decrease problems with mosaicism.[8] However, before applying the blastocyst biopsy technique, ART laboratories should operate at a high level of excellence with optimised culture system, a robust cryopreservation programme and skilled embryologists.

The webinar described the different strategies for blastocyst biopsy in terms of when and how zona drilling and TE cell excision should be applied, as well as technical difficulties depending on morphology and quality of the blastocysts, their expansion, and the position of the inner cell mass. The webinar was interactive and all participants had the opportunity to ask questions. This is an overview of the most frequently asked questions:

1. Questions on biopsy media

- In which medium do you biopsy?
- Do you add albumin to HEPES for biopsy?
- Is it OK to use normal culture media instead?
- Can we use calcium and magnesium-free medium for TE biopsy?

Answers: Blastocyst biopsy may be performed either in HEPES-buffered culture media on a warmed stage, or in standard culture media if your microscope and micromanipulator system are placed within a special chamber maintaining a controlled CO_2 enriched environment and stable temperature. The use of albumin should be in accordance with your culture system. Magnesium-free medium should not be used for blastocyst biopsy.

Questions on the timing of blastocyst biopsy

- Do you do day-4 embryo biopsy?
- Why is day 5 preferred for TE biopsy?
- What are the advantages of day 5 biopsy ?
- And day 6 if there were no blastocysts on day 5?
- What is your opinion of day 6 blastocyst biopsy?
- Can you perform TE biopsy beyond day 6?

The webinar can be found on the PGD Consortium web page - at https://www.eshre.eu/Data-collection-and-research/Consortia/PGD-Consortium/Archive/Webinar-on-trophectoderm-biopsy.aspx

Answer: The timing of blastocyst biopsy is an important factor for patient management. Although morula-stage biopsy has been proposed, few data have been produced to evaluate its actual feasibility; however, it is technically similar to cleavage-stage biopsy and thus shares the same drawbacks. To perform blastocyst biopsy, the ICM should be clearly identified.

Extended culture of cleavage stage embryos to the blastocyst stage has the following advantages: (i) selection of developmentally competent embryos for diagnosis, (ii) more cells may be removed and be available for analysis, (iii) biopsied cells derive from a non-embryonic portion of the blastocyst, (iv) biopsied cells constitute a smaller proportion of the whole embryo, in comparision to biopsy at the cleavage stage.

Blastocysts do not develop simultaneously and therefore not all may be ready for biopsy on day 5. In our experience, we have not seen a difference between day 5 or day 6 blastocysts (where there were no blastocysts on day 5) with respect to the efficacy of the technique, pregnancy or implantation rates. We do not culture embryos to day 7, but, according to recent studies in the literature, embryos developing to the blastocyst stage on day 7 have a higher aneuploidy rate and a lower implantation potential.

Questions on the opening of the zona pellucida

- Which is the optimum size for the biopsy hatching hole on day 3 and day 5?

Answer: On day 3 or 4 of development a zona opening of 25-30 µm is sufficient to encourage herniation of trophectoderm as it forms, while a zona drill on a developed blastocyst of around ~10 µm opposite the ICM is enough to accommodate the passage of several TE cells. For the zona opening the lowest setting of the laser should be used.

Questions on blastocyst development before biopsy

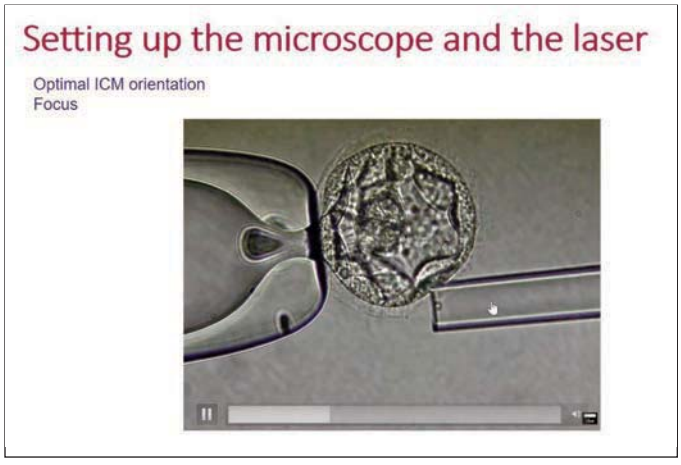
- What is the best stage to perform the biopsy?
- Are you doing biopsy on expanded blastocysts?
- Which blastocysts would you biopsy on day 5 and when would you culture to biopsy on day 6?
- Do you biopsy if you have full hatching blastocysts?

Answers: Blastocyst biopsy may be performed at any stage of blastocyst development, from the early blastocyst (once the ICM is clearly identified) to when the blastocyst is totally hatched from the zona pellucida (for early to hatching blastocysts,[3] for hatching to fully hatched blastocysts.[4,11]) Accordingly, the embryos may be cultured up to day 5, day 6, or even day 7, and biopsied exclusively after reaching full expansion.

Questions on blastocyst morphology before biopsy

- Do you biopsy bad quality blastocysts?
- Or poor TE blastocysts?

Answer: According to the scoring system of Gardner and Schoolcraft, all blastocysts from stage 3, 4, 5, 6 AA, AB, BA, BB, AC, CA on ICM and TE quality scores may be biopsied.[12] The TE grade is as follows: A, many cells organised in epithelium; B, several cells organised in loose epithelium; or C, few large cells. The ICM grade is as follows: A, numerous tightly packed cells; B, several and loosely packed cells; or C, very few cells.



Questions on the use of the laser

- Would you prefer using high power laser pulses with lower number of laser shots or lower laser power pulses with higher number of laser shots?
- Do you need to laser to perform flicking? Can it be done without laser before flicking?
- How do you make blastocyst collapse?

Answer: In general, I prefer using low power pulses positioned to the thinnest part of the aspirated cells and directed at the junctions between cells to disconnect the aspirated cells from the embryo proper. Simultaneous application of moderate suction of TE cells to the biopsy pipette to stretch the target cells overcomes the need for several pulses.

The laser is necessary for the flicking method, to allow the TE cells to be drawn in the biopsy pipette and ease their detachment from the blastocysts. Using the simultaneous blastocyst biopsy method, once the zona opening has been made the biopsy pipette is carefully pressed against the zona, gently expelling medium through the breach to release the TE cells from the internal surface of the zona. Then, once the TE is detached from the internal surface of the zona (slight collapse), TE cells may be aspirated into the biopsy pipette with gentle suction.

Questions on handling the biopsied TE cells

- How do you remove the oil from your pipette when aspirating the trophectoderm from the biopsy dish to the tube?
- Can you visualise the trophectoderm cells under the microscope as they are dispensed into the tube?
- Few of my biopsy cells lysed during washing. Are these cells suitable for PGD/PGS?
- Is it recommended to re-biopsy for material loss

during tubing or whatever? Is it a safe option?

Answer: The process of handling the biopsied material is crucial and involves transfer of the biopsied TE cells from the biopsy dish into the PCR tube (cell tubing). TE cell tubing is performed in a flow hood cabinet under a stereo microscope, using appropriate sterile capillaries or pipettes. To remove the oil from your capillaries/pipette, the biopsied TE cells are taken from the biopsy dish and moved onto a clean droplet of washing medium not covered with oil. The cluster of biopsied cells can then be washed two or three times in clean droplets of washing medium and then transferred into a small droplet of buffer in a 0.2 ml PCR tube. If the cells lyse during washing, washing buffer constitution or laser pulses power should be reconsidered. To ensure the biopsied cells are correctly deposited inside the PCR tube, the sample ideally should be viewed coming out of the capillary or pipette under the stereo microscope. In case of lost material during tubing, it is an option to re-biopsy the blastocyst after it has re-expanded following further incubation.

Questions on dealing with poor genetic outcome

- Reasons for degraded DNA diagnosis?
- Do fewer cells in the biopsy lead to inaccurate results?

Answer: For adequate genetic analysis the biopsied material should number between 5-10 TE cells and be undamaged by the laser. Fewer may lead to inconclusive genetic analysis.

Questions on vitrification of post-biopsy blastocyst

- What is the ideal moment to vitrify the blastocyst post-biopsy - after re-expanding or when collapsed?
- Is it possible to vitrify totally hatched blastocysts after biopsy?

Answer: The blastocysts can be cryopreserved immediately after biopsy, while still collapsed, and kept cryopreserved until use. Totally hatched blastocysts may also be cryopreserved.

Questions on reproductive outcomes

- What is the effect on implantation and miscarriage rate of removing as many as 10 cells (about 10%) from the embryo?

Answer: An early trial by Jones et al from 2003, showed that TE biopsy of approximately 8–20 cells may be removed from any blastocyst regardless of its degree of expansion.[8] The biopsy technique did not appear to have impact on the blastocyst's ability to re-form a blastocoele cavity and continue to grow and hatch from the zona pellucida, with no major signs of morphological damage at the light microscopic level.

Implantation and pregnancy levels were not the primary or secondary measures of this trial, but it was shown that transfer of biopsied blastocysts did result in a similar pregnancy rate (52%) to that following transfer of non-biopsied blastocysts to control patients not participating in the trial. Implantation rates were significantly higher following transfer of biopsied blastocysts. There was no significant difference in miscarriage rates.

Conclusions

In conclusion, the blastocyst approach shows no impact upon embryo viability and successful reproductive outcomes while ensuring accuracy and reliability in PGD/PGS programmes. The blastocyst stage biopsy strategies and methods may be selected and applied by skilled embryologists in order to perform TE biopsies on virtually all types of blastocysts.

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