focus on REPRODUCTION

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40 YEARS of test-tube babies - and here's the first

- Assessing the evidence for IUI
- ESHRE news
- Twenty years of ESHRE's PGD Consortium

// JANUARY 2018

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CHAIRMAN'S INTRODUCTION

AS the cold grip of winter gradually descends on Brussels, activity in ESHRE continues to keep us all warm and alert. It has been a busy autumn with several areas of development bringing change and challenge for the future. In particular, the ongoing strategic development of ESHRE to promote visibility, policy initiatives, education and membership has been championed by small groups of Executive Committee members to bear fruit in the future.

Impact factors for the ESHRE journals continue an upward trend. Of the four titles, three will need new Editors-in-Chief before the current editors retire at the end of 2018. Following advertisement, we are now ready for shortlisting and interviewing candidates in early 2018.

The theme and content for the ESHRE research grant applications for 2018 was made available at the end of last year so that members can apply before the deadline date of 1 April.

We are also pleased to announce that the Union of European Medical Specialists Council (UEMS) gave formal approval for ESHRE to become the Division of Reproductive Medicine under the section of Obstetrics and Gynaecology. This will add further momentum to the planned European Fellowship exam in Reproductive Medicine for clinical sub-specialist trainees supported by EBCOG. The Embryology Certification exam also received a boost from the UEMS assessors who came to study the entire process in Geneva. They noted many positive aspects in transparency, effectiveness, objectivity and efficiency in their report.

While learning facilities for ESHRE members have been traditionally well supported, we are often asked why, for example, there is no basic training in statistics. By way of reply, I can report that there are now three learning tutorials on statistics available to all ESHRE members. Just follow the e-learning button on the ESHRE website.

The Annual Assembly of ESHRE in Geneva heard that fertility awareness and infertility prevention should hold greater priority for ESHRE. As a consequence, a Fertility Awareness working group under the leadership of Søren Ziebe from Copenhagen has been set up so that progress can begin and a road map constructed. In particular, we're looking for young members to get involved.

November saw a lot of EU activity in collaboration with DG Sante and associated stakeholders. The finalisation of our meeting programme at the Council of Europe in Strasbourg scheduled for 22/23 February is complete. Registration for this ESHRE-sponsored event, titled 'Access to and diversity of medically assisted reproduction in Europe', is free and your support is warmly welcomed.

Roy Farquharson
ESHRE Chairman 2017-2019

// JANUARY 2018

Hola Barcelona

Barcelona abstract submissions: Must be with ESHRE by 1 February 2018

ESHRE's next Annual Meeting - from 1 to 4 July - will be held for the third time in Barcelona and for the fourth time in Spain. ESHRE's 4th Annual Meeting, in 1988, took place at the Princess Sofia Hotel in Barcelona with 800 attending; chairmen of the scientific committee were the late Jose Egozcue, who would become Chairman of ESHRE in 1995, and Pedro Barri, who will become an honorary member of ESHRE this year. Still in Spain, the 19th Annual Meeting was held in Madrid in 2003 under the local chairmanship of Antonio Pellicer and with 4547 in attendance.

Deadlines for abstracts and registrations this year are as in previous years, with all abstracts required online at ESHRE's Central Office before 1 February, and early bird registrations available up to the end of April. Full details can be found in the table opposite.

As in recent events, Barcelona will be a completely paper-free meeting run electronically through its own wireless network. The congress app will provide full programme and abstract details for laptops and mobile devices.

The scientific programme will open with its two usual keynote lectures on Monday morning, with the first speaker representing the most downloaded article from *Human Reproduction* in 2016, followed by a presentation from the Japanese biologist Katsuhiko Hayashi. It was Hayashi who reported in 2016 a series of experiments culminating in the birth of mouse pups derived entirely in vitro from pluripotent stem cells. The work was described as a monumental achievement, with speculation that, if scientists could use a similar technique to transform human stem cells into fertile eggs, it could offer wholly new fertility treatment or preservation possibilities - even if in the distant future.

REGISTRATION FEES AND DEADLINES FOR THIS YEAR'S ANNUAL MEETING

Main programme	Until 2 May 2018	After 2 May 2018	After 20 June 2018
Non-member of ESHRE	425,00	525,00	625,00
Member of ESHRE	325,00	425,00	525,00
Student or paramedical member of ESHRE	175,00	225,00	325,00
Precongress Course			
Non-member of ESHRE	225,00	325,00	425,00
Member of ESHRE	150,00	225,00	325,00
Student or paramedical member of ESHRE	75,00	125,00	225,00

* Prices are in euro and VAT is not applicable

As news reports in this issue of *Focus on Reproduction* suggest, AMH continues to be the hormone of interest in reproduction, but still a less than reliable marker of delivery after treatment. An invited session on Monday will focus on AMH, with presentations on how best to measure levels and on its role in the pathogenesis of ovulatory disorders. Antonio La Marca, who will present the second report, has already made strong claims for the role of AMH in personalising stimulation protocols.

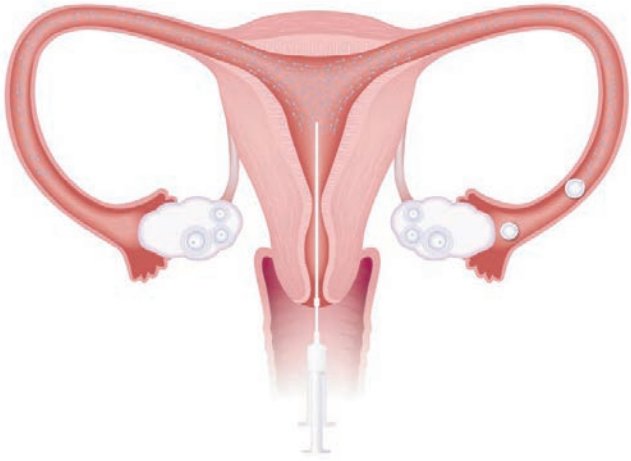
Tuesday's programme will begin with the male and a proposal from the distinguished andrologist John Aitken of a mechanistic basis for the effects of ageing. His fellow-speaker Jörg Gromoll from Germany will consider the germ cell in the ageing male.

Invited sessions later in the day on Tuesday cover PCOS (first-line treatment) and errors in the IVF lab ('a true analysis' from Maria Jose De Los Santos from IVI in Valencia). It was at last year's Annual Assembly of ESHRE members (also on Tuesday this year) that the Danish embryologist Søren Ziebe reminded ESHRE of its public responsibilities in infertility prevention. This led ESHRE to the formation of a working group briefed to consider opportunities, which may be helped by an invited session on fertility awareness for the public. Lone Schmidt will assess the impact of various fertility campaigns, while Régine Steegers-Theunissen from the Netherlands will consider the effect of lifestyle coaching as preconceptional care ahead of IVF based on results of a randomised trial.

ESHRE precongress courses are proving increasingly popular, with some courses now attracting upwards of 500 participants. This year, on Sunday 1 July, there will be 16 events, a congress record, with courses on male gametogenesis, culture systems for IVF, surrogacy and its ethical implications, assessment of early pregnancy, PCOS, the function and detection of genes in inherited disease, endoscopy, stem cell therapies and fertility preservation. In addition there will be the exchange courses of the ASRM (on the techniques of embryo transfer) and Middle East Fertility Society, and a course on academic authorship hosted by the ESHRE journal editors.

As usual, Barcelona will feature a programme of social events, beginning with the Opening Ceremony on Sunday 1 July followed by a welcome reception in the exhibition area. ESHRE will also host its annual charity run, now in its fifth year and in 2018 scheduled for Tuesday 3 July. This will be followed later in the evening by an ESHRE networking event at a venue yet to be confirmed, with fingerfood, drinks and entertainment. The Closing Ceremony on Wednesday afternoon will be marked by awards to the winners of this year's seven presentation prizes.

A new shine on the rough diamond of reproductive medicine



Despite big research gaps, IUI continues to find favour with clinics. A well attended Campus meeting in November heard the best and worst of the evidence.

It was clear from the 20 presentations at this popular Campus meeting that the 'revival' of IUI in unexplained and moderate male factor infertility is real - even if the evidence in favour of its resurgence is no greater now than it was in the doldrum days of 20 years ago. But cycle numbers are increasing (if we can believe the registries), and indications have now moved on beyond the treatment of lesbian and single women.

Anyway, who needs evidence? Egbert te Velde, speaking as an 'old-timer' of IUI, attributed the revival of IUI partly to a more inclusive understanding of evidence-based medicine and a recognition that multiple pregnancies were not - as had been feared - the inevitable outcome. But just how great that revival has been we have little chance of knowing from registry data. Diane De Neubourg from the Campus host city of Antwerp reported that IUI is much less frequently and less completely reported than IVF or ICSI, even though cycle numbers (according to ICMART data) seem to be increasing year on year. In Europe France seems to be by far the biggest user of IUI (around 50,000 cycles per year according to ESHRE figures), though registration of IUI cycles elsewhere seems rarely mandatory.

However, the Cinderella status of IUI seems no better illustrated than in the patchwork of evidence for its use. Willem Ombelet, joint organiser of this meeting, summarised the bottom line of clinical evidence as: 'If the tubes are open and total motile sperm count is adequate, there's no reason not to do IUI.' The patchwork of evidence, he added, was essentially how to improve results. 'Otherwise,' he said, 'IUI is proven, it's cost-benefical, and it's of psychological benefit.'

Ben Cohlen: 'Doctors believe in it, patients want it . . . '

The 'evidence' was sifted and analysed by Ben Cohlen from Zwolle in the Netherlands, who, with Ombelet and others, has been steering an apparently distant evidence-based guideline for the WHO. The questions for evidence to answer concerned when to start and in whom, for how many cycles, with or without ovarian stimulation, at what point in the cycle, how to prepare semen and how to prevent multiple pregnancies.

On the question of indication, and despite a 2016 Cochrane conclusion that 'we are not able to recommend for or aganst IUI in couples with solely poor sperm quality', Cohlen seemed to favour the conclusions of a 2015 multicentre Dutch trial that 'in couples with unexplained infertility and mild male infertility and a prognosis of spontaneous pregnancy of <30% within a year, it is recommended that IUI plus ovarian stimulation is the treatment of first choice.'[1] This conclusion was further underlined in a study reported at ESHRE last year which found a three-times higher live birth rate in couples having clomiphene-stimulated IUI than in expectant management controls. Again, this result seemed at variance with the neutral findings of recent Cochrane conclusions. So the evidence 'partly supports' IUI, said Cohlen, doctors 'believe in it' - and importantly, 'patients want it'.

Indeed, further evidence proposed by Cohlen suggested that patient preference (over IVF) would continue for at least three cycles of IUI 'as the most cost-effective option'. This preference, he added, seemed unaffected by any risk of multiples, though studies suggest that to avoid multiple pregnancies stimulation should be limited to clomiphene or a maximum of 75 IU gonadotrophins, or cancelled in the presence of more than two dominant follicles at the time of hCG.

So much for what we do know. The list of don't knows was reviewed by Aartjan Bijkerk from the Netherlands, who found 'research gaps' in cut-off levels of sperm parameters, single or double insemination, the most appropriate number of IUI cycles ('three to

Course organiser Willem Ombelet: 'If the tubes are open, there's no reason not to do IUI.'

six' most common), and semen preparation. Among these, said Bijkerk, there was an 'urgent need' for semen cut-off values and a clear definition (correlated to treatment) of mild, moderate and severe male infertility. Only RCTs could compare IUI, stimulated IUI and IVF/ICSI in these categorised indications, and that evidence was lacking.

However, on all these questions Willem Ombelet had a clearer idea of what was a 'bad' prognosis than a good one. He listed a duration of infertility of more than four years, poor sperm quality (a total motile sperm count of 3 million or less), female age over 40, untreated endometriosis and distal unilateral tubal factor as each associated with a poor outcome in IUI. Moreover, he was confident that ovarian stimulation was beneficial with IUI in cases of unexplained infertility, with endometriosis and in mild male factor (with total motile sperm count was at least 10 million), However, IUI had proved ineffective in cases of cervical factor.

Ombelet also reported intriguing data from his own centre in Genk that results seemed better when the IUI was performed by midwives and nurses. Would this, he asked, reflect a lower level of stress or a longer duration of procedure?

He also presented data on when to stop, somewhat following the conclusion of Cohlen 'that the majority of pregnancies occur in the first three cycles' - with a significant drop in results thereafter. He thus proposed 'a minimum of three cycles for those who have time up to six (and even nine) cycles'.

Simon Brown

Take-home messages

- IUI is a cost-effective first-line treatment for unexplained and moderate male infertility
- No single predictor of outcome
- Well timed IUI with ovarian stimulation in a well selected population (40 yrs or under, endometriosis treated, adequate sperm parameters) for at least three cycles can result in cumulative pregnancy rates of 40-50% (six cycles)
- IUI should be cheap, non-invasive, safe, patient-friendly
- Major risk = multiples
- More RCTs needed

Practice of short bed rest after IUI 'not justified', after RCT finds no benefit

A large randomsied trial whose preliminary results were presented at ESHRE's Annual Meeting in 2015 has now been published and reports that the practice of keeping female patients immobilised after IUI has no beneficial effect on pregnancy rates.[1] Immobolisation was, however, according to Aartjan Bijkerk in Antwerp, one of several 'research gaps' casting a shadow over IUI, which this trial apparently had not yet removed.

Its results, which were based on 498 couples diagnosed with unexplained or mild male subfertility, were contrary to those reported by another study of 2009. This, said Bijkerk, had merited testing by a larger RCT but now also raised a question mark over the validity of results.[2]

In this second trial patients were randomly assigned to 15 minutes of immobilisation immediately after insemination or to immediate mobilisation. Results showed comparable cumulative ongoing pregnancy rates per couple in each of the two groups (32.2% in the immobile group and 40% in the mobile group). These differences were not statistically significant, despite the trend, indicating no benefit from a brief period of bed rest after insemination. 'In our opinion,' said first author Joukje van Rijswijk from Amsterdam, 'immobilisation after IUI has no positive effect on pregnancy rates, and there is no reason why patients should stay immobilised after treatment. We believe our results in such a large randomised trial are solid, and sufficiently strong to render the recommendation for bed rest obsolete.'

Bijkerk, however, described the quality of evidence as 'moderate', no doubt in recognition of the inconsistent results of the two trials, and said the research gap persisted.

1. Van Rijswijk J, Caanen MR, Mijatovic V, et al. Immobilization or mobilization after IUI: an RCT. Hum Reprod 2017; doi.org/10.1093/humrep/dex302.
2. Custers IM, Flierman PA, Maas P, et al. Immobilisation versus immediate mobilisation after intrauterine insemination: randomised controlled trial. BMJ 2009; 339: b4080

First author of the study Joukje van Ruijswijk: 'Results sufficiently strong to render the recommendation for bed rest obsolete.'

How the past has shaped the future

● The ESHRE PGD Consortium celebrated its 20th anniversary with a Campus symposium in December attended by more than 200 participants

Alan Handyside, the Consortium's first Chair: 'A huge impact on establishing clinical validity.'

It is now 20 years since the PGD Consortium was founded at ESHRE's 1997 Annual Meeting in Edinburgh (a meeting, it was noted, that hosted no sessions on genetics in fertility treatment). According to Céline Moutou, chair of the Consortium's database working group, data collection has been not only its first declared aim but since then its greatest challenge, a 'saga' made all the more Odyssean by an ever-increasing number of reported cycles and an inadequate system to process the data. Thus, as the delay between data submission and publication grew and the processing system shifted from paper to digital, those annual reports would become between 2011 and 2015 two-year summaries. Now, with an online system in place, hopes are that data submissions for 2017 will be with ESHRE by March this year and ready for process.

Nevertheless, despite such challenges, Céline reported that a total of 57,000 PGD and PGS cycles have been reported over these 20 years, with around 10,000 babies born. Delivery rates, she added, have improved over time to around 25% per transfer, with female age and indication the greatest determinants of success. The data, said Alan Handyside, the Consortium's first Chair, have had a 'huge impact in establishing the clinical validity of PGD'.

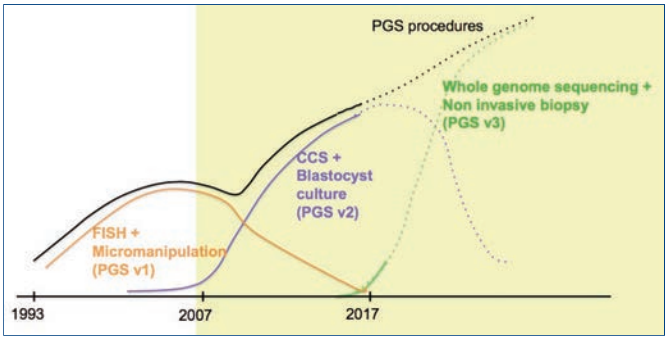
But beyond the data, this Campus meeting really showed from a 20-year history the remarkable speed at which change and development in the field have taken place. Of course, the structure of the meeting lent itself to such a view, with applicable sections (counselling, embryo culture and freezing, biopsy, testing, and safety) considered from a past, present and future perspective. But appealing though they were, those glimpses from the past now seemed like tales from ancient history: Luca Gianaroli's protocol notes scribbled on the back of an envelope (indeed, as nostalgic as the photo of his 1980s hair cut), and Alan Handyside, filmed by the BBC shortly after his first PGD report, removing a blastomere with the guiding pipette held between his lips like an unlit cigarette. Three hours of struggle, said Handyside, shrunk by the BBC into just a few minutes.

Time moved on so rapidly, though the biopsy remained a constant focus throughout these two decades: when to biopsy (polar body stage, cleavage stage, blastocyst?); how (FISH, arrays, NGS?); why (PGD, PGS?); and is it safe?

Already, said Santiago Munné, technology for PGS analysis has moved on from version 1 to version 2 and now to version 3. V3, he explained, would be NGS and non-invasive methods through the analysis of used culture media. Thus, the prevalent pattern of aneuploidy testing - in the US at least - is now whole genome sequencing with blastocyst (and never day 3) biopsy. One of the most recurring slides shown at this meeting was the conclusion of Scott et al from their persuasive 2013 report that cleavage-stage biopsy 'impairs implantation potential', while blastocyst biopsy does not.[1] Hopes for non-invasive PGS would lie with the genome sequencing of used culture medium, reportedly safer for the embryo and less expensive than biopsy techniques.

Moreover, said Munné, NGS will detect mosaics better than any other method, 40% of which 'can result in an ongoing pregnancy compared to 50-70% of euploid'. Thus, he proposed a new 'paradigm shift' in the classification of embryos: as normal, abnormal or mosaic, a scheme with a virtually non-existent error rate and a likely mosaic rate of around 20%. 'This way,' said Munné, 'we wouldn't discard embryos with any chance of implanting.'

Also speaking at this symposium were all the past Chairs of the PGD Consortium, as well as an A-list of those who helped develop the science. The



PGS procedures from versions 1 and 2 to version 3, according to Santiago Munné.

All Chairs from the Consortium's 20-year history spoke at the meeting. From left, Joanne Traeger-Synodinos, Gary Harton, Martine De Rycke, Joep Geraedts, Karen Sermon, Alan Handyside, Joyce Harper and Edith Coonen.

Consortium's third Chair, Joyce Harper, paid tribute to ESHRE's continued support. 'Going right back to our very first meeting at Central Office,' she said, 'we couldn't have survived without ESHRE. Data collection and analysis, meetings, working groups, our own scientific officer, a journal to publish in . . . '

Despite the ongoing output, however, it was not always plain sailing. 'We created guidelines, data reports and controversy,' said Joyce, referring not surprisingly to the huge debates on the viability of PGS and evidence for its role as a routine intervention to improve IVF results. Yet by the end of this meeting, as the whole affair was thrashed out yet again in a debate on the European and US approaches to PGS, there seemed less divergence between the two views than ever before.

Consensus appeared to be that infertile couples hoping to improve their chance of pregnancy with PGS should be informed of all the facts - advantages and disadvantages - before making their own decision. Thus Gary Harton, a former Chair of the Consortium, when asked to define the 'advantages', ignored the former attractions of higher delivery and implantation rates but confined his list to a lower chance of miscarriage and a reduced time to pregnancy, both likely benefits for women of an advanced maternal age. 'PGS can't make an embryo better,' said Harton. 'Maybe in the US we did go too far in saying that everyone would benefit from PGS.' Dagan Wells, who despite Brexit was inexplicably speaking with Harton on behalf of the USA, seemed to agree, accepting that the data were plentiful enough and that patient choice could and should be adequately informed.

And this conclusion seemed too to be shared by the Europeans, who quickly discarded their Yankee doodle dandy outfits ('We all used to be Americans') in favour of a more cautious 'holistic' approach. Paying due respect to last year's three big trials (Rubio et al, ESTEEM and STAR) Willem Verpoest from the Brussels group agreed that a few patients might well benefit from PGS. 'I think PGS with small advantages could be part of a programme for some patients,' said Verpoest, 'But we have to look at a broad picture of IVF in which PGS is there not just for those who can afford it, but really for those who need it.' Right now, especially in view of the Rubio trial, the PGS advantage seems to be concentrated on a reduced miscarriage risk, fewer transfers, and a shorter time to pregnancy.[2]

So, if as Joyce Harper claimed, the PGD Consortium has produced its share of controversy, as well as guidelines and data reports, harmony finally seemed a little nearer at this meeting, in a more vocal understanding that PGS can't improve the quality of an embryo and that any advantage is probably more subtle and selective than delivery rate alone.

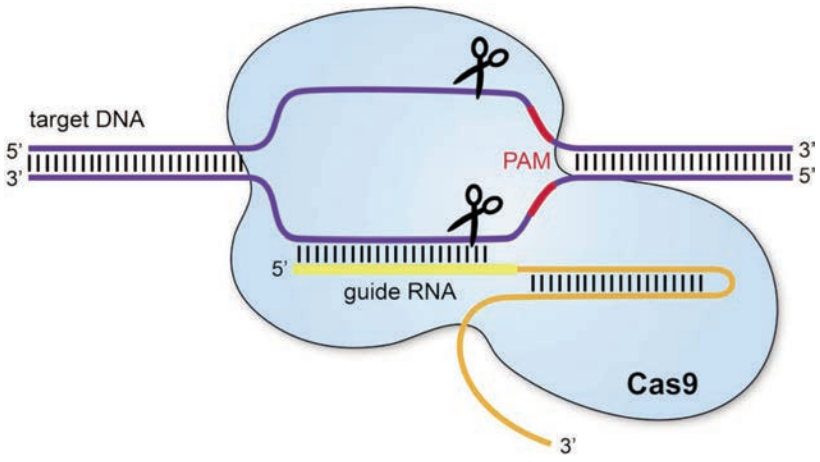
It was noticeable too that many of the speakers had quickly adapted to the new nomenclature of ART and were seamlessly referring to PGT-A and PGT-M without relapse to PGS or PGD. So what next for the Consortium after 20 years? The PGT Consortium, and a new era of consensus?

Simon Brown
Focus on Reproduction

'We all used to be Americans.' Edith Coonen and Willem Verpoest before removing their US outfits in the PGS debate in favour of a more restrained European style. Joyce Harper, below, singled out the controversy over PGS as one feature of the Consortium's history.

1. Scott RT Jr, Upham KM, Forman EJ, et al. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril 2013; 100: 624-630.
2. Rubio C, Bellver J, Rodrigo L, et al. In vitro fertilization with preimplantation genetic diagnosis for aneuploidies in advanced maternal age: a randomized, controlled study. Fertil Steril 2017; 107: 1120-1129.

CRISPR-Cas9 technology identifies gene necessary for embryogenesis



CRISPR-Cas9: A guide RNA designed to target a specific sequence of DNA directs the Cas9 system to the target DNA. Cas9 is then able to cut out the mutant DNA sequence and deactivate the offending gene.

In a remarkably short period of time the genome editing technique of CRISPR-Cas9 has been used to identify the necessary role of the pluripotency transcription factor OCT4 in human embryogenesis.[1] By 'efficiently and specifically' deactivating the gene encoding OCT4 in diploid human zygotes, a large group of international scientists collaborating with Kathy Niakan from the Francis Crick Institute in London found that blastocyst development was compromised; by contrast, presence of the gene ensured that blastocyst development was established.

As a conclusion to the study, the group explained that CRISPR–Cas9-mediated genome editing is a powerful method for investigating gene function in the context of human development. 'One way to find out what a gene does in the developing embryo is to see what happens when it isn't working,' Kathy Niakan explained to the Reuters news agency. 'Now we have demonstrated an efficient way of doing this, we hope that other scientists will use it to find out the roles of other genes.'

To test if OCT4 is required in human embryos, the group performed CRISPR–Cas9 editing on thawed surplus IVF zygotes. The gene encoding OCT4, POU5F1, is first transcribed at the 4-8 cell stage. coincident with embryo genome activation. Thus, by the eight-cell stage, cleavage arrest was observed in 62% (23 of 37) of the targeted embryos compared to 53% (9 of 17) of the control embryos. These effects are reported as 'due to the loss of OCT4'.

The implications of the study - that genome editing can be used efficiently to modify the DNA of a human embryo - prompted an editorial in *Nature* 'to take stock and discuss how they should navigate this type of research'.[2]

The question at the heart of the debate, as has been reported here before, is that scientists can now make permanent modifications to the human germ line. A statement from the US National Academies of Science, Engineering, and Medicine, summarised at the ESHRE Annual Meeting by Robin Lovell-Badge, advised that editing the human germ line could be justified for the scientific purpose of research into fundamental biology. Clinical applications might only be considered after requirements of strong research groundwork and oversight have been met.

'Regulators, funders, scientists and editors need to continue working together to define the details of the path forward for germline genome editing,' the *Nature* editorial concludes.

1. Fogarty NME, McCarthy A, Snijders KE, et al. Genome editing reveals a role for OCT4 in human embryogenesis. Nature 2017; 550: 67-73.
2. Take stock of research ethics in human genome editing. Nature 2017; 549: 307.

More studies to change point mutations

The OCT4 report appeared in *Nature* just two months after Shoukhrat Mitalipov of the Oregon Health and Science University had described correction of a mutation causing the heart condition, hypertrophic cardiomyopathy, using the CRISPR-Cas9 technology.[1] 'Every generation on would carry this repair because we've removed the disease-causing gene from that family's lineage,' Mitalipov told the press.

The claim has since been disputed, with one group of scientists saying the results of the study only show 'an absence' of the disease-causing mutation, not a repair.[2] Mitalipov has promised to respond.

Meanwhile, what appears to be an advance on the CRISPR-Cas9 technology has been partially successful in changing the base pair.[3] 'We are the first to demonstrate the feasibility of curing genetic disease in human embryos by base editor system,' said the Chinese researchers.

The experiment took nuclei from skin cells taken from a patient with beta-thalassaemia, and inserted them into empty donor eggs (by somatic cell nuclear transfer), thus creating human embryos carrying the mutation. They then scanned the 3 billion base pairs DNA in the embryos for the specific beta-thalassaemia point mutation, and changed it back to its correct sequence using an enzyme.

The paper drew the usual share of cautious comment. However, just weeks afer this first DNA surgery paper had appeared in *Nature*, two further developments were reported, each claiming to be a further advance on the 'blunt instrument' of CRISPR technology.

Two research groups, each from the Broad Institute of MIT and Harvard in Massachusetts, announced techniques that allow targeted alterations to DNA and RNA.

In what *Science* called 'a new frontier' for the CRISPR technology, editing

High levels of mitochondrial DNA predict failed implantation in chromosomally normal embryos

Previous findings confirmed in first prospective blinded study

Two years after Elpida Fragouli and colleagues raised the potential of mitochondrial DNA quantification as a marker of embryo viability in IVF, the same group has now confirmed their findings in a blinded prospective study with highly significant results.[1,2]

The results, which were presented in preliminary form at ESHRE's 2016 Annual Meeting, replicate what the earlier studies had suggested - that euploid blastocysts of good morphology but with high mtDNA levels have a greatly reduced implantation potential. Such a relationship, the investigators suggest, would thus partly explain the paradox that at least 30% of chromosomally and morphologically normal embryos fail to produce an ongoing pregnancy. This latest study is the first test of mtDNA quantification in a prospective, blinded study.

The study was a mtDNA analysis of 199 chromosomally and morphologically normal blastocysts of which nine (5%) contained unusually high levels of mtDNA. Of the others, 121 (60%) led to ongoing pregnancies, 11 (6%) led to biochemical pregnancies, and 10 (5%) spontaneously miscarried. All (100%) of these blastocysts had mtDNA levels considered to be normal/low. This left 57 embryos which failed to implant, including the nine with high mtDNA levels.

First author Elpida Fragouli: more evidence that mtDNA is a 'new biomarker' of embryo viability.

This meant that the ongoing pregnancy rate for morphologically good, euploid blastocysts, with normal/low levels of mtDNA was 64%. In contrast, the ongoing pregnancy rate for the same type of embryos but with elevated mtDNA levels was 0/9 (0%). This difference was highly statistically significant (P <0.0001).

The results, say the authors, 'provide further evidence that mtDNA quantification has the potential to serve as a new biomarker of embryo viability', adding that a higher mtDNA level was accompanied by implantation failure in all cases in which it was detected.

However, the authors also note that other studies over the past two years have not always been able to replicate these results, finding no association between mtDNA quantity and implantation potential. This 'controversy' has been somewhat played out in the journals, with Fragouli et al here explaining the discrepancies by 'technical issues' and 'clinic-specific factors'. They thus remain a little circumspect in their conclusions, noting that mtDNA quantification 'has the capacity' to identify a subset of blastocyst stage embryos with highly impaired implantation potential. They also note that an explanation why some non-viable blastocysts exhibit elevated mtDNA levels 'remains to be determined'.

Thus, Dagan Wells, one of the authors of this study, reiterates in a *Fertility and Sterility* opinion piece that not all studies of mtDNA in human embryos have been able to detect the pattern seen here, adding that 'further work is needed in order to categorically confirm or refute its existence', ultimately, another randomised trial.[3]

1. Fragouli E, Spath K, Alfarawati S, et al. Altered levels of mitochondrial DNA are associated with female age, aneuploidy, and provide an independent measure of embryonic implantation potential. PLoS Genet 2015; 11:e1005241.
2. Fragouli E, McCaffery C, Ravichandran K, et al. Clinical implications of mitochondrial DNA quantification on pregnancy outcomes: a blinded prospective non-selection study. Hum Reprod 2017; 32: 2340-2347.
3. Wells D. Mitochondrial DNA quantity as a biomarker for blastocyst implantation potential. Fertil Steril 2017; 108: 742-747.

responsible for inheritable disease

RNA would remove some of the ethical concerns about DNA editing.[4] The study authors developed a new version of the DNA cutting enzyme - called Cas13b - to correct multiple mutations, which, they say, might not alter disease risk alone, but combined might have additive effects and disease-modifying potential.

The second report describes new developments in rewriting individual base pairs of DNA.[5] This ability to alter single bases, says *Nature*, means that researchers can now attempt to correct more than half of all human genetic diseases. 'These new techniques are more like precision chemical surgery,' added David Liu, a chemical biologist at the Broad Institute.

The first reported base editor system could achieve only two kinds of chemical conversions: a cytosine (C) into a thymine (T) or a guanine (G) into an adenine (A). The latest technique works in the other direction, converting T to C or A to G. It can therefore undo the most common types of 'point mutation', which involve single aberrant bases.

1. Ma H, Marti-Gutierrez N, Park S-W, et al. Correction of a pathogenic gene mutation in human embryos. Nature 2017; 548: 413-419.
2. Egli D, Zuccaro M, Kosicki M, et al. Inter-homologue repair in fertilized human eggs? BioRxiv 2017: doi.org/10.1101/181255.
3. Liang P, Ding C, Sun H, et al. Correction of β-thalassemia mutant by base editor in human embryos. Protein Cell 2017; doi.org/10.1007/s13238-017-0475-6
4. Cox DBT, Gootenberg JS, Abudayyeh OO,. et al. RNA editing with CRISPR-Cas13. Science 2017; http://dx.doi.org/10.1126/science.aaq0180
5. Gaudelli NM, Komor AC, Rees HA, et al. Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. Nature 2017; http://doi.org/10.1038/nature24644.

AMH 'a poor prognostic indicator of live birth' . . .

Study finds conception probablity no different with low or normal levels of AMH

There was never any strong evidence that anti-müllerian hormone was effective as a marker of fertility. Studies suggested that it was useful as a predictor of response to ovarian stimulation for IVF, and possibly of menopause onset, but never a marker of pregnancy or delivery.

Yet a press release issued by *JAMA* highlighting a study of AMH as a marker of fertility claims that 'biomarkers of ovarian reserve are being promoted as markers of reproductive potential'.[1] The study, in finding no association between time-to-pregnancy and levels of AMH, advises that 'women should be cautioned against using AMH levels to assess their current fertility'.

The study, which took place at the University of North Carolina at Chapel Hill, was a prospective cohort study starting in 2008 of 750 women aged 30-44 years with no history of infertility. They had all been trying to conceive for three months or less. From blood samples taken at baseline (and with adjustment for BMI, smoking and age), follow-up showed that women with low AMH (<0.7 ng/mL) did not have a significantly different predicted probability of conceiving by six cycles (65%) from women with normal values (62%) - or after 12 cycles of trying. Similar results were found for inhibin and FSH values.

An accompanying editorial confirms that AMH measurement has been part of the clinical evaluation of infertility for more than a decade, and that 'knowing a woman's AMH before she begins stimulation is helpful in medication management'.[2] Low AMH levels, adds the commentary, might help the physician proceed with a more aggressive protocol, but remain a poor indicator for live birth.

The commentary goes on to note that the large size of the North Carolina study, its community-based 'robust' measurement methods give the findings much credibility, thus suggesting that 'it may be necessary to reevaluate what an AMH level really means for a woman's reproductive health'. What the author clearly has in mind - as has the *JAMA* press release - are 'commercial applications by the entrepreneurial sector'.

'Some websites,' the commentary notes, 'offer fertility assessment . . . and if AMH, among other tests, indicates low ovarian reserve, referral to a fertility specialist or egg freezing is recommended. Such a thought process assumes that a lower-than-normal number of remaining ovarian follicles may suggest a lower likelihood of future fertility.'

Lead author Anne Steiner told the Reuters news agency that, while 'these blood tests do predict how well a woman will respond to fertility treatment, they do not predict her likelihood of conceiving naturally. This challenges the clinical dogma that diminished ovarian reserve is a cause of infertility.'

In IVF, female age has long been considered the most accurate predictor of ongoing pregnancy, with AMH (and AFC), added to age, useful predictors of response to stimulation, especially poor response.

1. Steiner AZ, Pritchard D, Stanczyk FZ. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. JAMA 2017; 318: 1367-76.
2. Santoro N. Using antimüllerian hormone to predict fertility. JAMA 2017; 318: 1333-1334.

Acceptance of ART more than GDP determines uptake

A study aiming to determine the financial, demographic and cultural determinants of ART treatments in Europe has found that the 'normative cultural acceptance of ART' is the major driver, above and beyond differences in a country's wealth, demographics and religious composition.

The findings were based on a study of more than 30 European countries in 2010, where prevalence of ART uptake was cross-linked to demographic and cultural factors.[1]

Although the analysis showed that a 1% increase in national GDP was indeed associated with 382 additional ART procedures per million women of reproductive age, this was reduced to 99 when cultural and demographic factors were accounted for. A one-point increase in 'average approval' of ART in a country was associated with 276 additional treatments per million women of reproductive age.

1. Präg P, Mills MC. Cultural determinants influence assisted reproduction usage in Europe more than economic and demographic factors. Hum Reprod 2017; doi: 10.1093/humrep/dex298.

. . . while an individualised approach based on AFC makes no difference to cumulative birth rate

● High doses of FSH 'will not improve outcomes in predicted poor responders'

The OPTIMIST study, a large prospective study performed in the Netherlands in which two randomised trials were embedded, indicates that individualised FSH dosing based on antral follicle count makes no overall difference to outcome when compared with a standard protocol.[1] The same conclusion was reached in each of the two embedded RCTs, where dose was adjusted for predicted poor or hyper-response.[2,3] In the latter trial, however, a lower FSH dose did reduce the incidence of mild and moderate OHSS, but had no impact on severe OHSS.

The results of the studies were presented in preliminary form at ESHRE's 2016 Annual Meeting in Helsinki, where an individualised approach to stimulation for IVF was a notable feature of proceedings. The ESTHER trial, for example, also described in Helsinki, similarly found comparable outcomes ('non-inferior') and a lower incidence of complications when individualised dosing was stratified according to AMH and other baseline characteristics and compared to a standard approach.[4] This and other studies were deemed by the OPTIMIST investigators as of 'no sound evidence' for the widespread practice of dose adjustment based on ovarian reserve - hence the need for their trial.

The study was performed between 2011 and 2014, with subjects allocated to the cohort study or two trials depending on their baseline AFC: predicted poor response trial (RCT1) AFC 0-7 and 8-10; predicted hyper-response (RCT2) AFC >15; or the cohort (AFC 11–15). In both the RCTs subjects were randomised to an individualised dose of FSH (RCT1 450 or 225 IU; RCT2 100 IU) or to a standard FSH dose (150 IU). Women in the normal cohort all received the standard dose of 150 IU. A total of 1515 women were included in the study, with roughly a third in each of three arms.

The authors state by way of background that currently AFC and serum AMH are 'the most practical and reliable ovarian reserve tests available' and are most often used for personalised dose adjustment in daily clinical practice. However, based on their results - 56% cumulative LBR in the individualised strategy and 58% in the standard - they now caution that 'individualized FSH dosing for the IVF/ICSI population as a whole should not be pursued as it does not improve live birth rates' and increases costs. 'Women scheduled for IVF/ICSI with a regular menstrual cycle are therefore recommended a standard FSH starting dose of 150 IU per day.'

These results were especially evident in the predicted poor responders trial, where upward adjustments of dose (to a maximum of 450 IU per day) made no difference to outcome - 42% cumulative LBR in the individualised dose group and 45% in the standard 150 IU group, thereby confirming that 'high dosages of gonadotrophins will not improve IVF outcomes in predicted poor responders'.

This trial and the cohort study also found that the individualised approach was more expensive than the standard - but did reduce the occurrence of mild and moderate OHSS in predicted hyper-responders, and subsequently the costs for management of these OHSS categories.

First author Charine van Tilborg presenting results of the OPTIMIST trial in Helsinki. The published study report now cautions that 'individualized dosing as a whole should not be pursued as it does not improve live birth rates'.

1. Van Tilborg TC, Oudshoorn SC, Eijkemans MJC, et al. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis, Hum Reprod 2017; doi:10.1093/humrep/dex321.
2. Van Tilborg TC, Oudshoorn SC, Torrance HL, et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder. Hum reprod 2017; doi:10.1093/humrep/dex318 .
3. Oudshoorn SC, Van Tilborg TC, Eijkemans MJC, et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder. Hum Reprod 2017; doi:10.1093/humrep/dex3.
4. Nyboe Andersen A, Nelson SM, Fauser BCJM, et al. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. Fertil Steril 2017; 107: 387–396.

No raised cancer risk in children conceived with donor gametes

A cross-linkage study of cancer risk in ART children by Alastair Sutcliffe and UK colleagues won the Clinical Science Award for oral presentation at the 2013 Annual Meeting in London. The study, which was later published in the *New England Journal of Medicine*, linked the HFEA records of all 106,381 children born after ART in the UK from 1992 to 2008 to national cancer records to calculate the number of ART children who subsequently developed cancer.[1] Results showed that there was no overall increased risk of cancer in the ART children born throughout the 17-year study period. Overall, 108 cancers were identified in the ART children, which was comparable with the 110 cases which would have been expected from general population figures.

The group's latest study, of a similar design and construction, has now analysed the link between ART and cancer risk in children conceived with donor gametes and again found no overall increased risk.[2]

This study again linked the records of all children born in Britain (via the HFEA database) after all forms of donor ART between 1992 and 2008 to the UK National Registry of Childhood Tumours (NRCT) to determine the number who subsequently developed cancer by 15 years of age. Twelve cancers were detected against 14.4 expected in the general population, again providing results described as 'reassuring for families and clinicians'. The group's earlier linkage study did not include children born after donor ART.

1. Williams CL, Bunch KJ, Sutcliffe AG. Cancer risk among children born after assisted conception. NEJM 2014; 370: 975-976.
2. Williams CL, Bunch KJ, Murphy MFG, et al. Cancer risk in children born after donor ART. Hum Reprod 2017;

US clinics failing to follow single embryo transfer guidelines

SART study confirms lower LBRs with SET, but significantly lower rates of multiple delivery

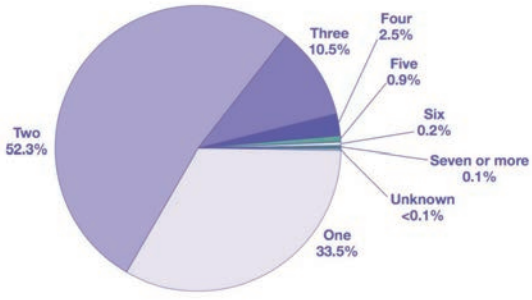
Single embryo transfer was linked to a 10-15% lower live birth rate than double embryo transfer but a 47% lower multiple birth rate in a new analysis of US ART data submitted to SART between 2204 and 2013.[1] The findings, says SART, 'present an opportunity to increase the rate of SET across the United States and thereby reduce the multiple birth rate and its associated poor perinatal outcomes'.

Similar sentiments are echoed in an accompanying journal editorial, which lists improvements in embryo selection, more blastocyst transfers and cumulative outcomes with sequential SET as likely 'to convince physicians, patients, and insurance providers of the benefits and feasibility of SET'.[2] A healthy singleton delivery should be the goal of all IVF cycles, and 'this is best achieved by SET', the editorial says.

The study population of the SART analysis included more than 200,000 women having fresh autologous or donor IVF, or subsequent frozen cycles. In those with a favourable prognosis - defined as younger maternal age, with blastocyst transfer, and additional embryos cryopreserved - the gain in the live birth rate from SET to DET was around 10–15%; however, the multiple birth rate increased from approximately 2% to greater than 49% in both autologous and donor fresh and frozen–thawed transfer cycles.

The study also made other findings which in the report are presented as 'predicting high pregnancy rates with SET': maternal age, blastocyst transfer in fresh cycles, and additional embryos for freezing. For example, when no embryos were frozen in both cleavage-stage and blastocyst transfers, the LBR was lower and declined with advancing maternal age than with transfers in which embryos were frozen.

However, the editorial describes the decline in LBR between SET and DET treatments as 'not attractive to either physicians or patients, for whom IVF pregnancy rates matter a great deal'. Such sentiments no doubt account for the continuing high twin delivery rate in the USA, which SART says have been rising since 1980, reaching an all-time high of 23% in 2014.



Numbers of embryos transferred in all US transfers in fresh non-donor cycles in 2015: CDC data.

As a result, the ASRM earlier this year revised its guidelines on embryo transfer to call for SET for women under the age of 38 with a favourable prognosis.[3] However, according to this latest SART report, in 2012 the average number of embryos transferred was 1.9 in women aged <35 years, 2.2 in women aged 35–40 years, and 2.7 in those aged >40 years. The US rate of eSET in patients aged <35 years) was 15.3%.

1. Mersereau J, Stanhiser J, Coddington C, et al. Patient and cycle characteristics predicting high pregnancy rates with single-embryo transfer: an analysis of the Society for Assisted Reproductive Technology outcomes between 2004 and 2013. Fertil Steril 2017; 108: 750–756.
2. Van Vourhis B, Mejia RB. Single-embryo transfer point—it is the way forward. Fertil Steril 2017; 108: 757.
3. Practice Committee of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of embryos to transfer: a committee opinion. Fertil Steril 2017; 107: 901–903.

Live birth and miscarriage both linked to better outcome in next two IVF treatment cycles

● Results 'reassuring' to those considering further treatment after pregnancy loss

A cohort study based on seven-year data from the HFEA database indicates that women who had miscarried or had a live birth in their first complete cycle of IVF had a higher chance of live birth in their next two cycles of treatment than those who had no pregnancies.[1] This, say the authors, is the first time that cumulative chances of conception have been calculated after IVF miscarrage.

The retrospective study, which was based on a cohort of 112,549 women who started their first IVF treatment between 1999 and 2008, found that those who miscarried during their first cycle had a 40.9% chance of having a baby over their next two further cycles. However, those who had not conceived in their first cycle had only a 30.1% chance of live birth, while women who had given birth following their first full cycle of IVF had a 49% chance of giving birth again in subsequent IVF cycles.

The study's lead author, Natalie Cameron from Aberdeen, UK, pictured left, told the BBC that miscarriage can be devastating for any couple, but especially those who have already struggled with infertility.

'This,' she said, 'coupled with the emotional and financial burden of multiple cycles of treatment can make many couples lose confidence and give up. We hope our findings will provide reassurance to these couples as they consider their options for continuing treatment.'

Indeed, say the auhors in their conclusion, 'although both pregnancy loss and non-pregnancy are viewed as a "failure", our results show that the two have very different prognoses'.

As background to the study, the investigators cite increasing maternal age, previous miscarriages and PCOS as risk factors associated with miscarriage, with additional IVF-specific risk factors noted as the transfer of frozen embryos, cleavage-stage embryo transfer, poor response to ovarian stimulation (linked to maternal age), previous miscarriages in IVF conceptions and certain causes of infertility such as uterine factor and endometriosis.

The authors also add that cumulative LBRs are a better representation of success rates than traditional live birth rates - 'so our analysis of success rates over multiple complete cycles will aid informed decision-making and help tailor expectations for these couples'.

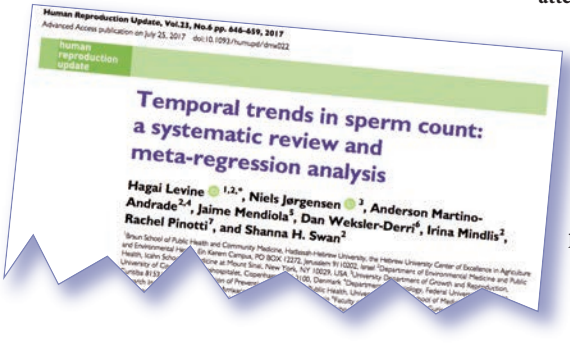
1. Cameron NJ, Bhattacharya S, Bhattacharya S, McLernon DJ. Cumulative live birth rates following miscarriage in an initial complete cycle of IVF: a retrospective cohort study of 112 549 women. Hum Reprod 2017; 32: 2287-2297.

Declining sperm counts: expert calls for more research into lifestyle factors

Niels Skakkebaek, the Danish andrologist whose 1992 study of dramatically declining sperm counts caused huge controversy, has called for urgent research into male fertility following further reports of declining sperm counts.[1] A meta-analysis earlier this year concluded that Western sperm counts had fallen by 52% between 1973 and 2011 - a warning described by investigators as 'the canary in the coal mine'.[2]

Writing in the *British Medical Journal*, Skakkebaek said the decline in sperm counts should be compared to trends in testicular cancer, where a clear inverse correlation was evident. 'This leaves little doubt,' he wrote, 'that we should look into environmental causes – including lifestyle effects.' He also urged more research into the impact of hormone-disrupting chemicals, such as pesticides, and said that maternal exposure could be linked to testicular dysgenesis syndrome, a male reproductive condition.

In 1992, Skakkebaek and colleagues found a 'genuine decline' in semen quality over the previous 50 years. The study had analysed a total of 61 reports published between 1938 and 1991, providing data on almost 15,000 men, and found that mean sperm count had fallen from 113 million/ml in 1940 to 66 million/ml in 1990.


Human Reproduction Update, Vol.23, No.6 pp. 646-659, 2017
Advanced Access publication on July 25, 2017 doi:10.1093/humupd/dmx022
human reproduction update
Temporal trends in sperm count: a systematic review and meta-regression analysis
Hagai Levine [1,2,*], Niels Jørgensen [3], Anderson Martino-Andrade [2,4], Jaime Mendiola [5], Dan Weksler-Derri [6], Irina Mindlis [2], Rachel Pinotti [7], and Shanna H. Swan [2]

1. Skakkebaek N. Disturbing trends in men's reproductive health demand urgent attention. BMJ 2017; 359: 4517.

2. 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; 23: 646-659.

3. Carlson E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during the past 50 years. BMJ 1992; 305: 609-13.

ESHRE takes next steps for subspecialist training

● Successful application for formal status as accredited education provider

ESHRE is facing an ever-growing demand from reproductive medicine centres across Europe to provide subspecialist training for young clinical trainees who have successfully completed their basic training in Obstetrics and Gynaecology. In the past, an enhanced syllabus for training in accredited centres was supported by an electronic log book for trainees to record all their education and competence steps over the three-year training period. This educational opportunity was (and still is) particularly welcome in many EU countries where a recognised training authority cannot provide subspecialist training and where ESHRE can help to fill this gap.

Now, however, in a logical move to enhance ESHRE's role in the provision of subspecialist training, the Society has successfully applied to UEMS (Union of European Medical Specialists) to be recognised as the first subspecialist organisation in O&G and as the first provider of subspecialist training in reproductive medicine. ESHRE is now recognised as the 'Division of Reproductive Medicine' within the UEMS Section of O&G, which means that ESHRE can now develop its own specialist examination in reproductive medicine.

This specialist exam (EFOG-RM, the European Fellowship in Obstetrics and Gynaecology for Reproductive Medicine) is being developed in conjunction with several educational experts from EBCOG. This is now moving ahead rapidly in order that the first exam may be held in Barcelona in July to coincide with the Annual Meeting. A great deal of help from the SIGs has been invaluable here in creating a pool of MCQ, EMQ and SBA questions.

● The advantage of being an ESHRE accredited training centre is twofold and not only restricted to providing the full ESHRE syllabus of reproductive medicine: first, training itself may encourage the retention of a future generation of specialists in reproductive medicine; and second, the Executive Committee of ESHRE hopes to extend its present travelling fellowships to encourage and financially support young ESHRE members to spend 3-6 months in an ESHRE-accredited centre pursuing research or advanced training to complement their educational portfolio.This fellowship scheme began well with ESHRE's collaboration with the ReproUnion centres in Scandinavia.

The list of ESHRE-accredited centres can be seen above, while the EBCOG website hosts a list of recognised centres for basic training in O&G.

Anis Feki
ESHRE Lead for Subspecialist Training in Reproductive Medicine

ESHRE-accredited centres

Country	Centre	Valid until
Austria	Vienna University Hospital (AKH)	31.08.21
Belgium	Universitair Ziekenhuis Brussel (VUB)	31.08.20
Belgium	University Hospital Gasthuisberg, Leuven	31.12.20
Greece	University of Athens Medical School	31.03.19
Greece	University Hospital of Larissa	30.09.17
Greece	Aristotle University of Thessaloniki	30.09.20
Italy	Humanitas Research Hospital, Milan	30.03.20
Slovenia	University Medical Centre Ljubljana	31.10.21
Slovenia	Hospital Univerzitetni Klinicni, Maribor	30.06.21
Spain	Instituto Bernabeu, Alicante	**30.06.16**
Spain	IVI Madrid	**30.06.18**
Spain	IVI Valencia	31.01.18
Sweden	Karolinska University Hospital, Stockholm	31.12.18
Sweden	Uppsala University Hospital	31.12.18
Switzerland	Basel University Hospital	31.07.16

Subspecialist in reproductive medicine: what it means

The Reproductive Medicine Subspecialist is a specialist in O&G who has had advanced theoretical and practical training in:
1. Medical and surgical management of infertility
This may involve treatment of the male if practised by the gynaecologists in that country. It will involve a range of ART techniques.
2. Reproductive endocrinology
Comprehensive management includes diagnostic and therapeutic procedures and audit of outcome.
After completion of their training, subspecialists continue to devote at least half, and probably more, of their working time to reproductive medicine.
ESHRE emphasises that the role of a subspecialist is complementary and not competitive to the specialist in O&G.

Representing the interests of ART sector in EU tissue developments

● Greater interaction between ART and authorities

In October ESHRE as a collaborating group with specific interest in ART took part in a 'dissemination' meeting of ARTHIQS (Assisted Reproductive Technologies & Haematopoietic Stem Cells – Improvements for Quality & Safety), a joint action financed by the European Commission and led by the Agence de la Biomédecine, France.

ESHRE's participation reflects the specifics which the ART sector now requires in application of the 2004 EUTCD (European Union Tissues and Cells Directive) with respect to the regulation of ART activities and inspections of ART establishments.

The project also recognises as very beneficial the interaction of competent authorities with professionals and professional societies, and to this end ESHRE was the scientific society in ART chosen to participate in this event. Borut Kovacic, a member of the ESHRE Executive Committee, presented the position of the 'ART Professional and Scientific Society', while others presented the view of different national authorities in subjects such as governance and regulation in ART, inspections, role and missions of CA, and ART activity registers.

In these past few years both professionals and competent authorities have worked towards co-operation and learning; indeed, cross-participation in meetings such as this may help to strengthen common understanding and goals.

One major outcome from this event was the establishment of a network of European ART-dedicated competent authorities which may share resources from European member states on sensitive ART areas such as information to donors and recipients, or follow-up of offspring through appropriately adjusted registers. It is also hoped that such a network will allow efficient paths of communication between competent authorities and professionals, to integrate discussion on key challenges at the legal, social and ethical levels.

'Dissemination', the subject of this October meeting, is one of five work packages within the project's organisation. More information at http://arthiqs.eu

Carlos E. Plancha
Chair of Organising Committee
Dissemination Meeting of the European Joint Action ARTHIQS

Remote exam for embryology certification

A pilot project to allow ESHRE-member embryologists to sit their certification exams in their home country will take place later this year. The scheme was proposed by the Indian Fertility Society and now, having been examined and developed by ESHRE in collaboration with IFS, will allow Indian embryologists to take the certification exams in New Delhi at the same time as the regular exams are happening in Barcelona.

'If succesful, the scheme will allow candidates in distant countries to complete their certification without having to travel long distances,' said Borut Kovacic, Chair of the Certification Committee.

The online exams will take place at the All India Institute of Local Self Government in New Delhi on 30 June. Mock exams were trialled last year, with 12 candidates tested within ESHRE's guidelines and strict invigilation policy.

The trial of e-exams in India will allow ESHRE to assess their suitability for other certification exams at the Annual Meeting or even in other parts of the world, being of huge benefit to hundreds of members who for financial reasons are not able to travel to Europe for the exams.

ESHRE centre certification to go ahead in 2018

The Executive Committee has agreed to go ahead with a scheme to award ESHRE certification to those centres which meet an agreed and clear set of standards. These will be defined by 'general criteria', laboratory and clinical criteria, and results. Centres would apply for certification and be evaluated by a team of three trained assessors.

Initial applications will be made by a check-list form covering basic details of staffing, facilities, treatments available and quality management. Assessments would follow to ensure compatibility with the required criteria.

The proposals for centre certification were made last year by former Chairman Luca Gianaroli, who now heads the working group developing the programme. He expects operations to begin in early 2018 with a call for inspectors, qualified professionals who will be specifically trained to carry out site visits at applicant centres. Centres will be encouraged to contact ESHRE's Central Office about applications in Spring 2018.

What will clinics gain from ESHRE certification? 'There are several things,' says Gianaroli. 'Quality management and improvement, an objective quality assessment for patients and professionals, and reduced fees for staff members attending ESHRE educational activities.' During the initial phase of the project, only European centres will be entitled to apply. This will allow validation of the programme before any wider introduction.

Luca Gianaroli: Multiple gains for centres achieving ESHRE certification.

The challenge of 'vigilance' for European ART analysis

- Can registries keep pace with ART's advances?
- The limits of cross-sectional data analysis

Within the past 18 months ESHRE's European IVF Monitoring (EIM) Consortium has published three reports on data generated by European registries in IVF - for the years 2011, 2012 and 2013.[1,2,3] Centres participating in the scheme - which represent around 90% of all ART treatments performed in Europe - have just completed their data submissions for 2014, which will be presented in preliminary form in Barcelona later this year. All submissions are now completed via an electronic system, which has made the exercise more efficient for centres and for ESHRE's analysis.

Indeed, says the EIM's new Chairman Christian De Geyter, the gap between data submission and publication could not now be as short as three years without the online system. 'The software has much improved the completeness and the quality of the incoming data,' he says. 'It's reduced the work load, and helped to speed up data analysis and interpretation.'

However, adds De Geyter, despite the record number of centres participating (85% of all European institutions), data collection is not complete, and this remains one of several challenges now facing EIM. The main explanation for the continuing shortfall is the apparent discrepancy between voluntary and compulsory data reporting, the latter, says De Geyter, 'being more complete and of better quality'.

A further challenge is the huge change which ART has experienced in the past few years - cross-border care, cryopreservation of gametes, tissues and embryos, elective single embryo transfers, segmentation of treatments, and long-term follow up. Can the EIM registries keep pace with these advances?

'From the outset,' says De Geyter, 'our data collection was cross-sectional, with results reported each year. But cross-sectional data analysis cannot reflect today's clinical reality of segmentation and cryopreservation unless we can incorporate cumulative data analysis. Similarly, cryopreservation of gonadal tissues at all ages is slowly becoming more routine and surveillance of these procedures can only be assessed with a long-term vigilance approach.'

And vigilance is what really interests the political observers of EIM data, not so much its cycle numbers, huge though they may be.

De Geyter's vision is that any initial movement towards ART and/or cryopreservation of gametes or tissue would be identified by a unique individual code, which would become 'an integral part of early infertility care', and thus a quality label for all stakeholders.[4]

'The code should follow the individual or couple during the various steps of infertility care,' explains De Geyter, 'even if it changes the treatment unit or the country of residence. All reporting to the national ART registry should be accompanied by this individual code and all treatment results should be labelled with the code, even after ten or more years. This system woul allow the true cumulative data analysis.'

Such a system, he suggests, would be the biggest challenge of the next five years, enhancing the development of EIM 'from mere ART surveillance to real vigilance'.

Swiss gyneacologist Christian De Geyter, new Chairman of the EIM steering committee.

Meanwhile, EIM's safety monitoring remains confined to data on multiple deliveries, prematurity, OHSS, and incidental complications after oocyte collection. This, however, has been no small contribution, as today reflected in the continuing decline in multiple transfers and reduction in ART complications, especially OHSS. Already, public reassurance in ART must owe much to the continuing EIM reports, however great their remaining challenges in vigilance must be.

1. Kupka MS, D'Hooghe T, Ferraretti AP, et al. Assisted reproductive technology in Europe, 2011: results generated from European registers by ESHRE. Hum Reprod 2016; 31: 233-248.
2. Calhaz-Jorge C, De Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2012: results generated from European registers by ESHRE. Hum Reprod 2016; 31: 1639-1652.
3. Calhaz-Jorge C, De Geyter C, Kupka MS, et al. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. Hum Reprod 2017; 32: 1957-1973.
4. De Geyter Ch, Wyns C, Mocanu E, et al Data collection systems in ART must follow the pace of change in clinical practice. Hum Reprod 2016; 31: 2160-2163.

Ireland at last commits to ART legislation

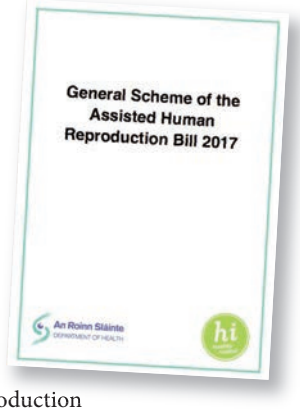
- Government approves proposals, which are expected to become law in 2018
- Reporting ART results hoped to become mandatory

Twelve years after Ireland's Commission on Assisted Human Reproduction report containing 40 recommendations was published, the Irish Government has finally put forward a Bill on Assisted Human Reproduction and is planning to introduce state-funded ART support for patients.[1,2] Proposals have been agreed by the Irish Parliament whereby an Assisted Human Reproduction Bill would cover 'the whole area' of ART. This, said the Health Minister, would include ethical considerations and state funding. 'I made it very clear that I want to put in place supports to help subsidise the cost of IVF for families,' added the minister.

The bill was approvd by the Irish government in October, and, following cabinet approval, the proposals seem likely to become law in Ireland sometime in 2018, with public subsidies introduced a little later.

As in Poland, progress with legislation in ART has been complicated by the strong opinion of the Roman Catholic Church. Termination of pregnancy remains a matter of political debate in Ireland, with pro-life/pro-choice campaigns lobbying politicians before a promised amendment to the Constitution, which will need to be put forward by referendum.

The ART proposals also make provision for an independent Assisted Reproduction Regulatory Authority to oversee clinics and regulate the conditions surrounding the broad practice of ART, including gamete and embryo donation. Regulations are expected to include prohibition of commercial surrogacy and payment for donor gametes. All research involving embryos and stem cells will be regulated. The authority will also have responsibility to ensure 'the welfare and best interests of children' born through ART.



Irish IVF specialist and EIM steering committee member Edgar Mocanu: 'The decision is long over due.'

Edgar Mocanu, a member of ESHRE's EIM steering committee, Past-Chair of the EU Affairs committee, and an IVF specialist in Ireland, told *Focus on Reproduction*: 'The decision to regulate the practice of ART in Ireland is long overdue. An ending to this legislative vacuum in this fast-advancing and far-reaching field of medicine promotes the interests and protects the patients and their future children.

'At the same time, it clearly establishes practitioner responsibilities and practice boundaries. In recent times, the Irish government has sought expert opinions from countries where ART laws have been in place for many years and we hope this process of due diligence will result in a fair law, one that offers access and is not over conservative.

'The regulatory authority will assume an overarching role to ensure that patients receive appropriate care delivered by qualified practitioners. Furthermore, it is hoped that reporting ART result will become mandatory, a significant change from current reporting which is voluntary and vastly missing.

'We all welcome this initiative and look forward to working with the Department of Health and legislature towards implementing a fair law that benefits everyone in the ART field, and a law that can also quickly adapt to practice changes and societal needs.'

1. http://health.gov.ie/wp-content/uploads/2014/03/Report-of-The-Commission-on-Assisted-Human-Reproduction.pdf.
2. http://health.gov.ie/blog/publications/general-scheme-of-the-assisted-human-reproduction-bill-2017/.

A public campaign for fertility awareness

ESHRE has established a working group to develop campaign tactics for enhancing public fertility awareness and prevention of infertility. The move follows a comment made by the Danish embryologist Søren Ziebe at last year's Annual General Assembly that ESHRE should do more in the public's awareness of infertility. The result is a working group set up under his chairmanship to consider ways in which public awareness might be increased. Included in the programme is the 'Fertility on Tour' programme of talks for university students, whose pilot edition in Barcelona last year proved so successful. 'Young people' are one of the declared objectives of the working group, to ensure they have 'the right information to make an informed choice about their own fertility'.

The Danish gynaecologist Anja Pinborg has recently joined ESHRE's Executive Committee but will be best known for her studies on ART safety derived from the comprehensive national registries of the Nordic countries. She explains what we have so far learned from these studies and how reliable they are.

Reliance on registries

'We have seen a twin rate of 30% reduced to 5% in some countries.'

FoR: Anja, you're well known to ESHRE members for your registry studies on the safety of IVF. How did they begin?
AP: The Danish Fertility Society had been recording all IVF treatments in Denmark and based on that the Danish IVF registry was set up in 1994. It was Professor Anders Nyboe Andersen and consultant Anne Loft at Rigshospitalet in Copenhagen who had the idea of using this data much more. We started slowly, first looking at risks in IVF twins. A few years later we got involved in the Gothenburg randomised trial of single and double embryo transfer, and this confirmed to me that twins were a higher risk outcome. This was part of my doctoral thesis and really started my interest in research. But I knew the work would include lots of figures and I had no wish to give up clinical work. But finally, I decided that the research would be very interesting. So it all started gradually.

And do you do any clinical work today?
Yes, I have a part-time clinic, and still do oocyte pick-ups and transfers. Anything in IVF. So for the last four years I've been doing one week in clinic and one week research. So about 50-50. From February I'll be head consultant and professor in Rigshospitalet and will then have to do a little less clinical work - but I won't skip the clinic.

So that's still your main interest?
Well, I'm vey interested in my research, but I think if you need inspiration for your research it's important to have contact with patients and do clinical work.

So the registry studies we know you best for are not such a big part of your work?
They *are* a big part of my work, but so are the clinical studies. People ask me when I'm lecturing, oh but you're not doing clinical work, but I tell them actually that's my main interest.

I guess a lot of your safety research - and indeed how you got started with it - is simply because Denmark has such comprehensive registries.
Yes. Like Sweden, Finland and Norway, we have a system in which every citizen has an ID number which allows us to follow the mothers and crosslink to the children. Because of this link between mother and child we can identify those born after IVF and follow their short and long-term health.

Do you think these registry studies are reliable? They're retrospective, observational, but the numbers are big?
Yes, I do. Their major strength is the big numbers, which to a large extend can compensate for their limitations. I think in the future we'll have to rely even more on

this kind of big data, because what we have found is consistency in the big Nordic registry studies. So if we in Denmark find that babies born after frozen embryo transfer are large for gestational age, we also find it in Sweden and Finland. We have never seen different patterns. OK, in some countries there might be less risk, in others higher risk, but we have always seen the same pattern regarding birth weight, gestational age, malformations. So I think we can rely on these studies because the numbers are so big and the findings consistent. Of course, there are mistakes and missing values, and we need to have randomised trials to compare the effectiveness of different treatments, but it's impossible to provide the safety data on children in a randomised trial.

What have you learned from the registry studies you've done? Would you say they've provided strong reliable conclusions that really will affect how IVF is performed?
I think the registries have shown beyond doubt the risks associated with IVF twins. Before these studies many people said IVF twins were dizygotic and so didn't carry the same risk as the naturally conceived ones. But we saw that they *did* carry the same risk. So there the registers have proved important. We've seen a twin rate of 30% reduced to 5% in some countries. And that's made a considerable contribution to the improved health of the children born after IVF.

And what else?
We shouldn't forget that many of our registry studies have been hypothesis-generating. For example, our findings on large-for-gestational age associated with frozen transfers has given us some evidence that you cannot just change your methods without having a longer-term effect. Things will influence the children.

But as I understand registry studies, their whole purpose is to generate a hypothesis to be tested.
Yes, the studies are hypothesis-generating, but they are also changing our minds about the different methods we use.

So frozen embryo transfers. They're increasing in popularity. What's your view?
In terms of safety I would still say it's best to transfer a single embryo and then freeze the rest. It is quite clear that outcome doesn't just depend on the couple, it also depends on what we do. It's the same with blastocyst transfer. We'll have to wait and see, but so far, on malformations, cancers, the evidence has been reassuring.

And we need the evidence for public reassurance as well?
Yes, very much so. We have to do these studies to show that we are committed to safety. To show that the treatments are to a large extent safe. Perhaps the most important purpose of these large-scale registry studies is to show that our IVF babies are healthy.

So overall you must feel that IVF is safe?
Yes, when I sit in front of an infertile couple I feel very comfortable saying that this treatment is safe. But overall, I think in view of the manipulations we do it's amazing that outcome is so good. Human embryos are very robust. I guess that is the most important finding of these registry studies. That's why we must keep surveying our new techniques.

Yes, there's a lot of public reassurance in these studies.
I'm sure this is the reason why IVF is so well accepted today. We *can* say that we have looked into this and know that there's a slight increase in risk here, we know that twins are linked to a higher risk. So we've done the work and can reassure the public. ESHRE has also ensured that knowledge of these registers is spread and made its own assessments of European IVF treatments. We now see registries throughout the world and they've had great impact on the acceptance of IVF - and even how it's funded - in many countries.

Do you see support of its registries as a big future challenge for ESHRE? You've joined the Executive Committee now, so you're in a position to know!
Yes, though I think PGS is still the big question for ESHRE - it's expensive, but is it effective, can it improve birth rates, are the children healthier? There are many questions still to be answered. These new technologies are another challenge for ESHRE as well as the data collection of the EIM Consortium.

Well, ESHRE has the PGD Consortium and ran the ESTEEM trial. That showed quite clearly that if your endpoint is a healthy baby, there's not much you can do about the quality of the embryo. That's a strong message to come out of the trial.
Yes, and that's why so many are worried about the cost of PGS. It won't be affordable for everyone, but there's still huge pressure to do it. This is what's happening in Denmark.

And your advice ?
I think they'll have to start it and monitor it, to get the knowledge and skills, but maybe not as routine treatment.

PROUST QUESTIONNAIRE*

- **What's your idea of perfect happiness?**
A career and family life that go hand in hand. And in Denmark a little bit more daylight in winter

- **Your greatest fear?**
Losing my children

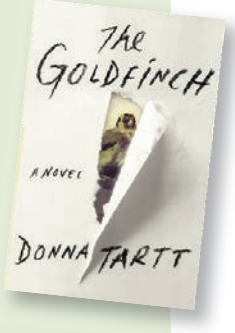
- **The trait you most deplore in yourself?**
My temper

- **And in others?**
Mediocrity

- **What's your greatest extravagance?**
Clothes and shoes

- **What quality do you most like in a man?**
His sense of humour

- **. . . and in a woman?**
Her sense of humour



- **What is your favorite pastime?**
Skiing

- **The last novel you read?**
The Goldfinch by Donna Tartt

- **. . . and your favourite writers**
Einar Mar Gudmundsson and Paulo Coelho

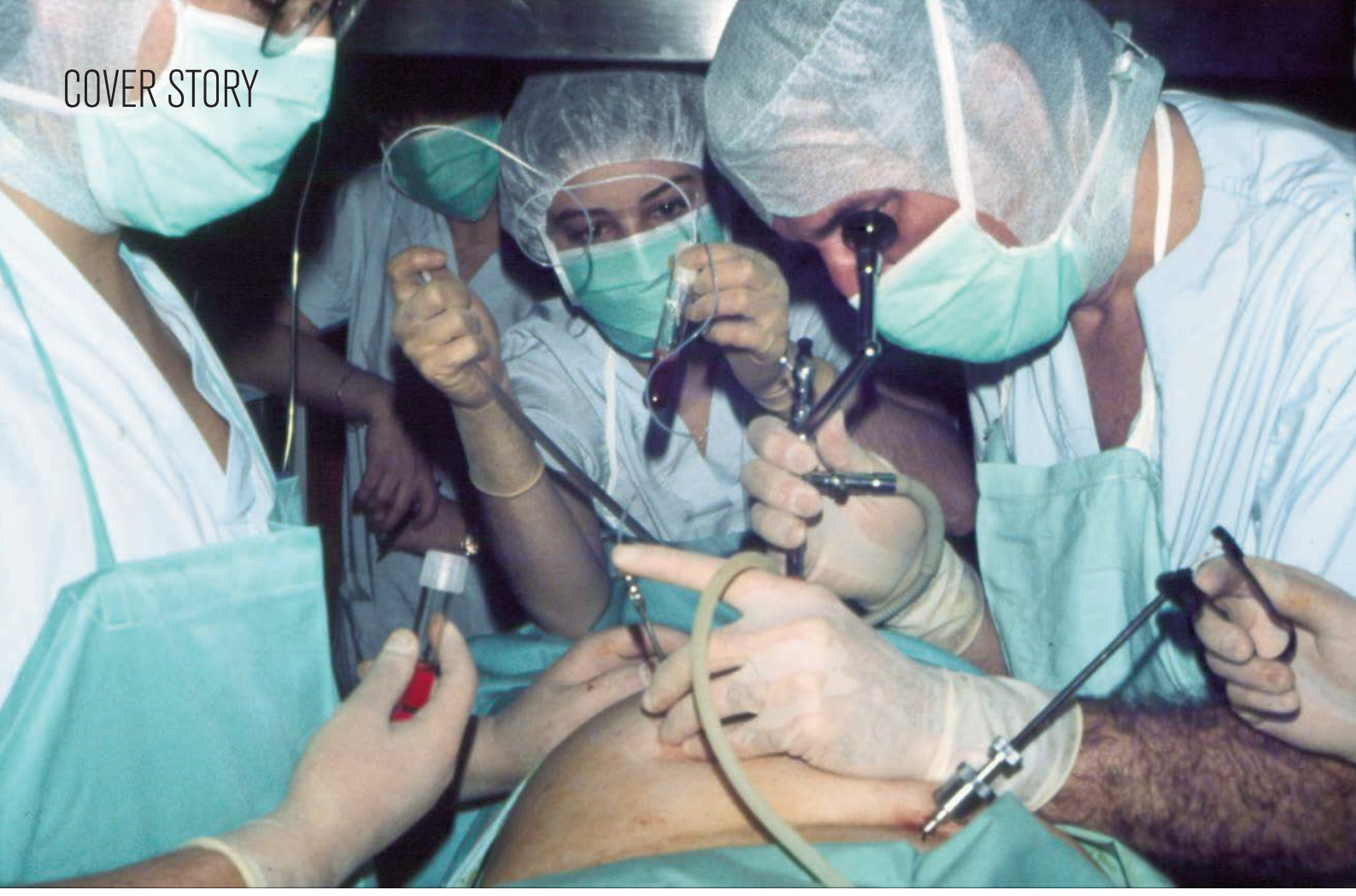
- **If not Denmark, where would you prefer to live?**
Amsterdam, Stockholm, Northern Italy

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

- **Which talent would you most like to have?**
To be musical

- **Groceries online, or the supermarket?**
Both, traditional stuff online and exciting stuff in the shops

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



From biology to embryology

40 years in the IVF lab

As we mark the fortieth anniversary year of IVF, embryologist Anna Veiga, who was the biologist responsible for Spain's first IVF baby in 1982, highlights the landmark developments of those four decades in the IVF lab.

In July this year Louise Brown will turn 40. She was born in the UK and is the first human being conceived in vitro. Amandine, Oliver and Maria (36 this year), Tina, Stephanie, Troels and Alessandra (35), Victoria, Antti and Mona (34) and Isidoros (31) followed Louise - in France, Germany, Sweden, Belgium, the Netherlands, Denmark, Italy, Spain, Finland, Norway, and Greece, and were the first babies born in their countries by the IVF technique inspired by Robert Edwards - 'Bob' to those who had the privilege of meeting him and learning from him.[1]

But it was not until the early 1980s that dedicated IVF laboratories really began to emerge throughout the world, closely following the lead of Edwards himself and centres in the USA and Australia. Europe, however, became rapidly and enthusiastically involved in this new and fascinating method of artificial conception. Most of the teams began as an initiative of local gynaecologists and biologists interested

in human reproduction - though fertility treatment was, at that time, quite limited. Ovulation induction was performed with the first gonadotrophin injections and vaginal or intracervical insemination was indicated for couples with male problems. But there was little else, and today, in just 40 years, it's remarkable to imagine that more than 7 million babies have been born throughout the world with the IVF technique. Moreover, ART has achieved complete social acceptance, for which a continuing bioethical debate on many aspects has been essential.

My professional activity as an IVF biologist (we were not known as embryologists at the time) started with Pedro Barri, head of the Reproductive Medicine at the Hospital Universitari Dexeus in 1982, and I believe my own personal experience was quite similar to that of many colleagues starting out in the 1980s.

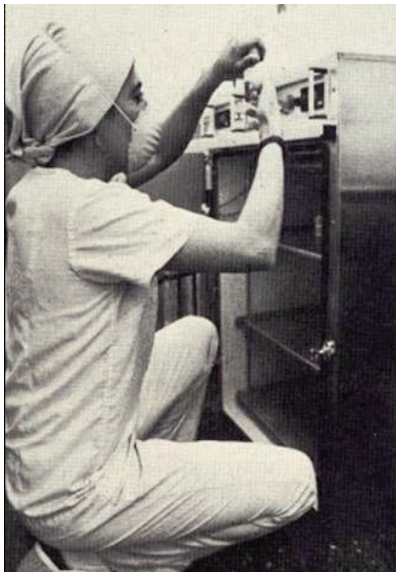
IVF laboratories were usually set up quite close to the operating theatres where the oocytes were collected - by laparoscopy at the time, as ultrasound-guided retrieval had not yet been introduced. In many cases, we had to rely on a few shelves in an incubator and microscopes from cell culture and genetic laboratories before any proper dedicated IVF lab was established. No specific material for the handling and culture of human gametes and embryos was available, and extrapolation from research labs working with the mouse model was the usual rule.

This scarcity of material and equipment posed a problem, especially in certain countries. In the case of our lab in Barcelona, for example, I would periodically have to drive to Montpellier for Falcon tubes, as none were available in Spain. The same with culture media. Most of the labs produced their own media with a very limited (if any) quality control. Others were using culture media designed for other species (the cow, for example). Yet today there are many companies producing reliable culture media for use in IVF laboratories. Quality control is compulsory and the results obtained are extremely consistent.

Training of professionals in both the clinic and the lab was also very complicated. No specific academic training existed at the time, with no postgraduate degrees in this specialty as we have today. Young students, both clinicians and laboratory specialists, can now be properly trained, with certification programmes put in place by scientific societies, with ESHRE at the forefront.

My initial contact with the real IVF world came in 1982, when I was admitted as a visitor to the IVF laboratory at the Centre Hospitalier Universitaire de Montpellier. Professor Bernard Hédon took me for three weeks to learn from their experience as one of the first IVF centres in France. I perfectly remember when Professor Flandre, the biologist in charge, asked me to remove my metal bracelets to enter the lab, as they were thought to transport ions detrimental to embryos!

ANNA VEIGA: 'IN MANY CASES, WE HAD TO RELY ON A FEW SHELVES IN AN INCUBATOR AND MICROSCOPES FROM CELL CULTURE LABORATORIES BEFORE ANY PROPER DEDICATED IVF LAB WAS ESTABLISHED.'



This was the first time I would actually see a human embryo, in that dark laboratory down in the basement of the Hôpital Arnaud de Villeneuve. This view of the first human embryo and the beating cardiomyocytes arising from embryonic stem cells I observed more than 20 years later are for me the most impressive views I have ever had looking down a microscope.

As I have already suggested, standardisation of methodology in IVF laboratories in the 1980s was very limited and we were mainly following what the pioneering groups published in the nascent literature. We established our own morphological criteria to assess embryo quality. Not surprisingly, the implantation rate of the embryos we produced at the time was much lower than we achieve today and, as a result, we replaced two, three, four and even more embryos to try to get one implanted. Twins, triplets and even higher order pregnancies occurred, something which would now be unacceptable in our present ART programmes.

It was in the 1980s too that the protocols for human embryo cryopreservation were developed, following initial pioneering work in animal models. The report of the first pregnancy after the transfer of a cryopreserved human embryo by Alan Trounson and Linda Mohr in 1983 in *Nature* would be the starting point of cryobiology in the IVF laboratories.[2] My own initial contact with cryopreservation was at the laboratory of Jacques Testart, the controversial IVF pioneer in France, where I learned how to freeze human embryos with a protocol adapted by the French group and widely used for many years to come. Incubators designed for premature babies were used in that lab for the culture of human embryos, a peculiar equipment that was abandoned later on.

Edwards and Cohen announced formation of a European society at the World Congress of IVF in Helsinki in 1984.The first issue of that Society's journal appeared the following year.

It was during the third World Congress of IVF and Embryo Transfer in Helsinki in 1984 that a European society was announced by Bob Edwards and the French gynecologist Jean Cohen. The first annual meeting was held the following year in Bonn with 650 participants, who were each welcomed individually by Bob, the first Chairman of the Society. And it was Bob, of course, who paved the way for the development of clinical and basic research in human reproduction and infertility. The journal *Human Reproduction* was launched in 1986 and is now the reference journal in the field.

New protocols for ovarian stimulation were developed and, as a consequence, more oocytes were collected. Methods in the lab also improved, with better culture conditions, better equipment and optimised culture media. We became aware that temperature should be checked and maintained for better embryo development. The culture of human embryos to the blastocyst stage was described in 1990 by Yves Ménézo with the use of feeder cells and this developmental stage became a factor in our labs at that time.[3] The first human blastocysts we saw looked to me much more 'real and alive' than the humble 4-cell embryos we had grown used to. In fact, Yves was one of the few biologists with a biochemical background, and this allowed him to understand the requirements of human embryos in vitro and to develop the only commercially available (and one of the most widely used) culture media at the time.

However, it was previous experience in animal models which usually paved the way for developments to improve our results with IVF. The first micromanipulation technique to facilitate oocyte/sperm interaction was described by Jacques Cohen in a letter to the *Lancet* in 1988, reporting a pregnancy with a technique called partial zona dissection (PZD), which we took up to overcome failed fertilisation.[4] This was followed by SUZI (nice name, poor results!). Finally, the development of intracytoplasmic sperm injection in 1992, initially indicated for male factor infertility and now universally applied (in certain centres and certain countries unnecessarily) changed the whole scenario in IVF. Gianpiero Palermo in the laboratory of André Van Steirteghem in Brussels 'inadvertently' injected a sperm into the cytoplasm of a mature oocyte - and the most efficient technique of assisted fertilisation was born.[5] Again, limited tools were available and we all became craftsmen, preparing glass pipettes in the lab with microforges and pulling equipment. A well-made ICSI pipette was a treasure at the time. What a huge difference today, with such availability of different sizes and types of micromanipulation pipettes.

Embryo biopsy

Two years before the introduction of ICSI, a report on pregnancies obtained after the transfer of biopsied human preimplantation embryos sexed by Y-specific DNA amplification was published in *Nature* by the group of Alan Handyside at the Hammersmith Hospital in London.[6] They reported two cases of X-linked disease in which sexing and the transfer of female embryos avoided the birth of affected offspring. Our own experience in PGD began in a similar way with the group of Jose Egozcue at the Autonomous University in Barcelona and we obtained a twin pregnancy in a couple in whom the woman was a hemophilia carrier - also by sexing the embryos.

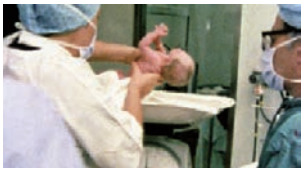
These first births after PGD were the demonstration that embryo biopsy could be performed to assess the genetic characteristics of an embryo through the analysis of one cell. Thus, the skills of the biologists in the lab were now needed not only for the preparation

In the beginning

in December 1968 Edwards, with colleagues Bavister and Steptoe, first described fertilisation of a human oocyte. A few years later, the Melbourne group of Carl Wood reported two IVF pregnancies, which were both lost.

- Edwards RG, Bavister BD, Steptoe PC. Early stages of fertilization in vitro of human oocytes matured in vitro. Nature 1969; 221: 632-635.
- De Kretzer D, Dennis P, Hudson B, et al. Transfer of a human zygote. Lancet 1973; 302: 728-729.

The first IVF birth



Louise Brown was born shortly before midnight at Oldham hospital in the north of England on 25 July 1978. Since then more than 7 million IVF babies have been born throughout the world.

- Steptoe PC. Edwards RG. Birth after the reimplantation of a human embryo. Lancet 1978; 2: 366.

Stimulated IVF

Although Louise Brown and Australia's first IVF baby were born following egg retrieval from a natural cycle, the USA's first IVF birth was in a cycle stimulated with hMG; Trounson in Melboure had described the first cycles stimulated with clomiphene citrate.

- Trounson AO, Leeton JF, Wood C, et al. Pregnancies in humans by fertilization in vitro and embryo transfer in the controlled ovulatory cycle. Science 1981; 212: 681–682.

Embryo freezing

Gerard Zeilmaker (1936-2002) froze embryos from three patients in Rotterdam in February 1983; one transferred in May resulted in the birth of twins, 'considerably before such a baby was born in Australia'.

- Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. Nature 1983; 305: 707-709.
- Zeilmaker GH, Alberda AT, van Gent I, et al. Two pregnancies following transfer of intact frozen-thawed embryos. Fertil Steril 1984; 42: 293-296.

Egg donation

The first report of a pregnancy resulting from the transfer of a fertilised donor oocyte came from the Monash group in 1983.

- Trounson A, Leeton J, Besanko M, et al. Pregnancy established in an infertile patient after transfer of a donated embryo fertilised in vitro. BMJ 1983; 286: 835-838.

NUMBERS

650 attended ESHRE's first Annual Meeting in Bonn in 1985; 10,379 took part in Geneva in 2017

2.4 million IVF cycles estimated by ICMART now performed each year worldwide

of glass pipettes but especially to perform an efficient biopsy on day 3 at the 8-cell stage without harming the embryo.

It was not possible at the time to diagnose specific genetic diseases because of technical problems, which have been largely solved today by molecular biology. As a result, all diseases with a genetic mutation in which the causative gene has been determined can now be detected in embryos; today this is performed in most centres by blastocyst biopsy and mostly by laser trophectoderm dissection. Laser technology had in fact been introduced in IVF labs for zona drilling to improve implantation, but is now extensively used for embryo and blastocyst biopsy. The first laser prototypes developed at the École Polytechnique de Lausane in Switzerland were so big that steps were needed to reach the eyepiece!

It was not until 1996 that Yuri Verlinski proposed for the first time the analysis of the chromosomal constitution of oocyte polar bodies to allow the replacement of euploid embryos; the aim was to improve IVF outcomes and reduce implantation failures and miscarriage.[7] The practice quickly moved to more invasive cleavage stage biopsies and more recently to blastocyst biopsy. Today, the analysis of the chromosomal constitution of human embryos and blastocysts is achieved by array comparative chromosome hybridisation and next generation sequencing, which both allow analysis of the 23 chromosomal pairs. The new nomenclature proposed for this technique is preimplantation genetic testing for aneuploidy (PGT-A).

Broader research fields have now been developed as a consequence of IVF and a publication in 1998 by James Thomson described for the first time the derivation of embryonic stem cell lines (hESC) from human embryos donated for research.[8] In fact, the methodology was a replication of previous work done by Martin Evans in the mouse model in 1981 in Cambridge, UK.[9] The pillars of research in pluripotency and regenerative medicine were thus established at that time.

Today, induced pluripotent stem cells (iPS) generated through the overexpression of pluripotency factors are an alternative to hESC.[10] Both cell lines are used for differentiation into a multitude of cell types, including gametes. Functional oocyte-like and spermatid-like cells have been obtained with pluripotent stem cells in the mouse model, with healthy offspring achieved in both cases.[11,12] It is a truly astonishing and very relevant achievement to reproduce gametogenesis in in vitro conditions. Meiosis in the petri dish! We could never ever have imagined this when we were starting out in IVF 40 years ago.

Reproducing similar results with human pluripotent stem cells in the human model will take some time. Ethical questions on the generation of embryos from in vitro-produced gametes will also need addressing. Confirmation of the safety of the methodology will be necessary before clinical application. And the very concept of infertility will need to be revisited after that.

Technical advances in the lab

New and very efficient techniques for oocyte vitrification are now routinely used in our labs, even for non-medical indications such as postponement of maternity.[13] And other equipment improvement is evident in the IVF lab. Laminar flows with gas and temperature control, incubators for individual patients and time-lapse monitoring of embryo development now represent reliable tools for the embryologists, suggesting that the complete mechanisation of the IVF laboratory will probably be a reality sooner or later.[14] This will

Vitrification

was introduced and tested around 2005 - mainly in Japan - with excellent results with embryos and later oocytes.

● Kuwayama M, Vajta G, Ieda S, Kato O. Comparison of open and closed methods for vitrification of human embryos and the elimination of potential contamination. Reprod Biomed Online 2005 ;11: 608–614.

Oocyte freezing

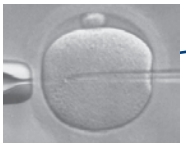
The first successful attempt at freezing and thawing a human oocyte was reported by Chen from Adelaide in 1986. The first live birth with vitrification of a human oocyte was reported by Gianaroli and colleagues from Bologna working with Trounson in 1999.

● Chen C. Pregnancy after human oocyte cryopreservation. Lancet 1986; 327: 884-886.

● Kuleshova L, Gianaroli L, Magli C, et al. Birth following vitrification of a small number of human oocytes: case report. Hum Reprod 1999; 14: 3077-3079.

ICSI

ICSI was developed - somewhat accidentally - at the VUB in Brussels by the group of Van Steirteghem and Devroey, with first live births reported in 1992. By 2006, around two-thirds of all ART fertilisations in Europe were with ICSI.



● Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1992; 340: 17-18.

PGD

The first reported case of PGD was achieved by sexing embryos from the DNA of a biopsied cell by amplification of a repeat sequence specific for the Y chromosome by Alan Handyside et al in London in 1988, who later reported the first pregnancies using this same technique in couples at risk of transmitting recessive x-linked diseases.

● Handyside AH, Pattinson JK, Penketh RJ, et al. Biopsy of human preimplantation embryos and sexing by DNA amplification. Lancet 1988; 1: 347-349.

Fertility preservation

The restoration of fertility after the transplantation of frozen–thawed ovarian tissue was reported for the first time in the sheep in 1994, but not until 2000 was ovarian autotransplantation described in the human.

● Oktay K, Karlikaya G. Ovarian function after transplantation of frozen, banked autologous ovarian tissue. N Engl J Med 2000; 342: 1919.

19.2% estimated delivery rate per aspiration in ART worldwide

530,000 estimated ART babies now born each year

7 million estimated ART babies born since the first in 1978

allow embryologists to standardise their methods, minimise human errors and improve results.

But whatever the technical advances, professionals today are much better trained than we ever were and can interact with those from other fields to cover a much wider range in human reproduction and fertility. Such interaction is evident in reports describing the editing of the embryonic genome through CRISPR/Cas 9 systems with the purpose of repairing disease mutations or understanding the role of certain genes.

There are of course still many roads to explore in our specialty and young embryologists are now lucky to have the instruments to do so. We were also very privileged to participate in the exciting beginnings of IVF. So thank you once again to Bob and happy birthday to Louise and the rest of those original test-tube babies!

Anna Veiga was Chairman of ESHRE from 2011 to 2013, and is presently head of R+D+i Reproductive Medicine Service at Dexeus Women's Health, and Director of the Barcelona Stem Cell Bank at the Centre of Regenerative Medicine of Barcelona.


Daily Mail
WORLD EXCLUSIVE
And here she is...
THE LOVELY LOUISE

'So thank you once again to Bob and happy birthday to Louise and the rest of those original test-tube babies!'

1. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. Lancet 1978; 12; 366.
2. Trounson A, Mohr L. Human pregnancy following cryopreservation, thawing and transfer of an eight-cell embryo. Nature 1983; 305: 707-709.
3. Menezo YJ, Guerin JF, Czyba JC. Improvement of human early embryo development in vitro by coculture on monolayers of Vero cells. Biol Reprod 1990; 42: 301-306.
4. Cohen J, Malter H, Fehilly C, et al. Implantation of embryos after partial opening of oocyte zona pellucida to facilitate sperm penetration. Lancet 1988; ii: 162.
5. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1992; 340: 17–18.
6. Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature 1990; 344: 768-770.
7. Verlinsky Y, Kuliev A. Preimplantation diagnosis of common aneuploidies in infertile couples of advanced maternal age. Hum Reprod 1996; 11: 2076–2077.
8. Thomson JA1, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. Science 1998; 282: 1145-1147.
9. Evans M.J Kaufman M.H Establishment in culture of pluripotential cells from mouse embryos. Nature 1981; 292: 154–156.
10. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007; 131: 861-872.
11. Hikabe O, Hamazaki N, Nagamatsu G, et al. Reconstitution in vitro of the entire cycle of the mouse female germ line. Nature 2016; 539: 299–303.
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Time for Germany to revise its 'antiquated' embryo protection legislation?

● National Academy of Science makes proposals for new legislation in reproductive medicine

It's now almost 30 years since Germany's Embryo Protection Law was approved by Parliament, and since then in 1990 the statutes have never been updated except for a single paragraph on strict rules for PGD in 2011.

It has now been argued by the Leopoldina academy, presently the German National Academy of Science and one of the oldest science academies in the world, that the current law has not kept pace with today's rapid progress in reproductive medicine; it does not cover most of the ART techniques used or social and demographic changes. The Leopoldina largely represents the German scientific community and is known to speak out on social and political questions, providing a factual framework for discussion.

Currently, more than 80,000 ART cycles are performed each year in Germany, which is why there's been constant debate for more than a decade - among doctors, scientists, jurists, politicians and patients - to replace this antiquated Embryo Protection Law by a modern statute for reproductive medicine. However, no legislative initiative has been announced so far.

Now scientists of the German National Academy of Science Leopoldina have published a paper on this issue, demanding new legislation appropriate to today's reproductive medicine within the next legislative period. They and many other scientists firmly believe that many parts of the Embryo Protection Law are no longer appropriate in reproductive medicine and that the ban on certain techniques should be withdrawn.

The Leopoldina paper addresses some decisive needs, which should be regulated in new legislation:

- Elective single embryo transfer should be possible and encouraged. This would help reduce the number of multiple pregnancies without impairing success rates.
- Egg donation should be allowed, but any commercialisation should be avoided through strict regulation. Since sperm donation is allowed, a ban on egg donation clearly repesents an inequality which cannot be justified. Studies on children born after egg donation have found no negative effects on the parent-child relationship, nor any negative impact on child development.
- Embryo adoption is performed in Germany, but should be addressed and regulated in law.
- Aspects of family law should be updated and regulated for the benefit of children born after donor insemination to unmarried couples. Rights of parenthood should be guaranteed at birth.
- The family status of children born after surrogacy in foreign countries should be regulated. However, surrogacy in Germany isn't advocated in this statement.
- Conditions for elective 'social' egg freezing and fertilisation should be agreed and included in law.
- According to the Embryo Protection Law post-mortem use of semen for insemination is strictly prohibited. However, the application of this restraint is not clearly defined. Clarification of certain aspects - for example, time limits to the storage of germ cells or embryos - and clearly defined regulations are urgently needed.

The Leopoldina paper has now been distributed to members of the German Parliament and other stakeholders and has aroused tremendous interest.

The discussion paper in its German version can be found at: https://www.leopoldina.org/en/publications/detailview/publication/ein-fortpflanzungsmedizingesetz-fuer-deutschland-2017/

Thomas Strowitzki
ESHRE Executive Committee

Potential for a guideline on embryo transfer

Full house (almost) for first Campus on ultrasound in ART and early pregnancy

Meet our new Junior Deputy
Alessandra Alteri is an ESHRE certified Clinical Embryologist from 2015 and obtained her PhD in cellular biology and development at the Sapienza University of Rome. For the last six years she has been working as an embryologist in Italy, currently at the IVF Centre of San Raffaele Hospital in Milan. Alessandra's main areas of interest include safety and quality in the IVF laboratory, particularly with failure modes and effects analysis (FMEA) for identifying potential failures in the work processes.

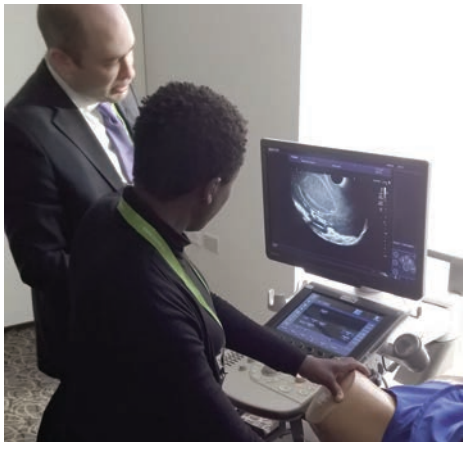
During her term as junior deputy, Alessandra will be our social media voice to publicise activities and news about SQART and to host our Facebook page. She is pictured below with Steering Committee colleagues: above from left, Kelly Tilleman, Daniela Nogueira, Ioana Rugescu, and below, Arianna D'Angelo, Zdravka Veleva, Alessandra Alteri and Enrico Semprini.

Campus course on ultrasound
The first hands-on **Ultrasound in Assisted Reproduction and Early Pregnancy** Campus course took place in Cardiff, UK, on 16-17 November 2017. The event was organised by the SIGs Safety & Quality, Implantation & Early Pregnancy, Endometriosis & Endometrial Disorders and the Paramedical Group in collaboration with the British Society of Gynaecological Imaging (BSGI). The meeting proved a mix of entertaining state-of-the-art lectures and practical demonstrations of ultrasound on mannequins and simulators. There was a participant limit of 70 to allow each to enjoy the hands-on practice without rushing. The course was almost fully booked and the delegates were divided into small groups moving from station to station to give enough time to fully practise the newly acquired skills and ask questions. This gave the opportunity to novices to learn the skills and to the others to validate their knowledge. Both trainers and trainees seemed to enjoy the experience very much. The take-home message from the course, clearly delivered by Arianna D'Angelo, Neil Pugh, Emma Kirk and Andrew Horne, was to be systematic in performing the ultrasound for the best quality and safest examination.

Roberto Marci showed an extensive range of ultrasound images related to adnexal pathologies, cleverly matched to corresponding laparoscopic and histological findings, thus giving the complete picture of the ultrasound potential as diagnostic tool. Zdravka Veleva pointed out how radiological contrast test like HSG are nowadays totally replaced by USS contrast test (HyCoSy,HyFoSy). Best ways to clean the USS probe and its safety implications were thoroughly described by Kelly Tilleman.

The need for setting standards on how to perform USS was also an important message. This was illustrated by Costas Panayotidis who described the most common shared practice in egg retrieval under USS guidance. Finally, an overview on training and certification was given by Grigoris Grimbizis and Nazar Amso, who both answered the many questions raised by the trainees. Education in USS is still poorly available during general training, the need has been widely acknowledged and it is in the ESHRE agenda. This course surely has the potential to be more than a one-off.

Quality and safety in embryo transfer
We have plans to develop a new ESHRE guideline on working standards for embryo transfer. The history of IVF has seen a dramatic reduction in the number of transferred embryos, from four and even more to just one or two. This transition has led to a decrease in the number of twins and higher order pregnancies, with an immediate effect on the number of obstetrical, neonatal and paediatric complications. The strategy to best minimise complications is the transfer of a single embryo. However, sometimes a strategy is lacking in cases where, for example, two embryos might be appropriate in combination with the presence or absence of a high quality freezing programme. What about the effect on reimbursement in the embryo transfer policy of certain centres?
To provide background and identify commonly



Surely more than a one-off. Almost a full-house for an ultrasound Campus training course in November,

perceived problem areas, we would like to ask your opinion in the following survey before taking the next step in this project. You'll find the survey at https://www.eshre.eu/sqart/questionnaire, or via the QR code opposite. Your input will be valuable.

If you wish to get in touch with us, you can find our contact info on the ESHRE SQART web page. Or visit our web pages for interesting reads, or follow SQART on Facebook (https://www.facebook.com/SafetyAndQualityESHRE/) and join our Facebook group for discussion, advice, feedback and remarks.

Kelly Tilleman
Co-ordinator SIG SQART

SIG PSYCHOLOGY & COUNSELLING

Now communicating with colleagues via social media

As noted elsewhere in this issue of *Focus on Reproduction*, the year 2018 represents the 40th anniversary of the birth of the first IVF baby, Louise Brown. Medical development and research have grown rapidly since then, now with highly advanced protocols and more than 7 million babies born - and hopefully many more. In the psychology and social fields, studies and perspectives on quality of life, communication, ethics, cultural inequalities or discrepancies and shared decision-making have emerged and gained recognition as highly valued knowledge areas, leading to improved patient guidelines, a focus on equality in fertility treatments and fertility awareness.

This focus on psychosocial issues is now underpinned by the need for a certification programme in psychology and counselling, which would provide the backbone for evidence-based patient care whether in a patient-centred manner in the clinic or as an appropriate intervention when counselling fertility patients. We are therefore happy to announce that a working group has been set up to work on prospects for future certification for third party-reproduction counselling.

Another step into the future for the SIG Psychology & Counselling is the use of social media. With Facebook and Twitter we are now hoping to reach more of our friends and colleagues and reach out to potential new members and collaborators with like minded interests. So to be updated with news of SIG activities please follow us at https://www.facebook.com/ESHRE PsychologyandCounselling.

We also have an exciting and interesting programme of activities for 2018, with a Campus meeting in Barcelona in January on egg donation, covering medical, psychological and ethical aspects. In March we will be hosting a basic training course on information provision and communication with patients – a course, co-organised with the Nurses and Midwives group from the Paramedical Board.

Finally, we are pleased to present the theme for our upcoming precongress course in Spain: **How to engage men within reproductive health and MAR**. Men have been overlooked in past decades; only few studies have included them and even fewer have focused on them. However, we hope to address this in Barcelona, and hope too that you will participate and communicate with us on this much neglected topic.

Yoon Frederiksen
Junior Deputy SIG Psychology & Counselling

Culture systems for 2018 precongress course

We held two very successful Campus meetings in the second half of 2017, In September we hosted an old favorite, **From gametes to blastocysts – a continuous dialogue**, in Edinburgh. This course has now been held several times and enjoyed by all, but especially now by those aiming to become ESHRE-certified embryologists. The success of the course has been due in large part to organisers Chris Barratt and Denny Sakkas, who have used innovative interactive problem-solving sessions to get everyone involved.

We followed this up in November with a course on **Reproductive medicine between science and commercialization** in Ljubljana. The course took a multidisciplinary approach to the safety and efficacy of infertility treatments by minimising the role of commerce. We thank all who made these courses possible - the local organisers, lecturers, participants, and, of course, ESHRE support staff.

Looking ahead

In May we invite you to Athens to study **Evidence-based practice in the IVF laboratory**. Evidence-based medicine should be a cornerstone in human ART. However, novel and less novel technologies and methods are not always applied with an appropriate validation of efficacy, efficiency, safety or quality. This course will review and critically assess those most widespread and significant introductions to the IVF laboratory, and consider the extent to which they conform to the criteria of evidence-based medicine. The scope of the course additionally includes the application of evidence-based medicine to improve performance of the IVF laboratory.

At the Annual Meeting in Barcelona we will, as usual, organise a precongress course which we hope will be of interest. As the title suggests, **Foundations and developments in culture systems in IVF** will offer a comprehensive review of the culture systems used in IVF and describe the various components of those systems. The course will also cover practical topics such as optimisation and limitations of time lapse microscopy systems.

To provide more flexibility and decreased travel costs, the SIG-E has made the decision to enter the exciting world of the webinar. We will start on a small scale to test if this is something worthwhile for our members. The two first webinars will cover KPIs and vitrification. Information on dates and how to attend will be sent out soon.

We are the largest of ESHRE's SIGs and we are really keen to hear from you. We encourage you to contact us with your ideas and thoughts on topics that you would like hear in upcoming Campuses and PCCs. This is an important way of letting us know what's important and interesting to you, so that we can keep organising attractive courses.

At the moment we have an ongoing survey on our online *Atlas of Human Embryology*. We want to know what you enjoy, what you are missing, what you would like us to develop. Please, give us a few moments of your time and give us your suggestions for improving the *Atlas*.

Membership

In addition to our current members, we are now happy to welcome all members of the Paramedical Group working as BSc-educated staff in an IVF lab whose primary interest lies in embryology. For its last two years of activity before being disbanded, Paramedical Group members are represented on the SIG-E steering committee by PG members Leonie van den Hoven and Yves Guns. So we are now all enjoying being part of a new SIG Embryology, with a broader range of members but still committed to future events focused on the common interest of all members new and old.

We have recently started a SIG-E group on Facebook, so please follow us there and visit us on the ESHRE website (https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Embryology) to make sure you don't miss news of our activities. Our E-campus pages hold videos from our previous courses – and please feel free to use Facebook to get in touch!

Susanna Apter
Co-ordinator SIG Embryology

Infertility: prevention as important as treatment

ESHRE has agreed to establish a work group for fertility awareness and prevention of reproductive diseases. It will operate as an activity of the SIG Global and Socio-cultural Aspects of Infertility.

The background to ESHRE's commitment to the prevention of reproductive diseases as a target is the embarrassing fact that, from the origins of our specialty, we as the experts in reproduction have never really addressed the topic of prevention. This is in contrast to our colleagues in almost all other areas of medicine (cancer, diabetes, cardiovascular diseases etc) who spend a significant proportion of their science, communication and discussion on preventing disease risks.

The establishment of this work group is actually a continuation and internationalisation of the ongoing work of the Danish-Swedish collaboration ReproUnion, which has shown that reproductive disease is now the most prevalent chronic disease of people aged between 25 and 44. Consider the figures: 9% of Danish children are now conceived in a fertility clinic; one in five Swedish and Danish men will never become a father; and one in ten women will either never have children or have fewer children than wished for.

Implicit in these figures and in the objectives of the work group is that we should change our perspective from treating childlessness to 'building families'. Indeed, infertility affects whole families, not just an individual couple.

It now seems clear that we as reproductive specialists should have addressed this a long time ago, especially as it's also clear that having children takes time. The more children you want, the earlier in life you should start.

We know that young people worldwide have significant knowledge gaps about their fertility and biology. We have a responsibility to start filling these gaps, for which education is essential for preventing reproductive recognition of lifestyle factors and sexually transmitted diseases.

We also need to address the myths and beliefs that cause young people to postpone childbearing and to remind politicians and policymakers that they have a pivotal role in the organisation of societies in a way compatible with young couples having children when and if they wish to.

We need to convince employers that having children is central to the lives of most of us and that this should be recognised and embraced by companies, universities and employers.

But most of all we should have the courage to address this message in the open.

Two meetings of this new work group have so far taken place, with the participation of Petra De Sutter (BE), Willem Ombelet (BE), Lone Schmidt (DK), Rita Vassena (ES), Søren Ziebe (DK), and Adam Balen (GB).

First steps are to draw up an inventory of what different countries are doing in terms of awareness and prevention with a view to what's working and what's not. Although not yet final, the following objectives have been agreed:

a) To decrease the prevalence of infertility.
b) To ensure that young people have a greater understanding and awareness of fertility and reproductive health so they are equipped with the right information to make an informed choice about their own fertility journey.
c) This includes increasing fertility awareness in the general public and providing continued education among healthcare professionals and educators.
d) To equip legislative and administrative bodies with evidence-based information for prioritised decision making, including the reproductive consequences of infertility.
e) To develop, implement and communicate solutions and strategies addressing reproductive challenges in Europe.

A brainstorming and inspirational expert meeting is likely to be held in March in Brussels, where words will hopefully be turned into action.

Søren Ziebe
Willem Ombelet, Co-ordinator SIG Global and Socio-cultural Aspects of Infertility

Danish embryologist Søren Ziebe, whose comments at last year's ESHRE Annual Assembly raised the neglected message of fertility awareness.

A monumental keynote lecture for Barcelona

I must confess that I am very excited after my first SIG business meeting! As the Co-ordinator of the SIG Stem Cells it is a pleasure to note that many of the upcoming ESHRE events will involve stem cells.

Firstly, at the next Annual Meeting in Barcelona the keynote lecture will be given by the widely acclaimed Japanese group leader Katsuhiko Hayashi. His group was able to produce mouse oocytes completely in vitro, starting from pluripotent stem cells and resulting in fertile pups. The method involved a fascinating 3-step in vitro culture system. I am sure that he will deliver a captivating presentation of this significant breakthrough.

Secondly, our upcoming precongress course in Barcelona will focus on **Stem cell therapies in clinical applications: Progress and challenges**. The course will include presentations on clinical grade stem cell banking and HLA typing, and will further discuss recent clinical trials of endometrial and other stem cells in female and male infertility. Finally, we will consider the possible future use of human pluripotent stem cells, with a focus on treatment of blindness and diabetes. Our aim in this PCC is to provide state-of-the-art insights into stem cell therapies in infertility and the tools required for future clinical trials in reproductive medicine.

Our next Campus event is a meeting on **In vitro modelling: from embryo to gametes**, which will be held in Bilbao on 20-21 September. We are extremely excited to invite several experts in 3D modelling of the embryo, ovary and testis, artificial human blastocysts, embryo imaging, novel in vitro implantation strategies for studying endometrial and blastocyst interactions, as well as the epigenetics of human primordial germ cells. Right now. these are the most trending topics in the fields of early development and gametogenesis, currently providing a greater understanding of previously uncharted in vivo processes. These investigations will certainly contribute to the future of reproductive science and even future treatments for infertility. This Campus event is already announced on the ESHRE Education pages, so please do not forget to register!

I am also pleased to announce a few further details on the 2019 Annual Meeting in Vienna. First and foremost is that the subject of one of the opening keynote lectures will be the much acclaimed gene editing technology of CRISPR/Cas. I am sure the audience will be very excited to hear the latest news on this breakthrough in both the stem cell and reproductive fields.

I should further add that our main session topic in Vienna will focus on 3D reproductive organs. Here we will discuss the new biotechnological approaches of using stem cells to generate male and female organs.

Finally, we are planning two new Campus events in 2019. The first, organised with the SIG Reproductive Genetics and titled **Gene editing technology: will CRISPR/Cas be the future?**, will cover topics such as the CRISPR/Cas methodology, CRISPR tools, and experience in vivo, as well as its associated methodological limitations such as mosaicism in human embryos.

Our second Campus event will be organised with the SIG Embryology and will focus on **20 years of human embryonic stem cells**. Already planned for the programme are topics that couple stem cells with development, such as trophectoderm stem cells, the artificial blastocyst, pluripotency factors, the concept of potency (pluripotency, totipotency) and chromatin remodelling.

Both events will be very relevant for the entire reproductive community, providing the latest updates in both stem cell research and exciting future applications in the reproduction field.

Cristina Eguizabal
Co-ordinator SIG Stem Cells

Keynote attraction: Katsuhiko Hayashi, whose group was able in a series of experiments to produce mouse oocytes completely in vitro, starting from pluripotent stem cells and resulting in fertile pups.

A year for guidelines: ovarian stimulation and PCOS

Looking back

Last year was full of decisive events and fulfilments for the SIG Reproductive Endocrinology. After the success of our Athens Campus on female reproductive ageing and the sold-out precongress course in Geneva, we met again in September in Vienna with almost 100 participants considering the impact of adjuvant treatments on pregnancy potential in IVF. This very successful meeting was run under the graceful guidance of local organiser Professor Andrea Weghofer, to whom we offer our sincere thanks. Discussion and the interaction between speakers and audience were lively and open-minded, and the feedback received enthusiastically positive.

Last year was also notable for the strong progress made in our 'purely' ESHRE guideline development for ovarian stimulation and the collaborative comprehensive guideline on PCOS, developed in association with the Australian Center for Research Excellence in PCOS and the ASRM.

Please note too that our Junior Deputy, Julia Bosdou, now has responsibility for our social media and has created an amazing Facebook page. Just swipe your mobile and like us.

Moving ahead

A very productive meeting of the SIG-RE steering committee took place in Brussels in November. In a non-stop marathon from morning to evening, we addressed all the points of our full agenda, so defining our plans for the next two years. Great attention was given to forthcoming educational events.

Our Campus workshop on **The luteal phase, the neglected part of assisted reproduction**? will be held in Hamburg, Germany, on 25-26 May 2018, hosted by local organiser Georg Griesinger. Our objective here is to shed light on many grey areas of our everyday practice: the endocrinology of the luteal phase, the diagnostic tests of endometrial receptivity, new drugs and routes of administration for luteal phase support, the validity of luteal phase manipulations to increase ovarian response and adjuvant treatments at the time of embryo implantation. A vibrant programme has already been agreed and is available on the ESHRE website, together with all the information you may need to take part.

We also put the final touches to our precongress course for Barcelona later this year: if you are making plans to take part in the next Annual Meeting, don't forget to also register for our PCC **The PCO syndrome: from diagnosis to health risk management**. PCOS is back in the headlines, with breaking news on this old subject delivered by distinguished speakers from all over the world.

Let's communicate

We look forward to keeping in touch with all colleagues who share an interest in reproductive endocrinology: so in order to receive our newsletter, just flag the SIG-RE as your affiliation on the ESHRE website (under MYESHRE, Personal Details), or simply like us on our Facebook page ESHRE SIG Reproductive Endocrinology (search for @ESHRESIGRE to find the page easily!). We are becoming more and more social, and we hope to enrich our media supplies with Twitter, Instagram and LinkedIn accounts.

Daniela Romualdi
Co-ordinator SIG Reproductive Endocrinology

A full-house at our Campus meeting in Vienna, with faculty pictured right.

Planning under way for a third guideline on the management of endometriosis

We now have a Facebook page (https://www.facebook.com/EndometriosisAndEndometrialDisorders/), a social media connection between the SIG and its members to keep you informed about precongress and Campus courses and other developments. To date, our web page has more than 500 followers, so come on and join us!

Steering committee

A new steering committee was installed during last year's Geneva congress. Andrew Horne (Edinburgh) has now become Past Coordinator, and former Deputy Carla Tomassetti (Leuven) has taken over as Co-ordinator. Andrea Romano stays on as Deputy, and Antonio Simone Laganà – former Junior Deputy – joins as Deputy after being elected by our members. Our enthousiastic committee is very pleased to welcome a brand new member, Umberto Leone Roberti Maggiore, who was selected as Junior Deputy. He is a clinician and researcher interested in the diagnosis of endometriosis/adenomyosis, on the role of medical and surgical treatment for these diseases and on the impact of endometriosis on obstetric outcomes. The committee is completed by Lone Hummelshoj and Krina Zondervan (Oxford), who stay on for another two years as International Advisor and Basic Science Officer respectively.

Surgical management of endometriosis

Back in 2015, the chair of the Endometriosis Guideline Development Group and President of the European Society for Gynaecological Endoscopy (ESGE) began a project to develop a joint guideline on the surgical management of endometriosis, more specifically to describe technical guidance on how endometriosis surgery should be performed. The World Endometriosis Society joined later. The aim now is to provide information not only in written format, but also by video library with spoken comments.

ESHRE, ESGE and WES are now proud to present the result of the first phase of this project, a paper on recommendations for surgical treatment of endometrioma accepted for publication simultaneously in *HROpen*, ESHRE's open access journal, and *Gynecological Surgery*. Next will be a further set of surgical recommendations on the various types and presentations of deep endometriosis. The next work group meeting is planned for January, with further developments of this vast project.

Steering committee members, from left, Carla Tomassetti, Umberto Maggiore, Antonio Simone Laganà, Lone Hummelshoj, Andrea Romano, and Andrew Horne.

Events of 2017

In September last year our Campus meeting on **Methodological approaches for investigating endometrial function and endometriosis** took place in Edinburgh. The course, organised jointly by the ESHRE and ASRM SIGs, was a great success, with more than 80 attending. On the programme were state-of-the-art overviews of biobanking, genomics research, local steroid signalling and metabolism (intracrinology), biomarker discovery, research with animals and clinical trial design.

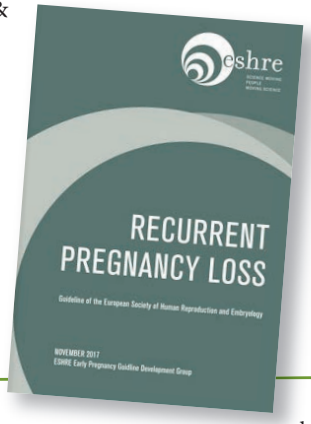
Of particular interest was the enlightening presentation of Siladitya Bhattacharya (Aberdeen) explaining how to design a randomised trial in endometriosis, while emphasising the numerous potential pitfalls - from the lack of objective outcome parameters to theoretical, statistical and interpretation biases. Final recommendations were to use pilot studies to test study feasibility, to select clearly predefined outcome parameters and report them correctly, to thoroughly discuss distinct aspects of the study in a multidisciplinary manner, and to take care with final data interpretation, weighting all biases that may have occurred.

Krina Zondervan opened the meeting with an elegant lecture on genome wide association studies and next generation sequencing. She explained the differences about study designs in genetics and genomics, and overviewed the latest data generated within the Endogene Consortium. She said that only 10% of disease heritability has so far been discovered , and we face challenges to better define and phenotype this disease. The emerging area of somatic mutation analyses, which is already changing some paradigms

Guidelines now out on recurrent pregnancy loss

We are excited to have just launched our guideline on the *Management of Recurrent Pregnancy Loss*. Its overall aim is to supply healthcare providers with the best available evidence for investigation and treatment of women with recurrent pregnancy loss. RPL is here defined as the loss of two or more pregnancies. It excludes ectopic pregnancy and molar pregnancy. The guideline provides an overview of suggested treatments for RPL, and which of those are recommended. In addition, recommendations are made on investigations to identify the origin of the pregnancy losses and possible therapeutic targets. There are also recommendations on the organisation of care for couples faced with RPL.

We have also been working with the SIG Safety & Quality in ART and SIG Endometriosis and Endometrial Disorders, with whom we jointly hosted a Campus Symposium in Cardiff in November on **Ultrasound in assisted reproduction technologies (ART) and early pregnancy**. There were interactive lectures on different aspects of ultrasound in ART, gynaecology and early pregnancy, plus a chance to practice skills on ultrasound simulators:. The three SIGs are planning to develop some good practice recommendations on the use of ultrasound in these areas, where often there is little or no good quality evidence to support practice.



Future events

At this year's Annual Meeting we will be running a precongress course on the **Provision of an effective early pregnancy assessment and support service**. We feel that this is a very important area as the provision of care for women in early pregnancy across Europe varies considerably. In some countries, dedicated Early Pregnancy Assessment Units have been created and have revolutionised the care for women with complications in early pregnancy. At recent Campus meetings and precongress courses, delegates have requested more information on how to provide such a service. This course would hopefully address these needs, with sessions on many general topics.

Venturing further afield, in April we are very excited to have been invited to host an ESHRE Campus meeting in Buenos Aires at the annual meeting of the Asociación Latinoamericana de Medicina Reproductiva (ALMER).

Emma Kirk
Co-ordinator SIG Implantation & Early Pregnancy

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in cancer research, was also illustrated by Professor Zondervan.

The final session was given by Caroline Gargett (Australia) on endometrial stem cell populations. She described the largely undiscovered journey that endometrial and progenitor cells undertake during the menstrual cycle in their migration from the basalis, through the functionalis until the luminal epithelium. She also emphasised how little we know about the endometrial morphological changes and molecular biology processes which underly these events and have such important impact on endometrial pathophysiology.

The syllabus and e-learning platform with full Campus content are available on the ESHRE website.

Guidelines on the Management of Endometriosis

In 2005 the first ESHRE guideline for the diagnosis and treatment of endometriosis was published, a landmark document which laid the path for many other ESHRE guidelines on different topics. In 2014 the second edition of the endometriosis guideline became available accompanied by an app and a highly popular patient-friendly version. Many countries have adopted this guideline for their national societies.

We are now keen to ensure that the guideline includes all newly available evidence. Consequently, the chair of the ESHRE Guideline Development Group for endometriosis, Christian Becker (Oxford), and ESHRE Research Specialist Nathalie Vermeulen, together with the current and past co-ordinators of the SIG, Carla Tomassetti and Andrew Horne, are currently re-assembling the development group for a third edition. More than 50 people replied to the members consultation put out last year.. The new guideline will build on the strengths of the previous two and in addition will include more patient representation and input in areas previously not included, such as psychology, pain medicine, sexology, imaging and physiotherapy.

Looking forward

In May this year during the Annual Scientific Meeting of the BSGE (British Society of Gynaecological Endoscopy) we are presenting a full day's precongress course focusing on **Advances in reproductive endoscopic surgery: robotics and new classifications**.

Continued over page

SIG ETHICS & LAW

Surrogacy for Barcelona precongress course

The new co-ordinator of the SIG Ethics & Law is Lucy Frith from the University of Liverpool, who replaces Professor Guido Pennings. Lucy is a bioethicist and a social scientist with a particular interest in the intersection between ethics and social science and empirical bioethics methodologies. She has published widely on a range of topics in bioethics, with a long-standing interest in the social and ethical aspects of reproductive technologies.

The SIG also has a new Deputy in Heidi Mertes. a Belgian bioethicist who has been a member of ESHRE for 12 years. She currently holds a position as a postdoctoral researcher at Ghent University and is also a founding member of the Bioethics Institute Ghent. She has described as 'enormously important' ESHRE's work in stimulating interaction between the scientific, clinical, psychological, paramedical, ethical and legal aspects of infertility.

STEERING COMMITTEE

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

Future events

We are organising a number of events in 2018, notably **Egg donation: medical, psychological and ethical considerations** on 26-27 January in Barcelona. This course aims to cover the latest developments in the ethical, psychological and social aspects of oocyte donation. There is huge variation in how oocyte donation is perceived and implemented across Europe. This variation is evident in recruitment methods, age limits for donors and recipients, and donor anonymity. While egg donation is still controversial and/or forbidden in some countries, others often struggle to meet demand for donor eggs. The course was designed to provide a general overview of all relevant issues related to oocyte donation. These include matters such as cross-border movement of patients and donors, recruitment of donors (including alternative systems such as egg sharing), genetic screening of donors, quality measures for egg banks, and donor anonymity and identifiability. The course will approach two issues in more depth: the organisation of the collection (recruitment) and distribution of donor eggs, and counselling of donors and recipients.

Our precongress course in Barcelona, **Surrogacy: a gift with consequences**, will focus on this highly complex and controversial technique, which is either banned in several countries, or allowed by law or contract with varied conditions both for the surrogate (and her family) and intended parent(s). The process requires a high level of knowledge and expertise to look after all parties of the contract, alongside the welfare of the future child. Commercialism is also hotly debated both at national and at international cross border levels. We will discuss the various aspects of the process, from indications to the social and ethical questions raised when the number of stakeholders is so varied.

The SIG is also planning more Campus Courses and working on a pre-congress course for Vienna 2019. If you have any ideas and topics you want us to address please get in touch.

Lucy Frith
Co-ordinator SIG Ethics & Law

Continued SIG Endometriosis & Endometrial Disorders

The aim of our precongress course at the ESHRE Annual Meeting – entitled **Endometriosis – from beginning to end** - is to understand how endometriosis affects women's quality of life and the risk of diseases that occur during peri-menopausal or postmenopausal ages, from a life-course epidemiological point of view. This will be addressed via lectures and open debates.

Later, in the second half of 2018, Campus courses on endometriosis and pain and on fibroids and heavy menstrual bleeding are being planned; in the course of the following weeks, more details can be found on ESHRE's website.

Carla Tomassetti, Co-ordinator
SIG Endometriosis & Endometrial Disorders

An inspiration from 40 years of IVF

Take our 20-question quiz and get ready for 2018

As we've seen elsewhere in this issue, we celebrate in 2018 40 years since the birth of Louise Brown. During this period, more than 7 million babies have been born through IVF while we have seen huge advances in the field of gynaecology, embryology and reproductive genetics, all applied with a single aim: the birth of healthy babies.

The incredible amount of knowledge that has accumulated over the years has influenced our everyday practice as scientists and doctors, and has inevitably led to more questions and a need to understand better the processes involved in the creation of human life. So it's a pleasure for the SIG Reproductive Genetics to recognise those scientific developments in a short multiple choice questionnaire to inspire all of us towards more learning!

Upcoming events

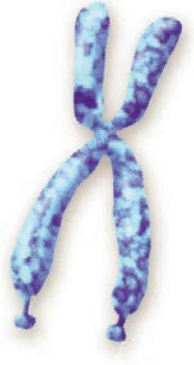
May we also note that in 2018 we look forward to our **Current approaches in genetics and reproduction** course, which will take place in Sofia, Bulgaria, from 26-28th April, to our precongress course at the Annual Meeting, which will focus on **Genes in gametogenesis and genetically transmitted diseases** and to a practical training course on SNP arrays, which is currently being organised by the PGD Consortium for October. For the Sofia course there is an abstract submission system in place for all participants (submission deadline 26 March 2018) and abstracts will be selected for poster/oral presentations. We await your contributions!

Georgia Kakourou, Claudia Spits, Francesco Fiorentino, Antonio Capalbo, Filippo Zambelli
On behalf of SIG Reproductive Genetics

20 multiple-choice questions. Answers at the end.

1. You see a patient with congenital bilateral absence of the vas deferens. For which genetic condition would you consider testing him?

a. Huntington's disease
b. Cystic fibrosis
c. Beta thalassemia
d. Fragile X syndrome



2. Carrying a pre-mutation in the Fragile X syndrome is a well-established cause of:

a. Polycystic ovary syndrome
b. Endometriosis
c. Premature ovarian insufficiency
d. Primary ovarian insufficiency

3. Haemophilia B is:

a. Autosomal recessive
b. X linked dominant
c. X linked recessive
d. Y linked

4. Women carrying heteroplasmic variants in their mitochondrial DNA will transmit them to the oocytes/embryos:

a. At the same frequency
b. At a higher frequency
c. At a lower frequency
d. At an unpredictable frequency

5. Which of the following is not true with regards to mitochondrial disorders and human reproduction?

a. Mitochondria have been found to play a role in both female and male fertility (oocyte ageing and sperm quality)
b. Mitochondrial replacement therapy aims to prevent transmission of disease-causing oocyte mtDNA
c. Preimplantation or prenatal genetic diagnosis may be used for homoplasmic or heteroplasmic mtDNA mutations to identify embryos with a reduced risk of mitochondrial disease
d. Attempts for therapeutic intervention in selected mitochondrial diseases involve use of engineered mitochondrially-targeted zinc finger nucleases (ZFN) and transcription activator–like effector nucleases (TALENs)

6. What are the most common segregation pathways leading to aneuploidy in IVF-generated human oocytes?

a. Reverse segregation (split of all sister chromatids at meiosis I) and precocious separation of sister chromatids (PSSC) causes the majority of aneuploidy in activated/fertilized oocytes as detected by direct Haplotyping and fluorescence time-lapse imaging.
b. Meiotic I non-disjunction of homologue chromosome is the main cause of errors in female meiosis.
c. Mitotic non-disjunction of homologue chromosome is the main cause of errors in female meiosis.
d. Several studies showed anaphase lag causes the majority of aneuploidy in activated/fertilized oocytes

7. Which of the following is true about human preimplantation embryo development?

a. The embryonic cleavage stage is characterised by chromosomal stability
b. Spindle assembly checkpoint controls chromosome segregation during meiosis but not mitosis
c. Spindle assembly checkpoint controls chromosome segregation during mitosis but not meiosis
d. Meiotic recombination affects homologue segregation at meiosis I

8. Which of the following is a pre-requisite(s) for a couple willing to undergo PGD with HLA-typing to achieve matched HSCT for their affected child?

a. Maternal age is less than 35-years-old
b. The affected child is over 5-years-old
c. Prospective parents should also require use of assisted reproductive technology due to infertility
d. An HLA-matched donor has not been found within the family or in national or international donor registries

9. Which of the following cases are expected to lead to the detection of at least three transferable embryos from a single ART-PGD cycle with 16 embryos biopsied for genetic diagnosis (assume all ART-produced embryos to be of good quality, reaching the blastocyst stage of development by day 5 and based on data that 50% of blastocysts are aneuploid)?

a. A couple undergoing PGD-HLA for identification of unaffected HLA-matched embryos to serve as donors for their child affected with beta-thalassaemia (autosomal recessive inheritance)
b. A couple (40-year-old female) undergoing preimplantation HLA typing with aneuploidy screening for identification of HLA-matched embryos to serve as donors for their child affected with acute lymphoblastic leukemia (acquired disease)
c. A couple undergoing PGD-HLA for identification of unaffected HLA-matched embryos to serve as donors for their child affected with severe congenital neutropenia-1 (autosomal dominant inheritance)
d. A couple (maternal carrier) undergoing PGD-HLA for identification of unaffected HLA-matched embryos to serve as donors for their child affected with X-linked adrenoleukodystrophy (X-ALD) (X-linked recessive)

10. Currently, use of aCGH and low-coverage genome sequencing in preimplantation genetic screening enables detection of:

a. Complex chromosomal rearrangements
b. Balanced chromosomal rearrangements
c. Whole-chromosome aneuploidies
d. Microdeletions

11. Which of the following is not true for whole genome amplification (WGA) methods employed in PGD/PGS?

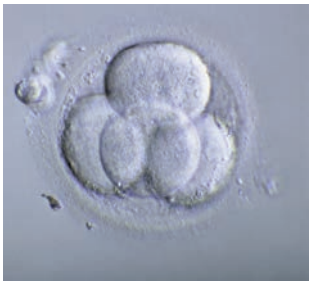
a. When applied on a single cell (7 picograms of DNA), nanograms of DNA are produced
b. PCR-based WGA methods are preferred for genotyping analysis.
c. Limitations of WGA include allele dropout, nucleotide misincorporations and chimera formation
d. Multiple Displacement Amplification (MDA) is a non-PCR based WGA method that employs random primers and high fidelity bacteriophage Phi29 DNA polymerase

12. Which of the following is not true with regards to advantages of single cell haplotyping by SNP arrays?

a. As a generic test, it does not require prior DNA testing of family members or optimisation
b. Can detect meiotic or mitotic origin of recombination and uniparental disomy
c. Can detect balanced chromosomal rearrangements
d. Can be used to detect both monogenic and chromosomal disorders

13. The potential of an embryo to successfully implant and grow has so far been associated with (choose the incorrect):

a. Genomic composition
b. Levels of mitochondrial DNA
c. Morphokinetic parameters
d. Epigenomic characteristics

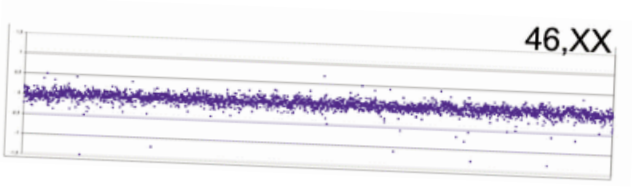


14. What is embryonic chromosomal mosaicism?

a. The presence of chromosomally distinct cell lines within the same embryo.
b. The presence of a mixture of blastomeres with different morphology within an embryo.
c. A phenomenon characterised by the presence of a mixture of blastomeres with different HLA within an embryo
d. An inherited disorder

15. Embryonic mosaicism arises from:

a. Mitotic errors occuring after fertilization
b. Meiotic errors occuring in sperm
c. Meiotic errors occuring in oocytes
d. Meiotic errors occurring after fertilisation



16. NGS may enhance detection of chromosomal mosaicism:

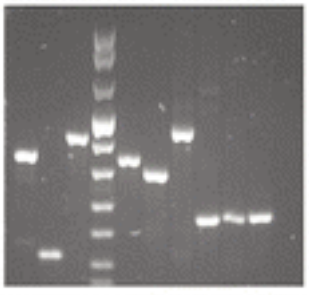
a. Because of the rapidity of the protocol
b. Because less DNA is required
c. Because quantification of sequencing read counts provides an improved dynamic range
d. Because it may also determine mtDNA quantity

17. Which of the following statements is not true?

a. Mosaic aneuploid/euploid blastocysts are able to lead to euploid pregnancies
b. Blastocysts contain relatively lower proportions of aneuploid cells than cleavage-stage embryos
c. Embryo self-correction involves the loss of aneuploid cells
d. Any level of mosaicism can very accurately be detected in a blastocyst biopsy

18. The most commonly studied foetal chromosomal aneuploidies by non-invasive prenatal diagnosis are:

a. Chromosomes 13, 18, 21, X and Y
b. Chromosomes 15, 16, 21, X and Y
c. Chromosomes X and Y
d. Chromosomes 15, 18, 21 and Y



19. Which syndrome is not caused by imprinting defects?

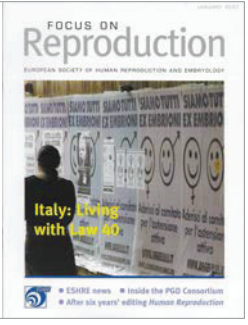
a. Angelman syndrome
b. Kearns-Sayre syndrome
c. Prader-Willi syndrome
d. Beckwith–Wiedemann syndrome

20. Selfish selection can happen in spermatogonial stem cells with:

a. No mutations
b. Neutral variants
c. Gain of function mutations
d. Loss of function mutations

Answers

1 b, 2 c, 3 c, 4 d, 5 c, 6 a, 7 d, 8 d, 9 a+d, 10 c, 11 b, 12 a, 13 d, 14 a, 15 a, 16 c, 17 d, 18 a, 19 b, 20 c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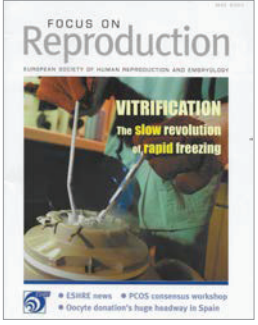
Reproduction
Italy: Living with Law 40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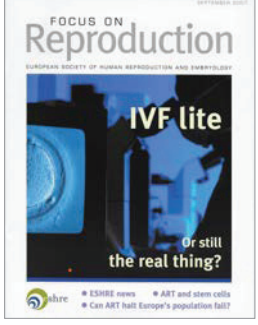
VITRIFICATION
The slow revolution of rapid freezing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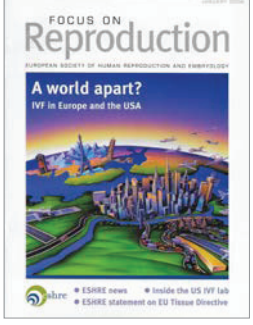
Reproduction
IVF lite
Or still the real thing?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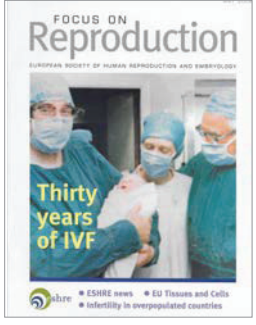
A world apart?
IVF in Europe and the USA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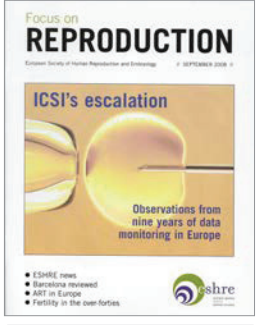
Reproduction
Thirty years of IVF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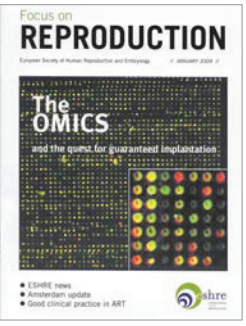
ICSI's escalation
Observations from nine years of data monitoring in Europe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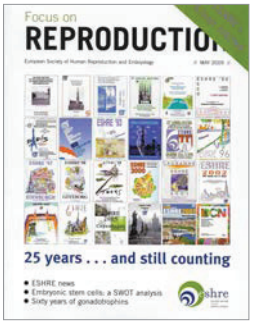
The OMICS
and the quest for guaranteed implantation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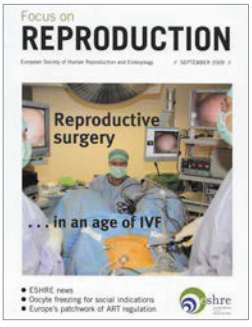
25 years . . . and still counting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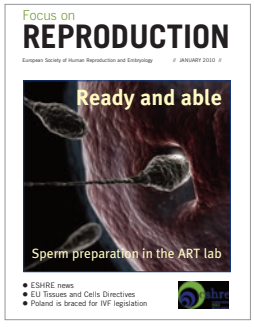
Reproductive surgery
. . . in an age of IVF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REPRODUCTION
Ready and able
Sperm preparation in the ART lab


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Crisis?
What crisis?
ESHRE's role in Europe's politics of population


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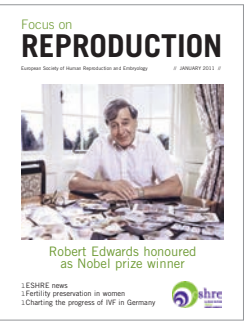
Sperm quality
The clinical implications of environmental factors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Robert Edwards honoured as Nobel prize winner


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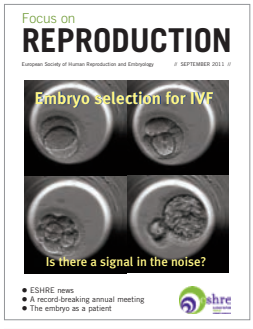
The rights and wrongs of egg donation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Embryo selection for IVF
Is there a signal in the noise?


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The urgent need for new sperm biomarkers


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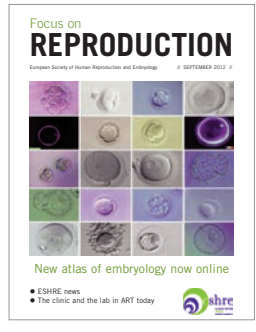
The problem with culture media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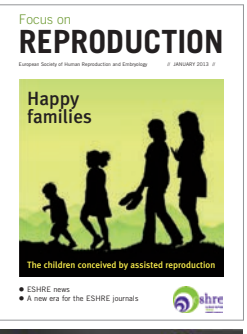
New atlas of embryology now online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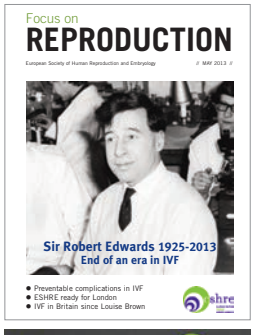
Happy families
The children conceived by assisted reproduction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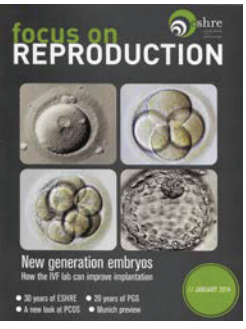
Sir Robert Edwards 1925-2013
End of an era in IVF


Focus on
REPRODUCTION
Welcome
Another record-breaking congress

From print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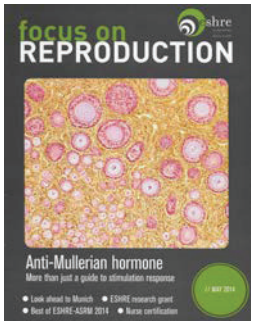
New generation embryos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Anti-Mullerian hormone


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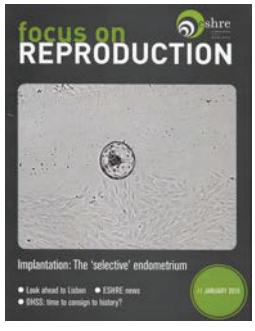
Much ado about Munich
Embryo selection still tops the agenda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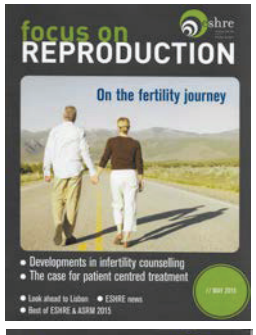
Implantation: The 'selective' endometrium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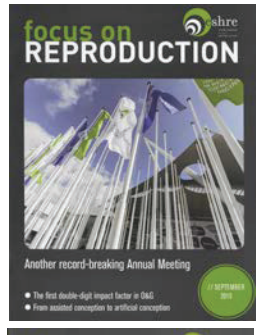
On the fertility journey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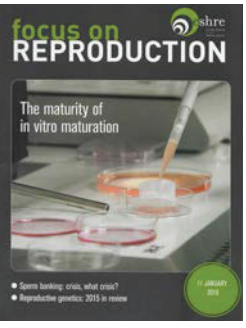
Another record-breaking Annual Meeting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The maturity of in vitro maturation


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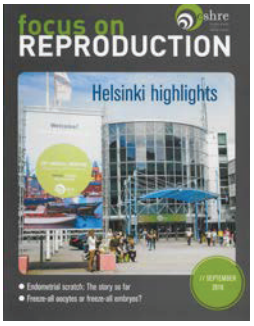
FREEZE ALL EMBRYOS?
Is the evidence there yet?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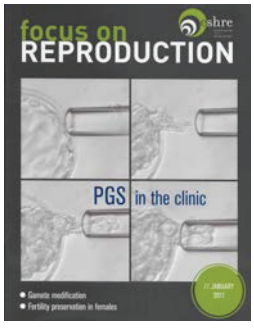
Helsinki highlights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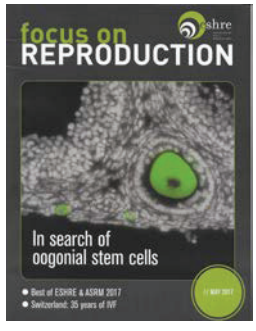
PGS in the clinic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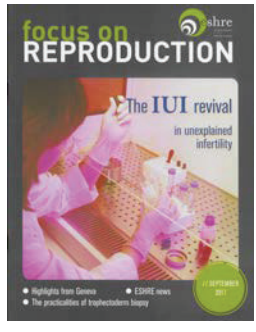
In search of oogonial stem cells


focus on
REPRODUCTION
The IUI revival
in unexplained infertility

From May Focus on Reproduction will be published from a new digital platform available from the ESHRE website and as an app for phones and tablets. News will roll as and when it happens; features will be multimedia. All you need to know and enjoy about ESHRE will be there.

This will indeed be the last word of *Focus on Reproduction* - at least in print. From the May issue onwards *Focus on Reproduction* will be an enhanced digital publication with its home as a micro-site on the main ESHRE website and as an app for phones and tablets. The online publication will continue to offer its regular menu of news and features and will thus maintain its central role in ESHRE's communications - but, as a print medium in a digital age, it must diversify and adapt to the inclinations of its readers.

News - both from the Society itself and from the broader field of clinical medicine and science - will be presented in a continuous flow, without the hard boundaries of an issue. The stories behind the news, currently seen in profiles and features, will continue but with added multimedia content in blogs, podcasts, forums, live interviews and rapid access to social media. We will also aim to cover all Campus meetings with short (and longer) reports of key conclusions.

. . . to digital

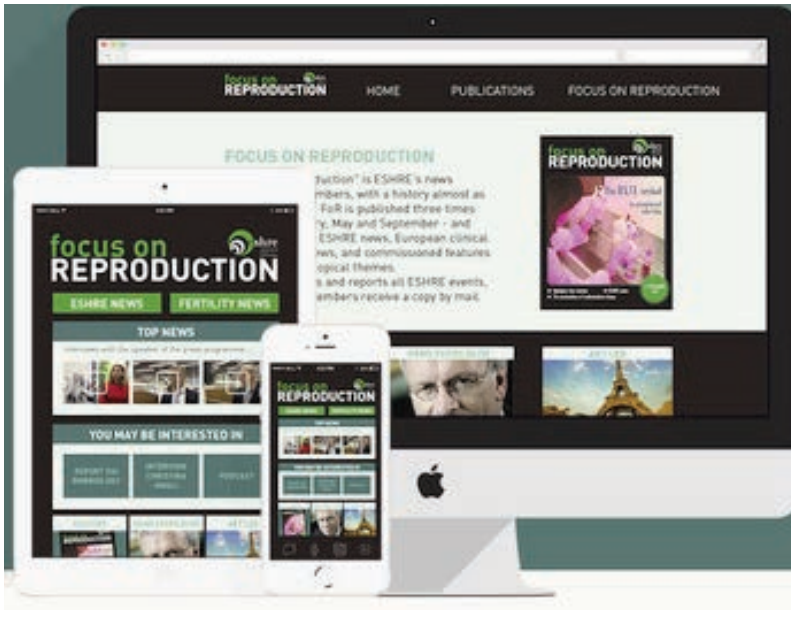
This inevitable next step of a *Focus on Reproduction* app will find its rolling content available for smart phones and tablets - and which hopefully can be personalised to each ESHRE member's interests.

As the front covers opposite indicate, *Focus on Reproduction* has had a vibrant 12-year run as ESHRE's members magazine. The title did exist long before then, but publication was erratic at best. When I was recruited as editor by Paul Devroey in 2006 to impose a strict frequency on publication and greater professionalism in production, it was, I am sure, my experience as a journalist which proved the attraction. And since then good journalism has been my guide, to present a well produced mix of ESHRE and clinical news, with background features for commentary behind the news.

Thus, our first issue of January 2007 led with the reality of ART in Italy, two years after the infamous Law 40 was introduced by the Italian Parliament. A 2005 referendum to review the legislation had failed to attract a required quorum of voters, though just two weeks before the referendum the Vatican newspaper *L'Osservatore Romano* declared on its front page that a boycott of the polls would be 'to defend human life'.

Focus on Reproduction also took up the case of IVF clinics in Poland in 2010, when the country's first legislative proposals to regulate IVF threatened to limit practice in much the same way that Italy's Law 40 had done five years earlier. Since then *Focus on Reproduction* has followed the vacillating legal position of IVF in Poland, from those initial battles of 2010 to the implementation of a supportive bill in 2015 and its peremptory withdrawal just a year later. The politics of IVF in Europe - and elsewhere - has been a recurring editorial interest.

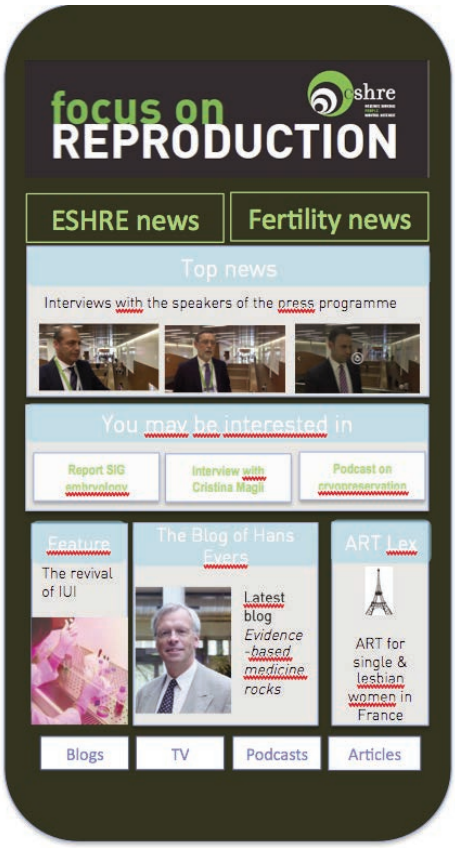
Cover features have also explored some of the most important emerging clinical concepts and controversies in ART: vitrification in 2007; mild IVF the following year; the apparent discrepancies between ART in Europe and the USA; the burgeoning preference of ICSI over IVF for oocyte fertilisation in 2008; the place of reproductive surgery in an age of IVF; the -omics in 2009; the decline in Europe's fertility rate; embryo selection by time-lapse



imaging; the composition of culture media in 2012; freeze-all embryos in 2016; and most recently the revival of IUI in unexplained infertility.

Focus has also kept abreast of the ongoing debates in PGS, most recently - and controversially - with a feature by the UK geneticist Darren Griffin which appeared to accept that a definitive answer to the question of efficacy was beyond the practical scope of a randomised trial and that new definitions of evidence were perhaps in order. That, however, was before the disclosure of results from ESHRE's ESTEEM trial, which appeared to confirm that PGS (in this case by polar body analysis) could do little to improve delivery rates. Embryos were just embryos, and no intervention could improve their quality.

As in this 40th anniversary year of the birth of Louise Brown, we have also kept up with the history of IVF. Robert Edwards himself, the 'father' of IVF and of ESHRE, has featured on two covers, first as the recipient of a Nobel prize in 2011, and second, sadly, on his death in 2013.



A Focus on Reproduction app as proposed by ESHRE's Central Office.

Print as a journalistic medium is now in serious decline. In my own country, the *Daily Express* had a circulation of more than 4 million a day at its peak in the 1950s and early 1960s. By 2017 that figure had collapsed to 392,000. However, not all declines in print have been so catastrophic. The *Daily Mail*, for example, still sells more than 1.6 million paper copies a day, not much less than in the 1950s, but this ever resourceful title also commands one of the world's highest online daily browser rates of more than 14 million - with numbers still increasing.

Focus on Reproduction will not compete with that, but we do hope its new online format will keep ESHRE members well informed and entertained. Last year's September issue of *Focus* was downloaded 1700 times from the ESHRE website, which, added to its paper circulation, suggests a very healthy readership. We hope that *FoR Online* will continue that trend.

Simon Brown
Focus on Reproduction

Some of the distinguished authors who have written features for FoR: From left. Alan Trounson in 2007 on ART and stem cell research; the late Lynette Scott on embryology in the USA; Bruno Lunenfeld on gonadotrophins; Juan Garcia Velasco on egg donation in Spain; Nick Macklon on endometrial receptivity; Simon Fishel on embryo selection in IVF; Petra De Sutter on safety in IVF; Susan Golombok on today's ART families; Filippo Ubaldi on the shift of influence to the IVF lab; and most recently Roy Homburg on the place of IUI in unexplained infertility.

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