focus on REPRODUCTION

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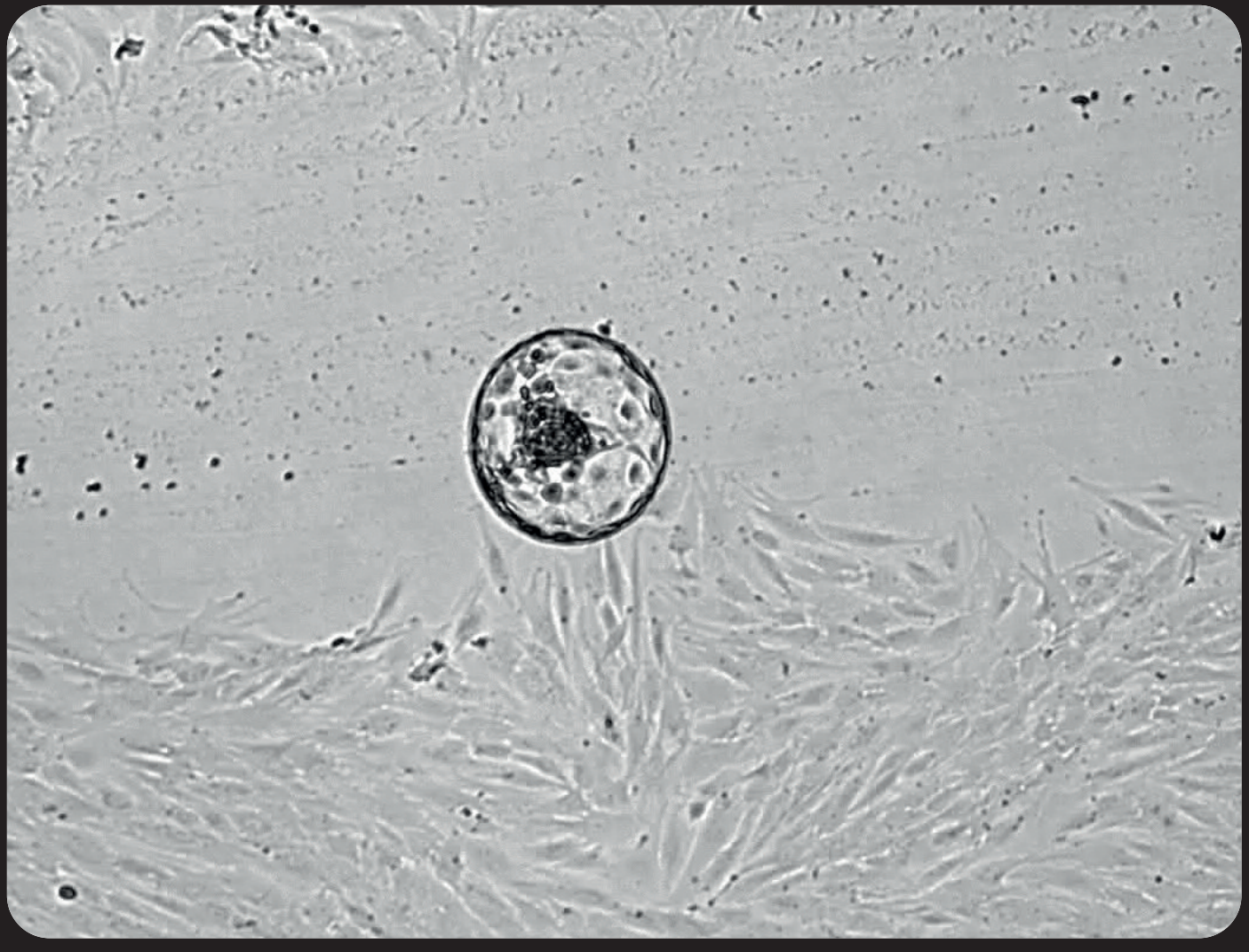

Implantation: The 'selective' endometrium

- Look ahead to Lisbon
- ESHRE news
- OHSS: time to consign to history?

// JANUARY 2015

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CONTENTS

CHAIRMAN'S INTRODUCTION

Statistics and our delegate satisfaction survey from the Annual Meeting in Munich showed that two-thirds of participants were clinicians or clinical scientists, 26% were embryologists or scientists, and 9% were paramedicals. Almost one in four (23%) said that their main interest was reproductive endocrinology, the same number had an interest in embryology, and 12% cited reproductive surgery. Interestingly, 50% of all those surveyed were from the private sector. As found in previous years, the majority of respondents considered the educational value of ESHRE's Annual Meeting 'very good' or 'excellent'.

As reported on page 12 of this issue of *Focus on Reproduction*, the Executive Committee has made its decision on the recipient of the first ESHRE research grant. A remarkable total of 259 applications were received, and we thought the overall quality was good. Eleven were selected for external review and all were of very high quality. This first experience suggests that our members are very active scientifically, and the range of interest is broad.

Our policy to tighten the organisation of Campus meetings and reduce their number to 12 each year was introduced two years ago. Our aim was to increase the number of participants and avoid overlap. Judged by attendance figures from this year's meetings, the policy is turning out to be good practice. Participation in our 12 Campuses and four basic semen analysis courses in 2014 has been generally very high - indeed, three recent meetings reported in this issue of *FoR* - on OHSS, epigenetics and fertilisation - each attracted well over 100 participants.

E-learning has been one the core projects of ESHRE and now a new platform has been developed and is in its final stage of completion. It is very flexible and user-friendly and will allow ESHRE members to select material of interest to organise their own personalised repository for continuous education. The Steering Committee of each Special Interest Group will be the quality control board of material and structure. The new e-learning portal will be introduced in 2015, hopefully in time for Lisbon.

Several new guidelines are in the pipeline. *Routine psychosocial care in infertility and medically assisted reproduction - A guide for fertility staff* from the SIG Psychology & Counselling will be on the ESHRE website soon, to be followed later this year by *Management of women with premature ovarian insufficiency* and *Revised guidelines for good practice in IVF laboratories*.

ESHRE is now well into its fourth decade. While the Society will continue to pursue its traditional aims and priorities of education and high-quality science, several new activities are under way. I hope to see you at one of these, the forthcoming Best of ESHRE/ASRM in New York in early March. A good number of people have already registered, which promises a successful event. And of course, I wish you all a Happy New Year for 2015.

Juha Tapanainen
ESHRE Chairman 2013-2015

// JANUARY 2015

Lisbon alert: Registration (and abstract) deadlines are earlier this year

● 2015 will be first paper-free Annual Meeting

ESHRE's Annual Meeting in the historical city of Lisbon - the first ever in Portugal - will this year take place two weeks earlier than usual, from 14 to 17 June.

The slightly earlier date means that both registration and abstract submission deadlines have also been brought forward by two weeks. As reported in September's *Focus on Reproduction*, all abstracts must be submitted online and must arrive at the ESHRE's Central Office no later than 14 January (23.59 CET).

Registration deadlines are also a little earlier this year, with early bird registrations now available up to 15 April, and final on-site registrations after 7 June. In setting the revised dates, ESHRE also reviewed its whole congress registration procedures to make the system easier to use for participants and administrators. As a result, the pricing structure - for both precongress courses and the main programme - will be updated for this year, with fees and deadlines as in the box opposite.

Registration fees are just one source of congress

REGISTRATION FEES AND DEADLINES FOR THIS YEAR'S ANNUAL MEETING

Main programme	Before 15 April 2015	After 15 April 2015	After 7 June 2015
Non-member of ESHRE	492,00	615,00	738,00
Member of ESHRE	369,00	492,00	615,00
Student or paramedical member of ESHRE	147,60	246,00	369,00
Precongress Course			
Non-member of ESHRE	246,00	369,00	492,00
Member of ESHRE	123,00	246,00	369,00
Student or paramedical member of ESHRE	61,50	123,00	246,00

* Prices are in euro and include VAT (Portugal) at 23%

revenue for ESHRE. The other main source is from commercial supporters, evident both in the exhibition areas and in the sponsorship of satellite symposia. This year, ESHRE has provided opportunities for all our commercial supporters, whatever their size, to host their own small-scale meetings in hour-long slots running throughout the day.

This year will also be the first official 'paper-free' annual meeting, even though trends have been moving that way in recent years. For example, uptake of the congress app increased substantially last year, with 60% of all participants downloading it. The move from paper to digital will provide accurate updates, search functions and interactive access to information that is not available on paper. Electronic also opens possibilities for a more personalised meeting, with opportunities for developing an individualised programme and itinerary, and social functions. Other congresses too - such as ASRM - are exploring their sustainability opportunities, and a paper-free congress is just one increasingly common approach.

The scientific programme will be organised in the usual format. Thus, the congress begins with two Keynote lectures on Monday morning (the Robert G Edwards keynote session) followed by parallel sessions of invited speakers, exchange sessions with other societies, oral communications and paramedical sessions. There will be one morning of live surgery, which always proves popular. Among the hot clinical and scientific topics will be new developments in PCOS (aromatase inhibitors for the induction of ovulation), debate on single step vs sequential culture media, artifical gametes, semen quality, the treatment of childhood cancer, telomeres in reproduction, the effect of environmental toxins on reproductive function, strategies for 'safer' IVF, fertility-sparing surgery, and new developments in stem cells. In addition, some provocative topics, such as 'Risks and benefits of being male' and 'Human development and evolution' will also prove popular. Among the sessions of the paramedical programme is a debate that the internet 'does more harm than good'.

We trust everyone - as ever - will find plenty of relevant, topical and useful information here for practical daily application.

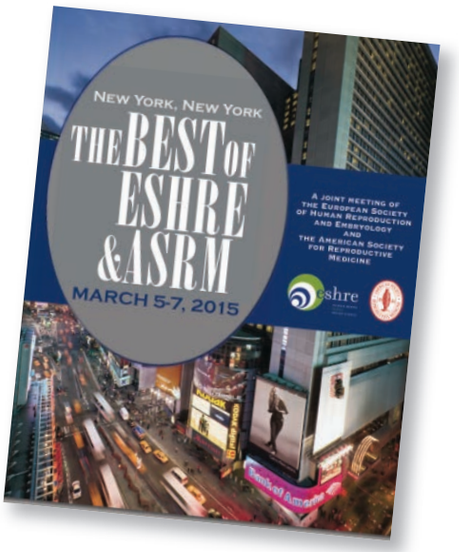
There will be 14 precongress courses organised this year by the SIGs and Paramedical Group, including exchange courses by the Middle East Fertility Society and ASRM. Programmes are already finalised and can be viewed on the congress website (www.eshre2015.eu).

The social programme will begin with the opening ceremony on Sunday evening and will include a very Portuguese moment which we hope will be memorable for all those attending. A charity run has once again been planned for this year, with a less formal congress party to follow on Tuesday evening. The idea behind this year's party is to keep costs down (for both participants and ESHRE) but to provide an entertaining evening in Lisbon for meeting friends. We foresee this new congress party format as an informal get-together for all participants, without the obligation of a high-price ticket or high-end venue.

Carlos Calhaz-Jorge
Carlos E. Plancha

Three days in March for the best New York times

Fourth joint meeting will assess established and emerging evidence from both sides of the Atlantic

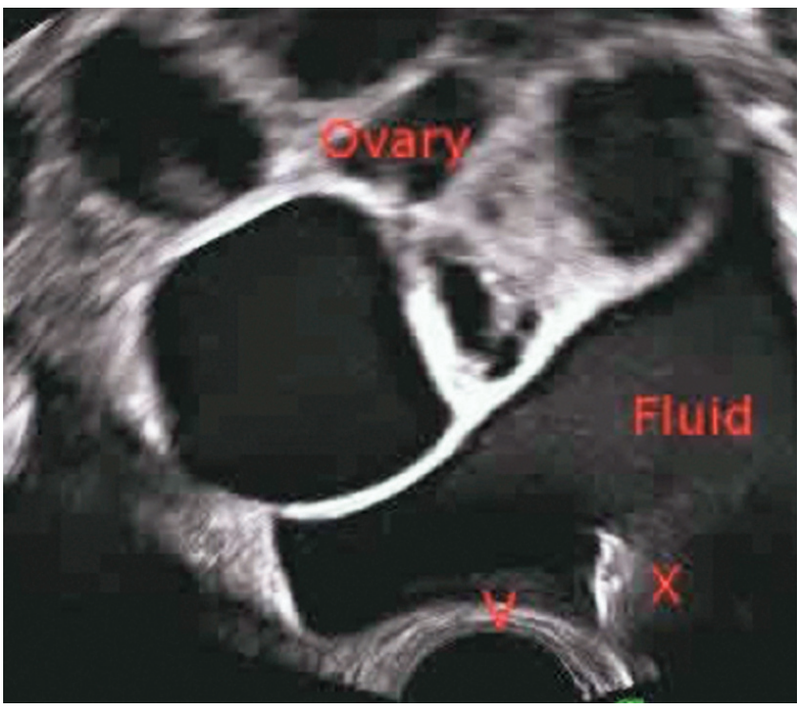


The fourth joint 'Best Of' meeting of ESHRE and the ASRM will take place from Thursday 5 March to Saturday 7 March at the New York Marriott Marquis hotel in New York.

The meeting continues a collaboration of the two societies at alternating venues in North America and Europe. The aim since inception is to provide clinicians and basic scientists with updates on the most current concepts in reproductive medicine and biology. There are also opportunies to socialise with colleagues and this year to enjoy the activities offered in the heart of Times Square.

The Best of ESHRE and ASRM is a CME-accredited programme intended to assess the evidence for both established and emerging approaches to the science and reproductive healthcare in a range of cutting-edge lectures, debates, plenary lectures and back-to-back sessions. Highlights this year include lectures on improving implantation in IVF, the treatment of mitochondrial disease and spermatogonial stem cell transplantation in male infertility. Debate and back-to-back sessions will address questions in male and female fertility preservation, stimulation strategies, time-lapse imaging for embryo assessment, PGS, European and US registry data, and a freeze-all embryo policy.

TIME	THURSDAY, MARCH 5	FRIDAY, MARCH 6	SATURDAY, MARCH 7
07:00 am – 08:00 am	**BREAKFAST**		
08:00 am – 08:30 am	Novel approaches to improving implantation in ART *John Aplin (UK)*	Treatment of mitochondrial disease by nuclear transfer *Mary Herbert (UK)*	Future of male infertility treatment – spermatogonial stem cell transplantation *Ans Van Pelt* (NL)
08:30 am – 09:30 am	Prepubertal boys with Klinefelter Syndrome should undergo testicular biopsy for fertility preservation *Herman Tournaye* (pro) (BE) *Robert Oates* (con) (US)	Options for female fertility preservation *Kutluk Oktay* (Ovarian tissue cryopreservation) (US) *Laura Rienzi* (Oocyte cryopreservation) (IT)	Time-lapse imaging morphometry is superior to classical morphology *Giovanni Coticchio (pro) (IT)* *Catherine Racowsky* (con) (US)
09:30 am – 10:00 am	Emerging therapies for endometriosis *Hugh Taylor (US)*	Patenting genes and natural phenomena *Jacques Cohen (US)*	Genetics of hypogonadotropic hypogonadism *Richard Reindollar (US)*
10:00 am – 10:20 am	**COFFEE BREAK**		
10:20 am – 11:00 am	Are ART results better in the US than in Europe? *Glenn Schattman* (US) *Bart Fauser* (NL)	Differences in ART registries between the US and Europe *Markus Kupka* (DE) *Judy Stern* (US)	Treatment of unexplained infertility *Owen Davis* (US) *Roy Homburg* (UK)
11:00 am – 12:00 pm	Preimplantation genetic screening to improve live birth rates *Richard Scott* (pro) (US) *Sjoerd Repping* (con) (NL)	Preventive egg freezing is preferable to reliance on donor eggs *Nicole Noyes* (pro) (US) *J. Garcia-Velasco* (con) (ES)	All embryos should be cryopreserved prior to transfer *Georg Griesinger* (pro) (DE) *Kurt Barnhart* (con) (US)
12:00 pm – 12:30 pm	Preconceptional counseling – state of the art *Joe Leigh Simpson (US)*	New directions in menopause therapy *Roger Lobo (US)*	Effect of environment on the embryo and offspring *Linda Giudice (US)*
12:30 pm – 01:00 pm	**LIGHT LUNCH**		
01:00 pm – 02:00 pm	Androgen therapy *Nanette Santoro* (women) (US) *Fred Wu* (men) (UK)		Stimulation strategies for the patient with diminished ovarian reserve *Marcelle Cedars* (US) *Frank Broekmans* (NL)



OHSS: Time to consign to the history of ART?

- GnRH agonist triggering the new 'gold standard'?
- Freeze all embryos a solution in high risk cases?

It's a mark of the importance now attached to OHSS that so many attended a Campus meeting on its prevention organised by the SIG Reproductive Endocrinology in November. More than 160 took part, attracted as much by the subject itself as by a globally distinguished panel of presenters. 'OHSS is a hot topic and getting hotter,' said course organiser Stratis Kolibianakis, in whose home town of Thessaloniki this two-day event was held.

Even though the *prevention* of OHSS was at the heart of the meeting, there was a sense in some presentations that *reducing* the risk was perhaps a more realistic objective - although many clearly supported the view that the 'segmentation' of high risk subjects (as proposed by Paul Devroey in 2011) had virtually eliminated OHSS from their programmes. Devroey's vision of an 'OHSS-free clinic' rested on the application of three segments: stimulation in a GnRH antagonist cycle, with oocyte maturation triggered by a GnRH agonist; vitrification of all embryos (or oocytes); and thus transfer in a non-stimulated natural or hormonally primed cycle. In such a way, wrote Devroey, could the concept of an OHSS-free clinic 'become a reality'.[1]

Although Kolibianakis described the vision of an OHSS-free clinic as 'utopia' if agonist triggering was followed by hCG supplementation without segmentation, some of the basics reflected in the various strategies to eliminate OHSS have been widely accepted with little question. Indeed, a 2014 update to the 2011 Cochrane review of agonist triggering concluded that the latter 'prevents OHSS' - but only to the detriment of live birth rate if a fresh transfer is performed.[2]

This latest Cochrane update was described in Thessaloniki by Frank Broekmans (in place of the indisposed Madelon Van Wely) but even his upbeat report raised concerns from the floor over conclusions drawn from so many disparate studies in the Cochrane analysis, particularly with respect to different protocols of luteal phase support and embryo freezing policies. The former - how best to preserve the viability of the corpus luteum following the short flare effect of the agonist trigger - proved central to the discussions of this meeting in the trade-off between OHSS safety and treatment outcome.

Such doubts were even more immediate in the light of rare but recently published cases of severe OHSS after agonist triggering alone with no corpora lutea stimulation. In these cases, apparently, even the short stimulation induced by the endogenous LH peak was enough to cause the severe form of the syndrome.

Luteal phase after oocyte maturation

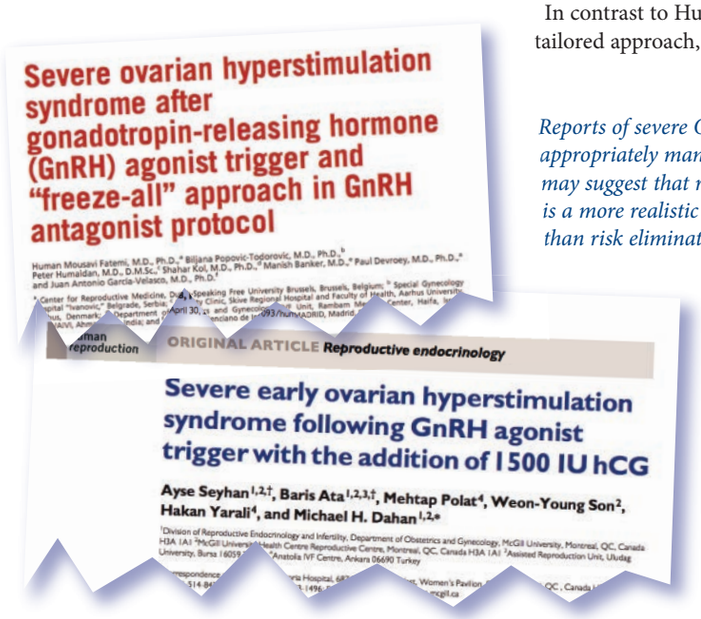
As Human Fatemi (formerly of the AZ Brussels and now based in Abu Dhabi) made clear, hCG used to trigger oocyte maturation in a conventional IVF cycle continues stimulation of the corpus luteum. A GnRH agonist trigger, because of its short action (around 20 hours) does not. Thus, in an early study performed by Kolibianakis, when he too was in Brussels, ongoing pregnancy rate in cycles with 'gold standard' hCG triggering was 41.7%, but in antagonist cycles with agonist triggering only 5.6%. The poor results were explained by a loss of function of the corpus luteum. 'Everything pointed to luteal phase insufficiency,' said Peter Humaidan from Odense University Hospital in Denmark.

Yet the logic of the agonist approach remained: OHSS is the result of gonadotrophin stimulation followed by hCG triggering of oocyte maturation; by contrast, a bolus of GnRH agonist in antagonist-suppressed cycles would induce the release of LH from the pituitary similarly to that seen in a spontaneous mid-cycle surge; luteal phase support from the agonist trigger would be necessary, with mid-luteal progesterone levels clearly associated with live birth rates. 'This was the dilemma,' said Claus Yding Andersen from University Hospital in Copenhagen. 'On the one hand we want to avoid OHSS by replacing hCG with an agonist, yet on the other we need to stimulate progesterone production by the corpus luteumm.'

There were several approaches to luteal support or 'rescue' reviewed in Thessaloniki. Notably, Humaidan described his own randomised trial of 2010 in which 1500 IU hCG administered at oocyte retrieval in high risk patients produced good delivery rates and no OHSS. Humaidan took this concept a step further in proposing an individualised approach in which luteal support with hCG was 'tailored' to each patient according to response to stimulation. A 2013 study from Humaidan and colleagues found, for example, that one bolus of 1500 IU hCG after GnRHa trigger tended (though not significantly) to reduce the OHSS rate in high risk patients (15-25 follicles ≥11 mm) and secure an acceptable ongoing pregnancy rate. However, in women at a low risk of OHSS in a second study (≤14 follicles) two cases of late-onset OHSS occurred in a group receiving an agonist trigger and two boluses of 1500 IU hCG.[3] Thus, Humaidan now proposed a 'future scenario' of agonist triggering in which all patients were started in an antagonist cycle with oocyte maturation triggered by a GnRH agonist. Subsequent treatment would depend on response: higher risk cases (15-25 follicles) would receive modified luteal phase support with 1500 IU hCG (and added estradiol and progesterone until week 7); and in very high risk cases (25-30 follicles) all embryos would be frozen for transfer in a later natural cycle following the segmentation strategy. 'We have to accept personalised treatment,' said Humaidan. 'There is not one protocol which fits all, but the agonist trigger should be the new gold standard for all patients at risk of OHSS.'

Stratis Kolibianakis, meeting organiser and Co-ordinator of the SIG Reproductive Endocrinology

In contrast to Humaidan's tailored approach, Lawrence Engmann from the University of Connecticut reported similarly persuasive results from an 'intensive' protocol of luteal phase rescue, which did not involve stimulation of the corpus luteum. Engmann described this protocol particularly in the context of egg donors, for whom OHSS, he said, is quite unacceptable. The intense supplementation comprised estradiol (transdermal) and progesterone (usually IM injection) every other day for ten weeks, with weekly blood monitoring and dose adjustment. Engmann said that the regular monitoring was 'essential' to maintain 'excellent' pregnancy rates.



Reports of severe OHSS in appropriately managed cases may suggest that risk reduction is a more realistic objective than risk elimination.

Freeze all embryos

It was the SIG's former co-ordinator Georg Griesinger who in 2007 described the effective vitrification of all embryos following GnRH agonist triggering. Now in Thessaloniki, it was Griesinger who reviewed this segmentation approach, whose applicability depends only on the estimate of OHSS risk, and whose prevention, Griesinger insisted, is the only reason for agonist triggering anyway.

Basil Tarlatzis, another Thessaloniki resident, put the current European incidence rate for severe OHSS (based on ESHRE IVF monitoring data) at 0.3%. This, however, is in contrast to the rates derived from published RCTs and to the 2011 Cochrane review, which found a 9% rate in GnRH agonist cycles and 3.2% in antagonist cycles. There is clearly much room for improvement in reporting OHSS to ESHRE.

As Human Fatemi also emphasised, the reliability of epidemiology as a marker of risk is grossly compromised by under-reporting. It was thus Griesinger's case that an estimate of who is not at risk of OHSS has greater

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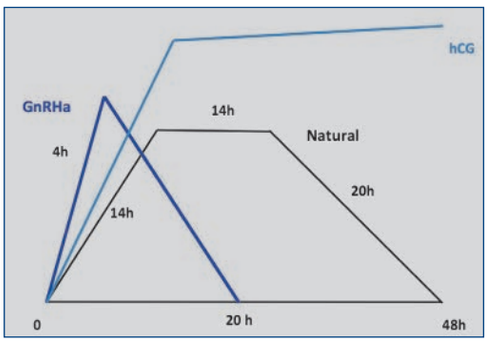


A much seen slide in Thessaloniki. Because the pituitary is not desensitised in antagonist cycles, the trigger of oocyte maturation can be achieved by a GnRH agonist. However, significant luteolysis occurs because of the short half-life of the endogenous LH produced. This effect is considerably shorter than in the natural cycle or following a conventional hCG trigger.

predictive value than a calculation of who may be at risk. He reported negative predictive values of more than 99% for risk of OHSS from two studies, as against positive values of around 4%. 'From these studies,' said Griesinger, 'we can say that patients with fewer than 18 follicles over 10 mm on the day of hCG are very unlikely to develop OHSS,' adding that '18 or 19' follicles is the best cut-off for clinical value.

However, while a recognition of risk factors - PCOS, young age, low BMI, high AMH and AFC, and a high dose of FSH for stimulation - and a reliable follicle count might give a reasonably accurate definition of risk, they will not eliminate the occurrence of OHSS. Moreover, in recognising that patients not at risk of OHSS can be reliably identified, Griesinger acknowledged that these are not a target population for agonist triggering.

But the rest, said Griesinger - those deemed at risk - should be triggered with an agonist (without hCG in the luteal phase) and allocated to a freeze-all strategy. Modified luteal support with hCG, he added, still requires the confirmation of large RCTs. And there were some at this meeting who also maintained that only 'a change of mindset', which took account of its restrictions and advantages, would make an agonist triggering and freeze-all policy (among patients and their doctors) routinely acceptable.

Despite the many questions raised by this Campus symposium, there has been much progress in reducing the risk of OHSS while maintaining delivery rate. And every speaker emphatically agreed that OHSS is a iatrogenic event caused only by the ovarian stimulation of the treatment. As such, its prevention is an obligation which comes right back to the very first Hippocratic principle. Indeed, in healthy egg donors - as Lawrence Engmann made clear - its occurrence is considered absolutely unacceptable.

Simon Brown
Focus on Reproduction

1. Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. Hum Reprod 2011; 26: 2593-2597.
2. Youssef MA, Van der Veen F, Al-Inany HG, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Datbase Syst Rev 2014; 10:CD008046. doi: 10.1002/14651858.CD008046.pub4.
3. Humaidan P, Polyzos NP, Alsbjerg B, et al. GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Hum Reprod 2013; 28: 2511-2521.

This was a very well attended Campus meeting, attracting more than 160 participants.

KISSPEPTIN FOR DIRECT HYPOTHALAMIC TRIGGERING?

The two models for triggering final oocyte maturation throughout the history of IVF have sought to exert an effect directly on the ovary (hCG) or on the pituitary (GnRH agonist). Now, the possibility of a new model of egg maturation, acting for the first time on the hypothalamus itself, was proposed by Channa Jayasena from Imperial College in London as a future trigger of ovulation. Kisspeptin - a peptide product of the KISS1 gene expressed in the placenta, hypothalamus and pituitary - has for more than a decade been known to regulate puberty and stimulate the release of LH in animal models and more recently in men and women through endogenous secretion of GnRH from the pituitary. Jayasena showed evidence of kisspeptin's presence in areas of the brain needed for ovulation and that blocking the effects of kisspeptin would also block ovulation.

Evidence that kisspeptin also triggers ovulation in infertile women has now been shown in a study reported by Jayasena in Thessaloniki in which 53 IVF patients were given kisspeptin for triggering oocyte maturation in three weight-related doses. Peak serum LH levels were achieved at around 6 hours, with between five and ten eggs retrieved per patient depending on dose. Overall pregnancy rate was 40%, with a LBR of 19%.

Jayasena described kisspeptin as a 'potent and safe' stimulator of gonadotrophins, with potential as a future hypothalamic trigger for oocyte maturation. Future studies will compare efficacy and safety with conventional approaches.

ESHRE's data collection: developments in online submission and in achieving greater coverage

- Progress identified in some national registries
- A flurry of legislative updates and introductions

EIM Consortium Chairman Markus Kupka: ESHRE monitoring represents 'around 80%' of total European ART activity

No other organisation in the world has a registry in reproduction to compare with ESHRE. The Society's European IVF Monitoring (EIM) Consortium is in its 15th year of data collection and has now passed the remarkable milestone of more than 1 million live births recorded. The Consortium is presently monitoring around 600,000 cycles a year in an ever escalating total of European ART activity. In 1997, the first year of EIM analysis, just 482 clinics in 18 countries were represented in 203,225 cycles of IVF and ICSI; in 2011, whose data are now being analysed, 1034 clinics in 33 countries were represented.

Speaking in November in Leuven at a closed meeting of Consortium members, EIM Chairman Markus Kupka estimated that the 600,000+ cycles now monitored each year by ESHRE represent 'around 80%' of total European activity - and that, he said, is good enough to provide a reasonably accurate snapshot of what's going on. But achieving a fuller, more detailed picture remains a huge challenge, not just to incorporate those countries with 'ongoing difficulties' in data collection, but also to ensure that the data which are collected accurately reflect the present trends in treatment. For just as ART itself continues to grow in complexity, so the task of data gathering also becomes more complex. Collecting data on a procedure such as 'egg donation', for example, is no longer a simple matter of recording a cycle, but must now acknowledge oocyte and/or embryo cryopreservation, transfer in a fresh or future (non-stimulated) cycle, and outcome, which may well be several years after the initial egg collection cycle.

And hanging over all the Consortium's difficulties lies the continuing challenge of online data collection. So it was good news in Leuven to hear Kupka announce that a Spanish company - which already works with the national IVF registry in Spain, has now been contracted to build a web-based platform to collect the ESHRE data. Plans are that the platform will be introduced in 2015. The same Spanish company will also create a tool to analyse incoming data for the annual report. 'So the whole process will be speeded up dramatically,' said Kupka, who added that the Spanish company will also be asked to create a data-collection tool for those countries with no online system. The current questionnaire is composed of eight modules (most of which are sub-divided) and 20 tables, set out over ten pages - and with a deadline for completion of around six months. For example, data for 2011 were asked for in Summer 2013, with a deadline of 31 December.

However, the Consortium's biggest everyday challenge still lies in data collection from those countries without national registries and with clinics reluctant to divulge their results. Data have never been received from Slovakia or Malta (which only recently joined the Consortium), while Albania, Bosnia, Croatia, Cyprus, Latvia, Romania and Turkey have provided only sporadic details. However, most of these countries were represented in Leuven, and their representatives were able to describe some progress.

Romania

'We want a national register, but there are still problems,' said Ioana Rugescu, who explained that legislation lay with the National Transplant Agency (and was thus based on the requirements of the EU Tissue and Cells directives). Any ART data collected were based on Eurocet forms (see box opposite). A voluntary scheme set up by the embryologists' association recruited only 50% of clinics.

Russia

Data collection is on a voluntary basis through the Russian Association of Human Reproduction and currently includes 138 clinics and around 63,000 cycles, around one-third of them under state control. From 2013 fertility treatment is covered by health insurance - patients can choose their clinic and their insurance company. However, 'around 25%' of data is not reported, and 'the register needs the support of the Ministry', said Vladislav Korsak (who has looked after the registry since its inception in 1995).

Cyprus

ART in Cyprus - around 2000 cycles a year - has been so far unregulated, but legislative proposals last year included a national ART registry and supervision by an ART authority. Historically, there has been a substantial trade in overseas treatments, mainly for gamete donation and sex selection (by PGD).

Malta

Data collection during 2013 (for the treatment year 2011) was Malta's first in the EIM Consortium, following the country's introduction of legislation in 2012 under control of the Embryo Protection Authority. The new legislation is quite restrictive, but treatment (up to three cycles) is fully reimbursed for women aged

25-42 years. Women must be in a stable relationship; embryo freezing is not allowed, but oocyte freezing is 'encouraged', said Jean Calleja-Agius. The new legislation requires details of every cycle to be submitted, with first data available after 2013.

Greece

Greece has consistently submitted data to the EIM , but on a voluntary basis, and with few details of deliveries. Triplet pregnancies have been a feature, with little regulation to guide treatment. Now, said Dimitri Loutradis, the situation is set to change with the introduction in 2015 of a National Authority for Medical Assisted Reproduction (NAMAR). Recently, ART has been hit hard by the financial crisis, with total cycles now at around 8000 per year. NAMAR will introduce a licence/code of conduct system for clinics, with a responsibility 'to collect results', and a restriction on the number of embryos transferred in each cycle (two in under 35s).

Croatia

Croatia has been able to provide registry data to ESHRE for only one of the past six years, but Hrvoje Vrcic reported that legislation introduced in 2012 included the development of a government registry in ART.

Other disclosures in Leuven described significant updates to the regulation and registry systems in some countries. Both Switzerland and Austria are now looking ahead to new statutes, the former with legislation now agreed by Parliament to include PGD, embryo cryopreservation and sperm donation (though not yet oocyte donation). Austria too agreed new draft regulations (just the day before the Leuven meeting!) which would also allow PGD, egg donation and treatment in lesbian couples. 'We were somewhat shocked,' said Heinz Strohmer, 'We now expect things to change dramatically in Austria.'

Poland too is set for dramatic change in its ART legislation. Reimbursement (of treatment and now of medication) has been introduced and a new law is 'waiting in Parliament'. ART has been hampered by religious objection in Poland, but that, with the acceptance of reimbursement, seems now more an academic than practical concern.

Chief among the reasons for inadeqaute national registries was money, with many smaller ART countries with voluntary registries seemingly the most affected. In fact, the split between voluntary and compulsory data collection among EIM countries is fairly equal, with some voluntary systems (Spain and Germany, for example) as comprehensive and successful in their registries as statutory (UK). Indeed, Germany operates its registry on a simple funding formula of 1.60 euro for each cycle started, and 'there's no problem to pay,' said Kupka.

The other main problem identified was an unwillingness to disclose results. Latvia, Ukraine and Slovakia had 'no data . . . and no will to have a registry'. Several delegates, particularly from countries with just a few private clinics, expressed doubts whether these clinics would ever reveal their results, for fear of league table competition.

Nevertheless, despite the problems inherent in a mix of voluntary and mandatory systems, 15 countries do now provide data derived from every clinic - Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, Hungary, Iceland, Norway, Portugal, Slovenia, Sweden, Netherlands, United Kingdom - while most others offer reliable returns from a large proportion of their clinics.

CONFUSION OVER EUROCET DATA COLLECTION

Several countries describing their efforts in ART data collection seemed under the impression that requests from Eurocet to provide ART reports would meet requirements on standards set out in the EU Tissue and Cells directives of 2004. However, there appears no confirmation of this, and said Kupka, 'it is difficult to know what Eurocet's objectives are' in data collection and under what authority it operates.

For its part, Eurocet describes itself as no more than 'a tool aiming to collect data on tissues, hematopoietic and reproductive cells'. Nowhere does Eurocet refer to its (or any) statutory right to collect ART data, only that the 'European Commission encouraged the use of Eurocet portal as a way to fulfil the obligations of the tissues and cells Directives'.

Eurocet is run by the Italian National Transplant Centre and appears to have no formal status within the EU, other than its self-styled role 'to respond to the obligations of the tissues and cells Directives'.

National representatives from the EIM Consortium meeting in Leuven.

ESHRE's first research grant awarded to joint UK/Italy project to prevent ovarian damage from chemotherapy

● Grant awarded with emphasis on originality, feasibility and expected impact

ESHRE's first research grant has been awarded to a project designed to prevent the loss of female fertility during cancer treatment. The grant - of €150,000 - will fund researchers at the Universities of Edinburgh and Rome Tor Vergata, led by Professor Norah Spears, to test the viability of tyrosine kinase inhibitors in protecting the ovary from chemotherapy-induced damage. The project will use a novel ovarian culture system allowing high-throughput and rapid quantitative analysis.

'Recent decades have seen a steady increase in the survival rates of cancer patients,' explains Professor Spears, 'and a key concern is the effect of treatments on subsequent fertility. At present, options are mainly concentrated on preserving fertility, though ideally treatments would prevent damage from occurring in the first place.' This project, she added, is to look for compounds which will protect the ovary against damage from the alkylating-like chemotherapy drug cisplatin. The long-term general aim is to establish the viability of this culture system for large-scale drug screening.

Associated in the project with Professor Spears are Francesca Gioia Klinger and Massimo De Felici at the University of Rome Tor Vergata, and her Edinburgh colleagues Richard Anderson and Federica Lopes.

The first announcements of ESHRE's research scheme were made early last year, with calls for proposals in March. Submissions reached a remarkable total of 259, all of which were sent to ESHRE's SIG and Task Force Co-ordinators and Executive Committee for initial review and scoring. The ten proposals with the highest scores were then selected for the second round of review.

Winning project co-ordinator Norah Spears: the 'ideal' option to prevent ovarian damage in the first place.

In this second round of evaluation, extended proposals were assessed and ranked by five leading experts, who were selected in consideration of the ten proposals to prevent conflicts of interest. The experts scored the proposals according to six criteria (originality, design, feasibility, quality of the consortium, expected impact, and appropriateness of the budget), and offered additional comment on the strengths and weaknesses of each.

Thus, their scores were explained and justified, so leaving the Executive Committee with the relatively straightforward task of selecting the winning proposal based mainly on the highest scores and opinions of the experts.

ESHRE's initial ideas for the scheme are that proposals for the research grant will be called for every two years, with only minimal eligibility criteria for applicants - that the co-ordinator submitting the proposal is an ESHRE member working in the field of reproductive medicine and biology, and that the co-ordinator and associated investigators represent at least two different entities/institutions - public and/or private - from the same or different countries.

FoR: Paper or PDF? Time for you to decide

During the coming weeks we will be asking how you wish to receive *Focus on Reproduction*. To continue as before with a posted printed copy, or to switch to a personally e-mailed PDF? Currently, all members of ESHRE receive *FoR* three times a year - mailed as a printed copy to the address we have on file. But, with a membership of well over 6000, some records are not up-to-date and around 400 copies of each issue are returned to ESHRE's Central Office as not delivered. This is expensive - as wasted postage and print cost.

Now, to cut down on these costs and pursue our paper-free commitment, we will be asking each ESHRE member if they wish to continue with paper copy delivery by post; otherwise, FoR will be sent as a PDF e-mail attachment. But remember that paper copies will only be mailed to those who specifically make that choice in their reply to our forthcoming question or through their 'Myeshre' function on the website. Meanwhile, *FoR* will continue as usual as ESHRE's news magazine, with three issues a year in January, May and September. The new distribution system will begin with the May issue.

Reduced drug costs, SET, and strict eligibility bring IVF in the Netherlands back on budget

Frank Broekmans, chair of a Dutch working group, describes how its proposals to trim costs have restored the provision of three fully reimbursed cycles of IVF for all in need

Despite the prevailing tendency of exploding healthcare costs in Europe, Dutch government policy has aimed to keep every bit of existing healthcare available to all citizens on the basis of almost maximal reimbursement by insurance companies. Nevertheless, in some sectors, notably contraception and ART, there has been an evident tendency to control these levels.

Thus, in 2011 announcements were made by the Dutch Ministry of Health to reduce the number of reimbursed cycles of IVF/ICSI to just one. In response, specialists from the Dutch Society for Obstetrics and Gynecology in collaboration with the patient group Freya convinced the government that an alternative way to make the desired cost savings was feasible - a total sum of €30 million on a yearly budget of €80 million for infertility care.

A working group was formed with representatives of all 13 Dutch IVF units which, in collaboration with the health insurance companies and the Dutch College for Health Insurances, began work on this alternative plan. The plan included:

- a strict policy of single embryo transfer in all women under the age of 38 and in the first two full IVF/ICSI treatment cycles
- infertility work-up and treatment limited to women under the age of 43
- the strict application of the Hunault model (for prediction of spontaneous pregnancy in infertile couples) and thus treatment in unexplained or mild male factor infertility limited to couples with a one-year prognosis under 30%
- the reduction of costs of medication by the use of urinary FSH preparations only
- the application of prescription rules to limit medication spilling.

The policy of the working group was to spend only limited time on bridging the various opinions and disagreements on this complicated dossier. Thus, instead of seeking full opinion consensus, a 'commitment' was to be obtained from participants on the execution of the various steps towards implementation of the proposal. Items which generated most discussion were a wish to base the proposed SET strategy on embryo quality, and the reduction in expenditure on FSH medication by switching to urinary products. On the former, it soon became clear that legislation already in place prohibited any further adjustment. On the latter it was felt that freedom to choose between multi-dosing devices or daily ampule preparations, and urinary or recombinant products had to be maintained, and a 'preference' policy in favour of urinary FSH did not achieve full commitment. Instead, the working group sought to achieve unit price reductions from the manufacturers, and so the desired savings on medication were mainly achieved by a combination of fewer treatment cycles (based on a more strict indication for ART) and lower unit costs for the medication. Currently, unit prices for FSH products have been reduced by 30%, and thereby a structural cost reduction for the years to come of approximately €9 million has been established.

The effects of implementation are now evident in registration data from all Dutch hospitals providing infertility care. The data first show a reduction in the overall number of IUI and IVF/ICSI cycles of around 10%. In addition, it could be shown that the strict SET policy had brought about a decline in the twin rate - from 10% in 2012 to a little above 5% in 2013. At the same time only a small reduction in overall ongoing pregnancy rates per started cycle, including frozen embryo replacements, was observed - from 27.5% per started cycle in 2012 to 25.6% in 2013.

Currently, the data registries have yet to show whether all the measures taken together have indeed brought about the €30 million budget saving, a target which must be reached for 2014. Still, the achievements mean that Dutch infertile couples have the certainty of three full reimbursed IVF treatment cycles available.

It is, however, clear that reproductive medicine and infertility are considered non-medical problems and thus easily deprived of regular insurance coverage. So far, the working group has succeeded in avoiding the latter, but continued efforts are still needed to keep infertility on the agenda as a recognised health issue with many features of a chronic disease.

Frank Broekmans and Sjaak Wijma on behalf of the Dutch Society for Obstetrics and Gynecology

Frank Broekmans: 'A decline in the twin rate - from 10% in 2012 to a little above 5% in 2013

Concerns in France over graduate eligibility for work in IVF labs

There are concerns in France that new regulations over the employment of staff in 'medical laboratories' are making it difficult for highly qualified biologists to be approved for work in IVF labs. Now, even those with a doctorate in reproductive biology find themselves ineligible for authorisation under the new regulations.

'If we are unable to have more scientists in the lab, there's a danger that we will lose the quality in our teams,' said Pierre Boyer, a member for France of ESHRE's Committee of National Representatives and head of the IVF lab in Marseille.

The problem dates back to the very beginning of IVF in France when biologists and clinicians were instrumental in setting up the first IVF programmes. This tradition was incorporated into the very first IVF regulations, when scientists without a medical degree could be approved, and then later into the statutes of 2004 following the introduction of the EU Tissue and Cells directives. The newly formed Agence de la Biomédecine (ABM) could still grant working approval to basic scientists in IVF labs subject to their experience and to working under the direction of a medical doctor in the lab.

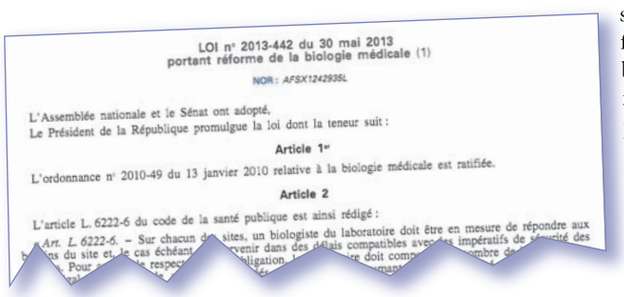
But new legislation introduced in July 2011 to improve the running of medical laboratories in France removed this function of practitioner approval from the ABM as the competent authority. From 2011 the evaluation of all staff in IVF labs would become the responsibility of regional health authorities to whom practitioners must demonstrate competence. However, even this concession was removed by the updated legislation of 2013 (Loi n°2013-442), and competence can now only be demonstrated by a medical or pharmacy degree or by a lab technician diploma. So now, anyone working in an IVF lab must be either a medical doctor or a pharmacist, or have a specialist diploma in 'medical biology'. However, even this diploma is not sufficient qualification for some procedures, notably in IVF ('activités biologiques d'assistance médicale à la procréation').

Any former exceptions to this medical or pharmacy requirement (by which other biologists could demonstrate competence) are now 'suppressed' under the 2013 legislation. Other standards - such as ESHRE's certification for embryologists - 'count for nothing in France', said Boyer.

Debbie Montjean, who gained her PhD in biology in 2011, took a hospital position in Marseille, but was not allowed under the new legislation to work as an embryologist in the IVF lab - which she wished to do. Her only way in, she told *Focus on Reproduction*, is to take a step back and gain the technical diploma. 'I guess the assumption is,' said Debbie, 'that, here, in France if you do the PhD you'll go on to research, not into clinical science.'

So far, added Boyer, the problem is not widespread in France, but may escalate as time goes on and more biologists look for employment in IVF. But the result is right now that a high postgraduate qualification in human biology is not an appropriate qualification for authorised employment in an IVF lab in France.

The 2013 legislation is part of a continuing drive in France to reform the 'medical laboratory' sector, and medicalise its functions ('L'acte de biologie est un acte médical.'). Among the proposals are that all French labs in France are accredited by the Comité français d'accréditation by 2020 .



LOI n° 2013-442 du 30 mai 2013
portant réforme de la biologie médicale (1)

NOR : AFSX1242935L

L'Assemblée nationale et le Sénat ont adopté,
Le Président de la République promulgue la loi dont la teneur suit :

Article 1er

L'ordonnance n° 2010-49 du 13 janvier 2010 relative à la biologie médicale est ratifiée.

Article 2

L'article L. 6222-6 du code de la santé publique est ainsi rédigé :

« *Art. L. 6222-6.* – Sur chacun des sites, un biologiste du laboratoire doit être en mesure de répondre aux

ESHRE postgraduate course at ASRM attracts strong attendance - despite the weather

Mona Bungum, Nico Garrido Puchalt and I had the pleasure of representing ESHRE at October's ASRM Annual Meeting in Hawaii, with a postgraduate course on **Spermatogenesis through laboratory choice for ART to more take home babie**s.

The course was very well attended with 146 registrations. ASRM was delighted with this response - they ran 20 courses with an average attendance of only 50.

The programme comprised presentations on spermatogenesis, semen analysis, novel biomarkers and sperm function tests, free radicals and antioxidants, preconceptional genetic testing of sperm donors, recurrent miscarriage, lifestyle hazards, the effect of sperm quality on ART outcome, and the paternal genome.

We each gave three lectures, followed by discusssion. The audience was around 50% clinicans and 50% embryologists, so that our questions were predictably divided between laboratory procedures and clinical meaning for patients. However, each discussion was vigorous and interesting, with conversations continuing all week.

The weather and location was a blessing and a curse. The overall number of delegates was considerably lower than the previous year in Boston, with Hawaii a 10-hour flight from the East Coast. Moreover, a hurricane had been forecast the previous week, so many had cancelled at the last minute. The hurricane turned out to be just a 'tropical storm', but even for someone coming from rainy Ireland, this was a new experience! Very heavy rain and wind, with flash flooding, and torches in our rooms in case the electricity failed.

The blessing was that we had a good crowd at an ESHRE course, and much interest shown by those attending. Delegate evaluations have just arrived on my desk, and we were very highly scored in all categories.

Sheena Lewis
Past Co-ordinator SIG Andrology

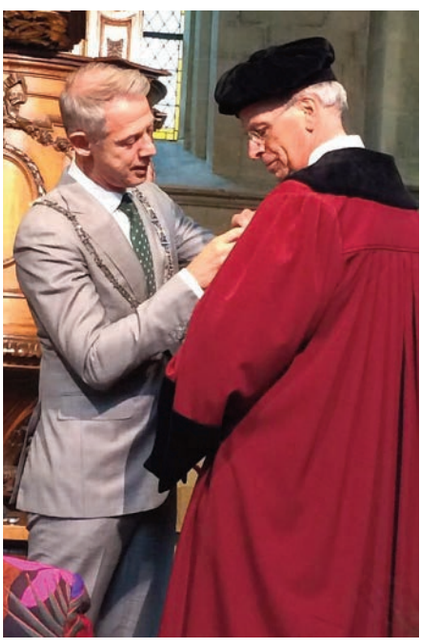
Honours for former ESHRE Chairman, as Evers retires from hospital clinic

Hans Evers, Chairman of ESHRE from 2001 to 2003 and currently editor-in-chief of *Human Reproduction*, formally retired from his post as Professor of Obstetrics and Gynaecology at the University of Maastricht Medical Centre in September last year.

The retirement ceremony culminated in the award of the Order of Orange-Nassau to Evers by the mayor of Maastricht on behalf of King Willem Alexander of the Netherlands. This chivalric and long established honour is bestowed on Dutch citizens who have 'earned special merits for society'.

Evers now plans to devote all his time to ESHRE's flagship journal. 'I feel I have failed to spend enough time on it so far,' he said, 'but this will change.'

Evers has long been a leading figure in ESHRE, even before he became Chairman in 2001 - he was a member of the editorial board of *Human Reproduction* since 1995, chairman of the 12th Annual Meeting in Maastricht, and co-ordinator of training activities from 1992 to 2000.



Hans Evers receiving the Order of Orange-Nassau from the mayor of Maastricht.

Having qualified in medicine in 1976 at Nijmegen, Evers was invited in 1982 to set up an infertility unit at the new university hospital in Maastricht, and here he would remain for the next 32 years.

He was a member of the editorial board of *Fertility and Sterility* from 1992 to 1997, a founding member of the World Endometriosis Society and served as its President from 2008 to 2011. Evers also received honorary fellowships from the UK's Royal College of Obstetricians and Gynaecologists and British Fertility Society, and is an honorary member of the Middle East Fertility Society, the Sociedad Argentina de Esterilidad y Fertilidad, and the Australian Gynaecologic Endoscopy Society.

ESHRE invited moderator at EU Council conference

ESHRE was an invited participant at a Ministerial Conference in October organised by the Italian Presidency of the Council of the EU. The two-day meeting - on a 'life course' approach to women's health - featured reproductive health in one of four sessions, with lectures on 'challenges' in the EU, preconceptional health, and pregnancy and delivery. Former ESHRE Chairman Luca Gianaroli moderated the discussion, in which Ministers of Health were invited to comment on policies implemented in Member States on the promotion of sexual health at different stages of a woman's life.

Of further interest to ESHRE was the fourth session on female cancers in which Eleanora Porcu, one of the pioneers of oocyte cryopreservation, reviewed the potential for fertility preservation in oncology patients.

'I think that the presence of ESHRE in events like this is very important,' said Gianaroli. 'It not only reinforces our role as a reliable interlocutor for national and EU institutions, but also allows us to raise current scientific and clinical issues in reproductive health among policymakers.'

. . . and the career of another ESHRE editor is honoured

Steve Hillier, Professor of Reproductive Endocrinology at the University of Edinburgh and editor-in-chief of *Molecular Human Reproduction* from 2007 to 2013, also retired from his academic post in October. Throughout his illustrious career Hillier, who enjoyed 22 years of uninterrupted funding from the UK's Medical Research Council, explained many of the cellular pathways controlling ovulation.

At a 'scientific afternoon' in Hiller's honour in Edinburgh, his particular branch of basic science was described as 'translational endocrinology', for many of his findings would indeed have clinical application, particularly in ovarian stimulation for IVF.

Hillier took over the editorship of *Molecular Human Reproduction* - which he quickly rebranded as the snappier *MHR* - at a time when it seemed the 'least loved' of ESHRE's three journals, yet within a few years he saw its impact factor rise to 4.5, only fractions of a point behind the flagship *Human Reproduction*.

Hillier, who will continue in emeritus place in Edinburgh, will be made an honorary member of ESHRE later this year.

Steve Hillier, retired from his post in Edinburgh after a hugely influential career in reproductive biology.

A world first to match the best in IVF

- First live birth announced after uterine transplantation
- Two further deliveries expected before close of 2014
- Treating 'the last untreatable form of female infertility'

Mats Brännström: Uterine factor 'the last untreatable form of female infertility'.

Formal announcement of the world's first live birth following uterine transplantation came online in *The Lancet* in October in a detailed nine-page report from Mats Brännström and colleagues at the Sahlgrenska University Hospital, Gothenburg.[1] Brännström had made it clear throughout the 15 years of this programme that case details (always anonymous) would only be described in a paper subject to peer review.

In an editorial accompanying the report, *The Lancet* listed Brännström's achievement alongside only three other milestones from the 'relatively short history' of fertility: 'the arrival of in-vitro fertilisation (IVF) in the late 1970s; the development of intracytoplasmic sperm injection in the early 1990s; the first ovarian transplant a decade ago; and [now] the first livebirth after uterine transplantation'.

The Gothenburg report described how a 35-year-old woman with congenital absence of the uterus (Rokitansky syndrome) received the donor uterus from a 61-year-old two-parous woman in 2013. The recipient and her partner had IVF before the transplantation, from which 11 embryos were cryopreserved. Following single embryo transfer, fetal growth parameters and blood flows of the uterine arteries and umbilical cord were said to be normal throughout the pregnancy. Pre-eclampsia shortly before term prompted a Caesarean section delivery at 32 weeks.

Brännström himself had described the background to the transplantation at last year's 'Best Of' joint meeting of ESHRE and ASRM in Cortina, Italy, with the surgical details published almost simultaneously in *Fertility and Sterility*.[2] Now in October the investigators reported their results as 'a proof of concept for this treatment of uterine factor infertility', adding that the efficiency of the technique 'is unclear and remains to be established'. In a press release issued by the University of Gothenburg Brännström described uterine factor infertility as until then 'the last untreatable form of female infertility'.

The series of patients in Gothenburg appears to comprise six other women with an absent or dysfunctional uterus who also had embryo transfer. Two of them were reported in December to have

Liza Johannesson, a gynaecological surgeon in the group, said the delivery brought hope to those couples who thought they would never have a child.

The Lancet editorial was also prelude to three reviews of fertility preservation (if not restoration), particularly in advance of cancer treatment. In the first, Herman Tournaye, Gert Dohle and Chris Barratt described sperm cryopreservation as an effective but underused method of fertility preservation in boys and men, noting how advances have been made in prepubertal germ cell storage for the later transplantation of testicular tissue and associated stem cells.

Fertility preservation for women - for both medical reasons and 'in the wider population' - was reviewed in two reports: first on oocyte and ovarian tissue storage in women with cancer (described as 'in its infancy', and compromised somewhat by demands of time to begin cancer treatment); and next, by Dominic Stoop, Ana Cobo and Sherman Silber, on social indications, described as 'increasingly popular to overcome the age-related decline in fertility'. While Brannstrom himself remained cautious about the routine application of uterine transpantation as fertility restoration, he was quoted in some press reports as suggesting its potential applicability after cancer treatment.

delivered, with a uterus donated by their mothers.

Two earlier cases of uterine transplantation had been reported, one from Saudi Arabia and another from Turkey, both of which were criticised ethically as experimentation on humans. The Gothenburg series, as Brännström explained in Italy, allowed no risk of such accusations, with a painstaking research approach progressing from mice to non-human primates.

Last year Brännström said in Cortina that seven of the nine recipients began menstruating from the second month. In this first successful case, the recipient's first menstruation occurred 43 days after transplantation and she continued to menstruate at regular intervals (median 32 days). Her first embryo transfer, which resulted in pregnancy, took place one year after transplantation.

The Gothenburg investigators have since this first birth made it clear that uterine transplantation is not likely to be routine procedure for many years. But speaking in a filmed interview after the delivery, Liza Johannesson, a gynaecological surgeon on the team, said: 'It gives hope to those women and men that thought they would never have a child, that thought they were out of hope.'[3]

In an interview with the Associated Press news agency, the mother, who wished to remain anonymous, said: 'As soon as I felt this perfect baby boy on my chest, I had tears of happiness and enormous relief. I felt like a mother the first time I touched my baby and was amazed that we finally did it.'

Roy Farquharson, a former co-ordinator of ESHRE's SIG Early Pregnancy, said that the many earlier reports of egg donation in postmenopausal women had already proved the principle that the uterus is able to function under hormonal stimulation. 'It's the eggs which matter,' said Farquharson.

Brännström and his group speaking at a press conference after the birth.

Nine women in the project received a uterus from live donors – in most cases the recipient's mother but also other family members and close friends (as in the first successful case). It is known that other groups - in China, France, Belgium, UK, Spain and USA - are working on similar projects, some with a uterus from a deceased donor.

1. Brännström M, Johanneson L, Bokström N, et al. Livebirth after uterus transplantation. Lancet 2014; http://dx.doi.org/10.1016/S0140-6736(14)61728-1.
2. Brannstrom M, Johannesson L, Dahm-Kahler P, et al. First clinical uterus transplantation trial: a six-month report. Fertil Steril 2014; 101: 1228–1236.
3. See https://www.youtube.com/watch?v=kujArjUSt5A.

Higher fertility rates may not be best response to ageing populations

The usual response of demographers to the decline in national populations has been to increase fertility rate to somewhere near its replacement level of 2.1 births per woman - and thus to encourage earlier pregnancy through social and fiscal incentives and even an increase state funding for IVF. The basis for this strategy has been economic, that health and social support for an ever burgeoning proportion of elderly citizens is simply not sustainable.

Now, a far-reaching and complex study from demographers in the USA based on National Transfer Accounts data for 40 countries suggests that moderately low fertility and modest population decline actually favour a higher living standard, even if fertility well above replacement would typically be most beneficial for government budgets.[1]

The paper comes as fertility in the USA has hit an all-time low of 1.86, comparable with that of many countries of eastern and Mediterranean Europe, and as the UN forecasts a world population increase from its current 7.2 billion to 9.6 billion in 2050 and 10.9 billion in 2100 (mainly explained by population changes in Africa).

By correlating national birth rates with economic data the US investigators have now concluded that a moderately low birth rate – a little below two children per woman – can actually boost a country's overall standard of living. Thus, while governments generally support higher birth rates to maintain the workforce and tax base needed to fund pensions, health care and other benefits for the elderly, it is, say the researchers, usually families which bear the brunt of the cost of having children.

'Higher fertility imposes large costs on families,' said investigator Ronald Lee. 'Instead of trying to get people to have more children, governments should adjust their policies to accommodate inevitable population aging.'

CURRENT UN FERTILITY RATES[2]

India	**2.55**	**Nigeria**	**6.00**
China	**1.63**	**Hungary**	**1.33**
Australia	**1.89**	**Austria**	**1.40**
France	**1.97**	**Germany**	**1.36**
Italy	**1.38**	**Japan**	**1.34**
Spain	**1.41**	**UK**	**1.88**

1. Lee R, Mason A. Is low fertility really a problem? Population aging, dependency, and consumption. Science 2014; 345: 229-234.
2. United Nations Department of Economic and Social Affairs, Population Division, World Population Prospects: The 2012 Revision (United Nations, New York, 2013).

The central role of data collection in ART

- No hard evidence to support non-anonymity in gamete donation
- Cycle-specific data needed to explain outcome differences between Europe and USA

A Campus meeting in Leuven on the importance of data collection in several disciplines of reproductive medicine not only provided something of an explanation for the divergence in results between Europe and the USA, but also suggested that Europe's move in favour of non-anonymous gamete donation was without the support of hard evidence.

Dmitry Kissin from the Division of Reproductive Health at the CDC argued that the apparent differences in ART outcome between Europe (LBR 23% in 2010) and the USA (LBR 30% in 2010) were the combined results of several factors, but notably the broader 'utilisation' of fertility treatments in Europe, a higher rate of multiple embryo transfers and egg donation in the USA, and cost. However, said Kissin, comparing overall success rates without taking into account such patient and treatment factors is misleading, and appropriate comparisons can only be made with cycle-specific data.

However, data - or a lack of it - does suggest that the reasons underlying Europe's move to remove the anonymity of gamete donors are misguided - and, said Veerle Provoost, co-ordinator of ESHRE's SIG Ethics & Law, reflective of a policy more led by ideology than empirical evidence. Provoost's case rested on the quality of evidence in the literature and the weak case of 18 papers routinely used to support non-anonymity in gamete donation. Yet on re-analysis, all these commonly cited papers were flawed to a lesser or greater extent - and in nearly all the authors failed to disclose or take account of any limitations to their studies. Many of the subject samples were self-selected (with limited acknowledgement), the analyses were flawed, and conclusions were often only tenuously linked to the data, with results overestimated. Among the assumptions of these conclusions was an overriding acceptance of the offspring's 'need to know', and the role of the donor's indentity in the identity-formation of the offspring. In fact, said Provoost, there is little evidence to support the view that one is 'required to know one's genetic origins', or that such knowledge is 'essential to human well-being', or 'harmful' if denied. Countries need to look at their legislations, said Provoost, as 'there's no good evidence to abolish anonymity'.

An ESHRE survey reported by Portugal's Carlos Calhaz-Jorge for the EIM Consortium suggested that gamete donation was governed by law in 24 of 29 countries responding. All of the 24 allowed semen donation, and all but four egg donation. Donation in most countries (17/24), however, was anonymous, although some of these jurisdictions did allow disclosure of donor identity at some point. Moreover, questions raised from the floor did suggest that many countries were moving towards systems in which donors were identifiable at some time - despite any strong evidence in favour of such a move.

Veerle Provoost: Move to non-anonymity driven more by ideology than empirical evidence.

EUROPE'S PATCHWORK OF REIMBURSEMENT

A survey on reimbursement in Europe performed with the support of ESHRE's EIM Consortium found a statistical correlation between ART volume and outcome (IVF/ICSI births) and reimbursement. Nearly all European countries (with the exception of Belgium) now have private IVF services, the majority (except the Netherlands, Slovenia, Germany) dominated by the private sector. Numerically, most private clinics are in Italy and Spain.

Among other findings reported by health economist Mark Connolly:

- 76% of private clinics receive some form of public reimbursement
- In 68% of countries patients cannot claim treatment costs on income taxes
- 44% of countries have eligibility restrictions based on age (majority) and number of cycles
- Few countries impose restrictions based on BMI, smoking and marital status, although 13 countries do impose restrictions on same sex couples
- 58% of countries have no or very short waiting-lists

Health economist Mark Connolly: some reimbursement available in most countries.

- Reimbursement is available in most countries, which may include doctor/medical costs (27 countries), laboratory costs (25 countries) or pharmaceutical costs (25 countries).
- Costs of frozen transfers are reimbursed in one-third of countries
- Other servicess, such as PGD, PGS, time-lapse microscopy, blastocyst culture, vitrification and embryo storage are not usually reimbursed

Maria José De los Santos, head of one of Europe's biggest IVF laboratories and Co-ordinator of ESHRE's SIG Embryology, on PGS, time-lapse microscopy and other challenges facing embryology today.

Maria José De los Santos: 'The key to more improvement will be a better understanding of embryo cleavage and implantation.'

Two labs, and more than 4000 cycles every year

'Technology has helped us explore many genetic and morphological aspects of embryo quality.'

FoR: You're head of the IVF lab at IVI Valencia, one of the biggest centres in Europe. First, tell us something about the programme.
Maria José De los Santos: Well, if we don't count oocyte vitrification, we do more than 4400 treatment cycles a year. Around 40% of these are egg donation and 60% regular IVF and ICSI. But they are two quite distinct programmes, with two separate labs. Around 25% of our non-donor cycles are PGS, which means a lot of work for the lab. In one lab we have 23 normal incubators, and two Esco and two time-lapse systems, and in the other 23 regular and two time-lapse incubators.

And you have responsibility for all this? How many are working in these two labs?
We have a total of 37 embryologists and technicians, with some additional administrative staff. Most of the embryologists are well trained, some to post-doctorate level.

And some are very well known for their research?
Yes, Marcos Meseguer's work with time-lapse microscopy and Ana Cobo's with oocyte vitrification all took place in our labs.

So how would you define your role within this huge organisation?
Well . . . I have to make sure that everything runs well, but to do that I have to delegate. So I am fortunate that many of my colleagues are very experienced. For instance, I rely heavily on Josep Lluis Romero to ensure that all our equipment is running well, and there are others who supervise different activities in the labs.

And are you involved in the clinical trials?
I try to be, but it's not easy because of time. I do try at weekends, and would like to give one day a week to our research. But sometimes it's just not possible, especially with my new ESHRE responsibilities. I can't get into the lab as much as I'd like.

So how does your average day work out?
I get up most days around 7, and have breakfast with my two daughters. Once they've gone to school I spend a little time at home planning what I have to do and preparing for the day - and if there's time

One of the two IVF laboratories at IVI Valencia.

reading some of the latest papers. Once I'm at the lab my life is one meeting after another and planning, and the day never ends before 6.30 or so.

It's obviously an intense working life. What about family life?
I suffer a lot. I have two daughters and I think for me - and for women in general - it's very difficult to find a balance between the demands of work and the demands of family. My husband helps a lot, but I don't think that's the same . . . I feel a strong responsibility which I can't always fulfil. There's always that fear that if you're not at home something goes wrong. It's not true, of course, but it's something that I feel.

And on top of this you're also now Co-ordinator of ESHRE's SIG Embryology.
Yes, and up to one year ago I was also chairing the embryology group in Spain. I am also involved in the standardisation programme for IVF labs in Spain - and now these responsibilities for ESHRE . . .

And what about projects for the SIG?
One of our priorities is to update the *Atlas of Embryology* so that it is available as an application for tablets and smart phones. This would make it more interactive, and of course more easily accessible. We are also updating the ESHRE guidelines for good practice in IVF laboratories.

The SIG Embryology is now ESHRE's biggest special interest group. What do you think has happened in reproductive medicine that embryology has become so important?
Well, the lab is now without doubt very important in IVF, that's for sure. But don't forget that embryology is still not recognised as a strong discipline in many countries, so there is till much work to be done there. It's true that technology has helped us explore many of the genetic and morphological aspects of embryo quality, but there is still much that we don't know about cleavage events. For example, all the studies we have done have not been able to demonstrate that time-lapse microscopy is actually helping in embryo selection. The only thing we know is that when you develop the embryos under very safe conditions, you are able to improve implantation and pregnancy rates, but we don't know for sure whether it's because of the algorithm per se or because of the incubation conditions. Even though I was involved in these studies I knew that our clinical trial was not a perfect study.

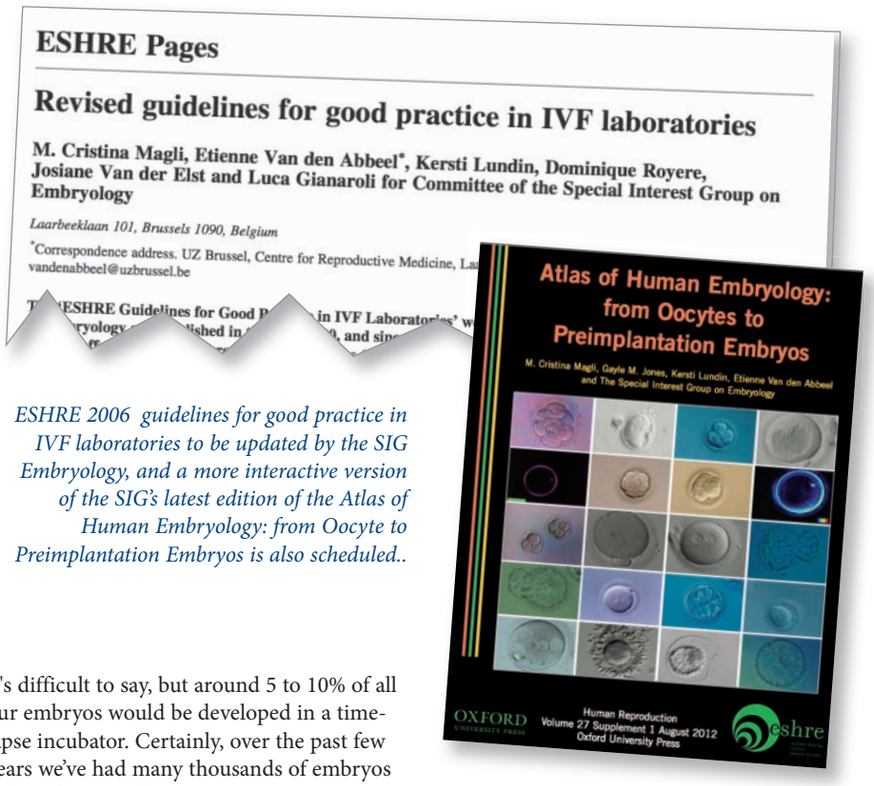
'We believe you have to do the randomised trials, but they are very difficult to complete. You need many patients, and sometimes it's just not possible to find enough, even with our numbers. So we have to be critical too, and recognise that our studies are rarely perfect.'

You say that 25% of all non-donation cycles in your labs are now PGS. I assume that you have to believe in the concept of PGS, despite the lack of trials?
We now do array CGH in all cycles, so we can screen for all chromosomes. Of course, I am aware of the disagreements between different clinics but I do believe it can be very helpful under certain conditions, and one example is advanced maternal age, because the proportion of abnormal embryos in those women is very high. Even though we can do one transfer after another until the woman gets pregnant, many of these women don't have time on their side. It's true that vitrification has been a very important tool here. We didn't do well with slow freezing, but now we are getting 99% survival with embryos and almost 90% with oocytes. It means that all the embryos created in a cycle can be available to our patients - but we have to play with time.

So advanced maternal age is your main indication for PGS?
Yes, it's a question of balancing the efficiency of the technique with time. But I have to say that we don't do PGS without a lot of consideration.

What other forms of embryo selection would you routinely perform in your labs?
Morphology and time lapse. Every embryo would be assessed morphologically, but we would also use the time lapse incubators if there is space. We have some patients who ask to have their embryos in the time lapse incubator, and they have to pay for that. But, if there's room, we use the time-lapse incubators for our daily practice - and we don't charge for that.

So at any one time how many embryos would there be in these time-lapse systems?



ESHRE 2006 guidelines for good practice in IVF laboratories to be updated by the SIG Embryology, and a more interactive version of the SIG's latest edition of the Atlas of Human Embryology: from Oocyte to Preimplantation Embryos is also scheduled..

It's difficult to say, but around 5 to 10% of all our embryos would be developed in a time-lapse incubator. Certainly, over the past few years we've had many thousands of embryos cultured in time-lapse systems.

These are huge numbers, which I suppose very few centres can match. We have seen it too in Ana Cobo's work with vitrification.
Ana has done wonderful research work, but it's also been very important in our everyday egg donation programme. Many patients come from abroad and for them it's very useful to have a specific date for embryo transfer. So having an egg bank is very important in the programme's organisation. It's very easy for patients to come to Valencia, have the transfer . . . and that's it, even though for the laboratory it's a lot of work, many procedures. Many of the eggs from our donors are now banked, but we do still use fresh transfers. I guess it's around 50-50.

What it all means, of course, is that IVI is in an almost unique position to perform large-scale clinical trials. What other groups could perform them in a single centre?
We believe you have to do the randomised trials, but they are very difficult to complete. You need many patients, and sometimes it's just not possible to find enough, even with our numbers. So we have to be critical too, and recognise that our studies are rarely perfect. We couldn't really prove the benefits of time-lapse because we didn't have enough patients for a third arm in the study. So we have to admit that it was not a perfect study.

Many of your studies are in egg donors. Where do these donors come from? Why do patients come to Spain?
Mainly historical, I think. IVI Valencia began its egg donation programme in 1990, so we have a lot of experience and that's well known. We do actively recruit and ask donors if they would donate again. Payment is not allowed in Spain, but donors can be allowed around 900 euro for expenses and time.

And what's your policy on OHSS?
We use an antagonist protocol in most patients - and certainly in all egg donors. We haven't had a case of serious OHSS for many years, and now when we see any signs we end up vitrifying the embryos. Even with no obvious signs, just a high estradiol and progesterone, we prefer to freeze the embryos.

And finally Maria, where do you think embryology will be in ten years?
I think we still have a lot to learn. We need to know more about the endometrium in the whole story. We need to find out which patients will benefit from cycle segmentation and develop a more personalised kind of treatment. When we started in 1990 our pregnancy rates were around 20%, now we are talking about 45% . . in egg donation 60%. So our delivery rates have already improved dramatically. But I think there's further to go and the key to more improvement will be a better understanding of embryo cleavage and implantation - and a more individualised style of treatment.

PROUST QUESTIONNAIRE*

- **What habit do you dislike in others?**
Lack of tolerance

- **And in yourself?**
Laziness - especially getting up in the morning

- **Which people do you most admire?**
Those who achieve their life fulfilment

- **Which talent would you most like to have?**
To play the piano

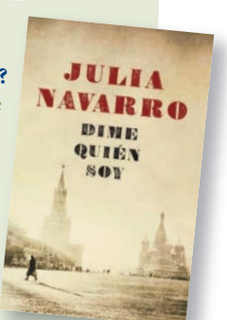
- **What do you consider your greatest achievement?**
Personally my family, professionally my job

- **Where would you most like to live?**
In a small town surrounded by mountains

- **Where did you spend your latest vacation?**
In a national park in the north of Spain

- **What is your favorite occupation?**
My work - although I dislike the administration

- **And your favorite writer?**
Two - Julia Navarro and Jose Luis Sampedro, a historical novelist and an economist



- **What was the last book you read?**
Dime quien soy by Julia Navarro

- **And the last film you saw?**
Viva la libertà, an Italian film about idealism, and *Malefica* with my daughters

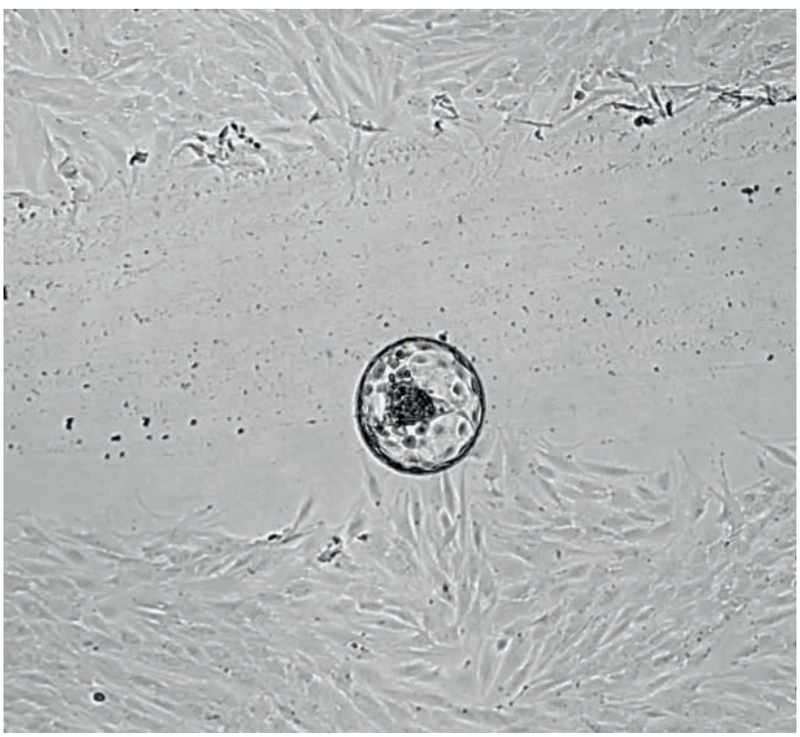
- **Your ideal dinner companion?**
My husband

- **And your ideal dinner?**
I prefer lunch on a sunny day near the sea. I will be more than happy with fresh bread, iberico ham and a fresh salad

- **Coffee, tea or Rioja?**
Coffee, and a Ribera del Duero

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

The listening endometrium



Implantation: the role of the selective uterus

Humans appear to be inefficient breeders, whether in spontaneous or assisted conception. As an explanation of their high rate of peri-implantation loss, Nick Macklon and Jan Brosens propose that the decidualised human endometrium is not just receptive to the implanting embryo, but selective too in determining which embryos actually do implant.

Despite advances in treatments and technologies, peri-implantation failure remains a common and frustrating result of IVF. Similarly, recurrent miscarriage has proved itself resistant to effective treatments. While a number of adjunctive therapies might be offered, to date no adjunctive intervention has been definitively shown to be effective in improving the chance of an individual embryo successfully implanting.

Are we missing something?

It has been known for some time that human reproduction is characterised by a high rate of peri-implantation loss, and this is not solely a feature of assisted conception treatment. The landmark studies of Wilcox et al revealed that, while implantation occurs in around 19% of potentially fertile cycles, more than a third are lost, the majority before any clinical sign of conception has occurred.[1] Indeed, it is estimated that around 50% of spontaneous human conceptions fail to progress to an ongoing pregnancy.[2] Given this high rate of peri-implantation attrition, it is clear to us that the development of effective interventions designed to prevent failure requires a deeper understanding of the mechanisms which determine the fate of the implanting embryo.

A combination of novel molecular analytic techniques and in vitro models is beginning to throw new light on this implantation 'black box', and it is now becoming clear that the endometrium plays a far more active role than previously thought in determining whether the embryo will be allowed to implant or not.[2]

The need for a selective uterus

Human embryos are intrinsically invasive, and yet recent studies have shown that many, indeed most, have some sort of chromosomal or other functional abnormality.[3] Thus, the high rate of peri-implantation losses in humans may derive from a high rate of embryo aneuploidy, which is estimated to be at least ten times greater than in other mammalian species. This rather perplexing feature of our species suggests that some sort of evolutionary advantage may be conferred by embryo aneuploidy. If so, the prevailing assumption that the optimal embryo for transfer is always the chromosomally 'perfect' may well be open to question.

Indeed it might be the case that a degree of genomic instability in embryos

may confer an implantation advantage. The cytogenetic anomalies often found in human embryos closely resemble those found in cancer cells, which are characterised by their invasive behaviour.[4] While the perfectly diploid human blastocyst may have maximal developmental potential, it may be less invasive than its aneuploid sibling. These ideas do need further testing, but it is clear that human embryos impose an important reproductive challenge: how can the mother facilitate implantation while simultaneously safeguarding against prolonged investment in potentially developmentally abnormal embryos?[5]

Recent work has shown that the uterus has a newly described attribute which may represent the answer to this question. The endometrium is not just receptive. It is selective.

The selective endometrium

In contrast to that of the mouse and many other species, the human endometrium decidualises in response to endocrine rather than embryonic signals. Hence, decidualisation is a feature of the mid-luteal phase in all ovulatory cycles, whether they lead to conception or not.

The first evidence supporting the concept that human decidualisation confers a selective ability to the endometrium emerged from in-vitro co-culture studies, which consisted of single hatched human blastocysts cultured for three days on a layer of primary decidualised human endometrial stromal cells.[6] The stromal cell production of cytokines and growth factors was seen to alter depending on the morphological quality of the embryo.

However, the nature of this response was contrary to what had been expected. The pervasive embryo-centric paradigm predicted that developmentally competent embryos would signal their viability to the decidualised stromal cells, which would then respond by upregulating production of pro-implantation modulators.

However, high-grade embryos had little impact on the supernatant concentrations of many of these factors, while low-grade embryos prompted a strong inhibition of these factors, including IL-1β, -6, -10, -17, -18, and HB-EGF secretion (see Figure 1). This biosensor function was shown to reside in the decidual phenotype, as human embryos did not trigger a response when co-cultured with undifferentiated endometrial stromal cells.

NICK MACKLON (left) and JAN BROSENS: 'TO DATE NO ADJUNCTIVE INTERVENTION HAS BEEN DEFINITIVELY SHOWN TO BE EFFECTIVE IN IMPROVING THE CHANCE OF AN INDIVIDUAL EMBRYO SUCCESSFULLY IMPLANTING.'

These experiments suggested that the endometrium was responding more profoundly to developmentally incompetent than competent embryos. This concept was supported by the finding that decidual gene expression was markedly dysregulated when cells were co-cultured with conditioned medium which had contained poor quality embryos, whereas co-culture with a medium which had contained good quality embryos caused a much less profound response. The most downregulated gene in the array analysis of exposed decidualised stromal cells was HSPA8, which encodes a protein involved in protein assembly and folding.[7] Knockdown of this gene in decidualising cells reduces the secretion of markers and induces endoplasmic reticulum (ER) stress, and it may be a mechanism by which the decidua senses the quality of the embryo.[8] This is supported by the observation that soluble signals from developmentally impaired human embryos induce a stress response in decidualising cells.

Is this selective response also seen in vivo? In short, yes. When the uteri of mice were flushed with conditioned human embryo culture medium, there were around six times as many genes showing altered expression in response to media conditioned by impaired versus competent human embryos.[8] However, the endometrial response to embryonic signals also demonstrated a component consistent with the established paradigm of a competent embryo evoking a supportive intrauterine environment.

A dual phase response of the endometrium can therefore be proposed consisting of 'recognition' and 'selection'. The ability of the luminal epithelium to 'recognise' a high quality embryo and modulate the decidual response it

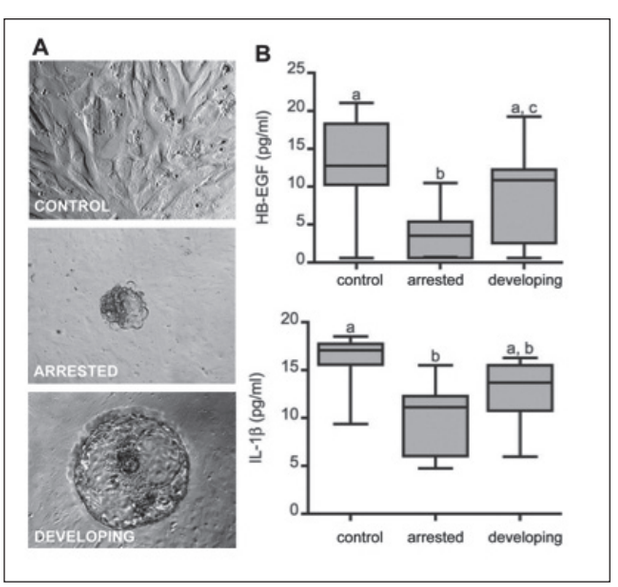


Figure 1. The in-vitro production of key pro-implantation cytokines by decidualised stromal cells is not increased by the presence of developing embryos, but is decreased by the presence of arresting embryos.

encounters on breaching the epithelium would aid subsequent nurturing and development in the post-implantation phase. This supportive implantation response is intrinsically lacking in the presence of a developmentally impaired embryo. However, chromosomal instability, invasiveness and the inherent unpredictability of low-quality embryos could mean that many will breach the luminal epithelium but are then selected against and disposed of as a consequence of the elicited decidual stress response.

This concept of the decidualised endometrium responding more profoundly to the developmentally incompetent than the competent embryo is consistent with previous studies suggesting that the healthy embryo, needing only to invest energy in growth and development, is metabolically 'quiet' in comparison to less viable embryos which must additionally engage in repair and apoptosis.[9] The 'quiet' embryo may therefore not be 'heard', triggering no destructive maternal response.

In contrast, the metabolically 'noisy' embryo may generate signals to which the decidualised stroma respond by deregulating a repertoire of genes implicated in implantation, and resisting the invading embryo. If these signals could be identified, this could clearly have considerable clinical implications for embryo selection after IVF and modulation of endometrial receptivity. Recently, evidence has emerged from both human and murine studies implicating embryo-derived serine-proteases as candidate signals. However, the precise nature and origins of embryo-derived serine proteases are not clear.

Invasion: is it all about the embryo?

For many years it has been thought that once the embryo has successfully breached the luminal epithelium it continues its journey into the endometrial stroma as the active party, 'invading' through what has been considered a mechanically passive decidual matrix. However, in vitro studies have demonstrated the remarkable migratory activity of decidual cells, which have been shown to accommodate and encapsulate the expanding conceptus.[10]

The active participation of the decidualised stroma in the encapsulation of the embryo illustrated by these studies raises the question of whether 'invasion' with its implications of offensive incursion is the appropriate term to describe this phase of human implantation. A more appropriate term may be 'embedding'.

Consistent with the cytokine response to embryo quality, the migratory response to embryos has also been shown to be selective. While decidual cells were seen to migrate towards high-quality human embryos, this was entirely inhibited in the presence of chromosomally abnormal tripronuclear (3PN) embryos (see Figure 2).[11] Taken together, these data indicate that decidual cells have the capacity to actively hinder invasion and outgrowth of abnormal human embryos that have breached the luminal epithelium.

Recurrent miscarriage or implantation failure

If the endometrium is not able to properly recognise or respond to embryonic signals of quality, an increased frequency of implantation of impaired embryos destined to fail as a clinical miscarriage would be expected.[13] Persistently impaired endometrial selectivity could therefore result in recurrent early pregnancy loss in conjunction with paradoxical 'superfertility'.

This hypothesis is supported by two studies showing that women with recurrent miscarriage often report a shorter time-to-pregnancy (TTP) than controls.[14,15] Both studies indicated that 30-40% of women with recurrent pregnancy loss could be considered 'superfertile'.

This concept has been further supported by in vitro decidual migration assays in which the suppression of stromal cell migration seen in the presence of a developmentally incompetent embryo did not occur when the decidual cells had been obtained from women with recurrent miscarriage (Figure 2).[11] Such clinical observations indicate that unrestrained endometrial receptivity and lack of embryo selection

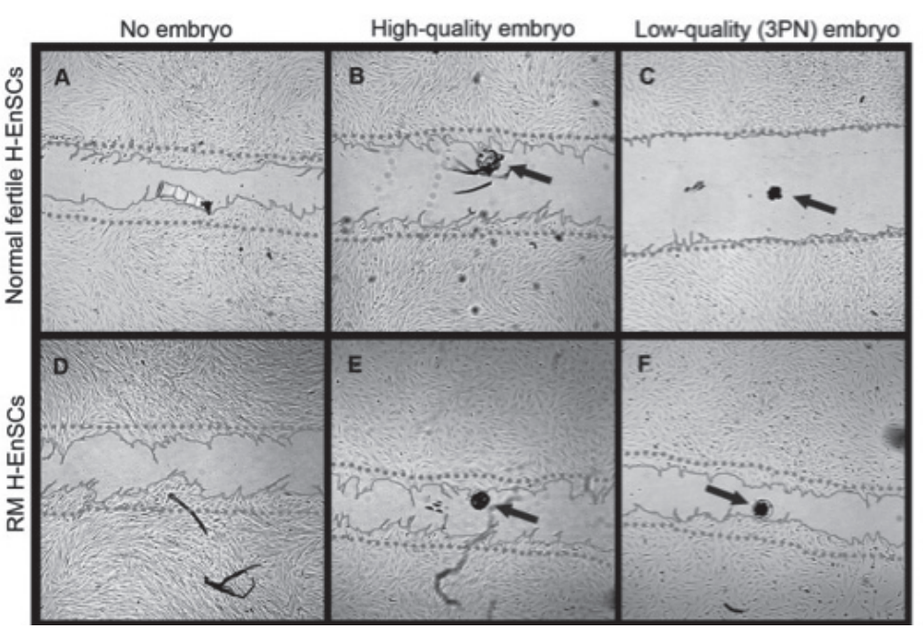


Figure 2. The migration zone after adding a high-quality, low-quality or no embryo. The migratory response of decidualised human stromal cells is affected by the quality of the embryo present. In normally fertile women (A–C) the presence of a low quality embryo is shown to discourage migration. However this effect is not seen when the cells are derived from women with recurrent miscarriage (D–F).[11]

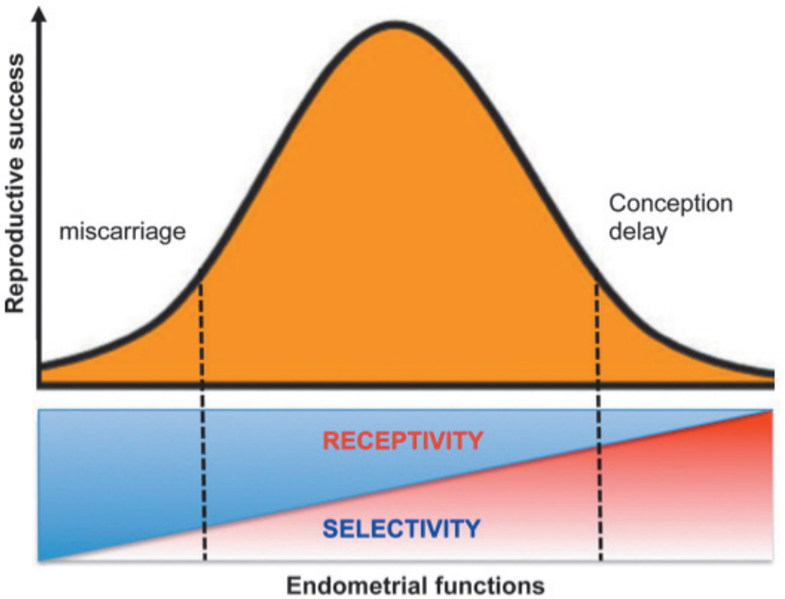


Figure 3. Balancing endometrial receptivity and selectivity. A highly receptive but poorly selective endometrium will allow implantation of poor quality embryos, leading to miscarriage. Conversely, excessive decidualisation will increase the barrier function of the endometrium and result in a highly selective but less receptive endometrium, reducing the likelihood of successful implantation.[16]

both contribute to subsequent pregnancy failure.

In contrast, an excessive decidual response could curtail the window of receptivity and increase the disposal efficacy of embryos, thereby reducing the incidence of miscarriages but also increasing the likelihood of conception delay or recurrent implantation failure after IVF (see Figure 3).

The decidualised human endometrium is emerging as an active gatekeeper to implantation in the human. The clinical implications of this are potentially far reaching. To date, clinical interventions aimed at treating recurrent miscarriage and implantation failure have been characterised by their similarity and disappointing efficacy. Further understanding of these dual processes may reveal that recurrent implantation failure and recurrent miscarriage are caused by an unbalancing of these functional endometrial traits, the former reflecting a net 'over selective' phenotype and the latter an inadequately discerning endometrium. If this paradigm can be substantiated, new and effective approaches to modulate implantation may follow.

Professor Nick Macklon, a former Co-ordinator of ESHRE's SIG Reproductive Endocrinology, is Professor of Obstetrics and Gynaecology at the University of Southampton, and Medical Director of the Complete Fertility Centre, University Hospital Southampton NHS Foundation Trust, UK.
Professor Jan Brosens is Head of Reproductive Health, Warwick Medical School, Clinical Sciences Research Laboratories, University Hospital, Coventry, UK

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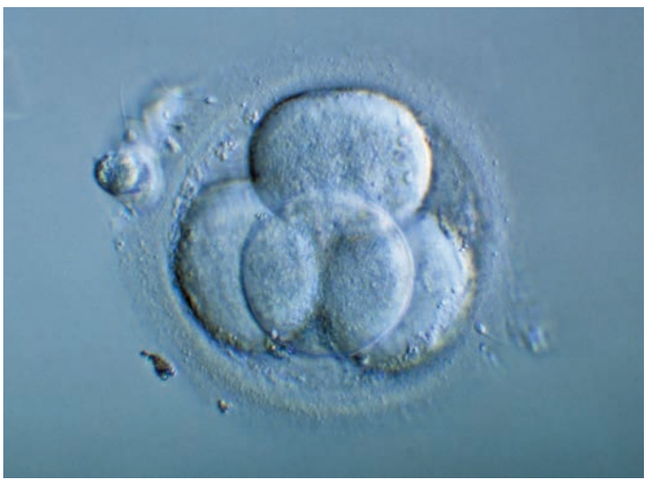
Applying the science of fertilisation and embryo development



PASCAL GOETGHELUCK/SCIENCE PHOTO LIBRARY

The whole cycle of gamete to blastocyst progression gave shape to a Campus workshop organised by the SIG Embryology and well attended by more than 100 participants in November. The meeting - on the continuous dialogue between reproductive cells in preparation for fertilisation and embryo development - was being staged for the third time by the SIG, this time in the Scottish city of Dundee and in the hands of local organiser Chris Barratt, editor-in-chief of *Molecular Human Reproduction*.

While the dominance of the oocyte as a determining factor in fertilisation and embryo quality (unequivocally illustrated by US data for age-related fresh and donor live birth rates), it was Barratt himself who emphasised the role of the sperm cell in this process. Indeed, said Barratt, 'the whole paradigm relies on the quality of the sperm cell', for the optimally selected sperm at fertilisation will bring to the egg high quality paternal DNA, the trigger for oocyte activation via calcium oscillations, the centrosome, a histone code, and many other contributions as yet unknown.

Indeed, one fact to emerge from this energetic workshop was how much is simply not yet known about the basic science of fertilisation. What is known, however, as was made clear by Barratt and his fellow speaker John Carroll from Monash University in Australia, is that an increase of calcium in the cytoplasm of the oocyte initiated by the sperm cell is the universal trigger for oocyte activation and fertilisation. Failed fertilisation may thus result from the sperm's inability to penetrate the zona and initiate a response.

Fertilisation itself stimulates a pattern of calcium oscillations in the oocyte which may spike at very short and regular intervals. This pattern of oscillation continues throughout the completion of meiosis, but not after the two-cell stage, which is triggered by a sperm-specific phospholipase known as PLC zeta. Mutations in PLC zeta may prevent calcium signalling, said Carroll, otherwise a well regulated pattern of calcium oscillations can be interpreted as consistent with fertilisation.

Barratt himself described the sperm's progress from ejaculation to fertilisation as 'an incredible journey', noting that the sperm cell will actually reach the site of fertilisation at a rate of one in 14 million. That ICSI embryologists try to repeat this odyssey in their sperm selection and injection reflects the challenge of the technique, for, as Barratt emphasised, not any sperm will do. 'We simply can't select the sperm cell as happens in the reproductive tract,' said Barratt. Morphology, swim-up and centrifugation tests will help, as may tests for DNA integrity - but surprisingly at this very interactive meeting very few participants expressed any confidence in these latter tests. Maybe more clinical trials are needed, said Barratt.

Carroll went on to explain that calcium signalling at fertilisation triggers within seconds further dramatic activations - of protein kinase C and calmodulin-dependent protein kinase II (CaMIIK), which each along their own pathways enable the oocyte to progress from the metaphase. Around 20 hours after fertilisation mitotic calcium transients stimulate mitochondrial activity, from which ATP production is necessary to maintain calcium oscillations in the oocyte.

Explaining developments even further downstream (towards

A total of ten lectures and interactive discussion sessions presented over 1.5 days was in the hands of just five scientists at this Campus workshop - from left to right, John Carroll, Aisling Ahlstrom, Kersti Lundin, Carlos Plancha, and Chris Barratt.

blastocyst development), Aisling Ahlstrom from Sahlgrenska University Hospital, Gothenburg, noted that blastomeres up to the 8-cell stage exhibit self-autonomy, while compaction and genome activation initiate a more coordinated pattern of development. However, embryonic genome activation remains repressed until the time in development for gene expression. These expression profiles, she explained, develop with each successive stage of embryo development culminating at blastocyst formation with the upregulation of tissue-specific genes.

Cell polarisation, said Ahlstrom, occurs parallel to compaction at around the 8-16 cell stage. It is important for establishing the embryonic-abembryonic axis and determination of inner cell mass and tropectoderm lineage. Nevertheless, she said, despite some understanding of the role of polarity in early embryo development, this remains another big area of uncertainty.

Barratt described the oocyte's progress through fertilisation to blastocyst formation as 'one of the most exciting areas of biology', while conceding too, as Ahlstrom had stated, that there remain 'a lot of unknowns'. 'How to set up an egg and sperm cell for viable fertilisation is a substantial issue,' he said. 'The sperm cell has the tools for the egg, and the egg just needs the appropriate stimulus of calcium to get going.' There is also the likelihood, he added, of scientific developments in this field moving very rapidly to the clinic - a test for PLC zeta, for example - and better ways of understanding why fertilisation does on occasions fail.

SIG EMBRYOLOGY

'Awesome' attendance for time-lapse precongress course

It is incredible that another year has passed, but I am pleased to report that the SIG Embryology has carried out and accomplished all the projects which we presented a year ago in *Focus on Reproduction*.

Last year's Annual Meeting in Munich gave us the chance to learn about new topics, to listen to the experts' opinions and, of course, to plan our future ESHRE activities.

But first I am proud to report that the precongress course in time lapse monitoring had an awesome audience and a high level degree of appreciation, with a total of 411 participants registered. However, although time-lapse technology is quickly becoming a useful tool in many aspects of IVF laboratory work, one of the more repeated questions in Munich was the urgent need for randomised controlled trials with the power to demonstrate whether this technology by itself is able to improve the IVF success rate.

Of course, every lab using time-lapse technology has the potential to perform a RCT, and I personally believe that it is our responsibility as embryologists to study every possible benefit of time lapse in an IVF programme before its widespread clinical introduction.

Campus events

The courses and activities organised by the SIG Embryology either separately or in combination with other ESHRE SIGs always attract many participants; they have a high degree of interest and generate valuable debate. The two more recent ESHRE Campus meetings took place in Lisbon and Dundee in September and November respectively last year. Both were very interesting for clinical embryologists, andrologists, and for those professionals eager to learn more. We have reports from both these meetings elsewhere in this issue of *FoR* - **Epigenetics in reproduction** in Lisbon in the report from the SIG Reproductive Genetics, and **From gametes to blastocsyt: a continuous dialogue** in Dundee in our own report opposite. The latter meeting, organised by the SIG Embryology alone and reported opposite, certainly raised our scientific understanding of some of the nicely orchestrated events related to gamete interaction, fertilisation and embryo development which occur on a daily basis in our IVF laboratories.

Two of the main future objectives of the SIG Embryology are the digital publication of the *Atlas of Embryology* and the revision of the current ESHRE guidelines for good practice in IVF laboratories. Both are on their way and both are expected to be presented in 2015.

Other events are still waiting in the pipeline, but we would certainly wish to see you all at the next ESHRE workshop on the modern techniques of cryopreservation, which will take place in Istanbul on 27-28 March. The course, which will feature a distinguished faculty of presenters, will review the fundamental aspects of cryobiology alongside the practical aspects of cryopreservation in oocytes, spermatozoa, embryos at different stages of development, and ovarian tissue for fertility preservation.

I would not like to finish this report without letting you know that we are always interested in your news and opinions. Your concerns are very valuable to the Steering Committee for planning future educational activities. Please visit our web page, get in contact with us and tell us the topics that you would like to know more about.

María José de los Santos.
Co-ordinator SIG Embryology

Shaping the epigenome before and after birth

The last decade has provided ample evidence that heritable changes in gene function can occur without a change in the DNA sequence. Constitutive epigenetic mechanisms contribute to chromatin remodelling in germ cell formation, differentiation and reproduction, and affect gene expression in the embryo and offspring. Changes in the epigenome can mediate adaptive responses to the environment but can also cause developmental abnormalities and (heritable) epigenetic disease, and are therefore of relevance for health and fertility of offspring. ART, life style, nutrition and environment may affect epigenomic events in potentially highly sensitive periods of germ cell formation and embryogenesis.

It was six years ago that ESHRE organised its first Campus workshop in Lisbon introducing epigenetics in reproduction. Since then there has been much progress in understanding its relevance to ART and reproductive health. In recognition of these developments, a second Campus course on **Epigenetics in reproduction** was arranged by the SIGs Reproductive Genetics and Embryology together with the TF Basic Science in September last year, once again in Lisbon and locally organised by Carlos Plancha and Paulo Navarro-Costa. More than a hundred took part, enjoying excellent contributions and animated discussions.

The course covered not only the basic mechanisms underlying epigenetic alterations in chromatin and regulation of gene expression by DNA methylation, posttranscriptional modification of histones and small RNAs, but also the essentials of genomic imprinting in male and female germ cell formation.

Speakers provided evidence that alterations in sperm DNA methylation (eg, mosaicism in methylation in sperm of oligoastenoteratozoosperic males, Sandra Laurentino), and changes in protamination of chromatin (Stéphane Viville) as well as alterations in presence of sperm RNA (Ester Anton) can all contribute to male subfertility and aberrant embryo development.

Tessa Roseboom's videotaped contribution provided updated evidence of transgenerational effects of the Dutch famine, now followed up to the fourth generation. There is evidence from experimental studies in rodents and humans that dietary restriction before, during and after conception can affect health and alter developmental programming in the conceptus and epigenome in offspring (Tom Fleming).

The group of Patricia Fauque found that ART does not influence DNA methylation in transposable elements in trophectoderm. However, Line-1 elements exhibited a greater tendency for hypomethylation in placenta of IVF/ICSI-derived pregnancies than spontaneous pregnancies, with unknown consequences for embryo health.

More than 100 took part in the second of ESHRE's Campus meetings on epigenetics.

In a session on the effects of the environment on epigenetics, Ursula Eichenlaub-Ritter reviewed the literature and observations suggesting that exposures to endocrine disrupting chemicals like bisphenol A can affect health and reproduction. This was recently shown to change DNA methylation in maternal imprint control regions of DNA in growing oocytes in chronic exposures to physiologically relevant low doses in vitro and in vivo. Although bisphenol A has not been detected in ART media - as pointed out by Arne Sunde - a healthy diet avoiding bisphenol A exposures from food wrappings and containers may help protect patients and germ cells from the adverse influences of endocrine disrupting chemicals.

Niels Geijsen discussed epigenetic reprogramming in the germline, emphasising the critical role of Dazl (deleted in azoospermia-like) coding for an RNA binding protein essential for germ cell specification, suppression of mRNA translation and regulation of expression of pluripotency factors. Another new/old player in the epigenetic regulation of oocytes, ATRX, was discussed by Lynne O'Shea, who said it may prove useful as marker in cumulus cells of follicular quality.

Ellen Anckaert described briefly the importance of dietary and culture media methyldonors, one-carbon metabolism and DNA methylation and their relevance for normal imprinting in follicle culture and in vitro maturation. The safety of embryo culture for epigenetic integrity was further discussed by Arne Sunde, who pointed out that ART in humans may be associated with a number of differences in phenotypes from spontaneous conceptions, which may relate to disturbances in epigenetic regulation. The potentially critical influence of growth factors, serum, and other additives to media were discussed.

Superovulation, shown to influence maternal imprint acquisition as well as maintenance of imprints in the mouse, is one example of how different mechanisms may lie behind changes in DNA methylation - either by directly changing imprinted loci induced by altered hormonal homeostasis or rather by exposures of the embryo to a hormone-

influenced suboptimal intrauterine environment.

The placenta appears to be an especially sensitive target for subtle changes in the epigenome in IVF pregnancies, which may contribute to changes in birth weight, DNA methylation, and relative gene expression - and may thus transmit disturbances from a subfertile mother to her offspring via mother-foetus interactions. Indeed, it was emphasised by Anja Pinborg that risks for preterm birth, obstetric complications and perinatal risk factors are higher in ART singletons than in spontaneous conceptions, although there is no evidence of any overall increased birth defects after cryopreservation. However, from present data it appears that frozen embryo transfer does increase risks of intrauterine overgrowth, and possibly perinatal and long-term mortality. Whether changes in weight are linked to endometrial and/or epigenetic modifications in germ cells is unclear.

However, it was reassuring to learn that trends over time for preterm birth and mortality rates in ART children have decreased during the last decades in the Nordic countries, suggesting that improved methods minimise the risks of ART, potentially including epigenetic effects. Considering the high risks of health problems in twin and multiple pregnancies, and the additional effects of subfertility itself, it appears that the risks associated with increases in epimutations are now at relatively much lower levels. There was, however, a general agreement that prospective follow-up studies and more experimental work are needed to assess the full impact of an altered epigenome on reproduction, germ cell formation, and the health of the embryo and offspring.

● Reproductive epiphenotypes were evident in a unique exhibit of African art organised by Carlos Plancha and Johan Smitz. This could be visited during the breaks at the meeting and, together with a visit to the spectacular Oceanarium in Lisbon, provided a taste of what lies in store in Lisbon in June.

Ursula Eichenlaub-Ritter

SIG REPRODUCTIVE GENETICS

Genetic markers of embryo quality on agenda for Lisbon

Campus meetings

There was agreement from speakers, audience and discussions that the Campus course organised with the SIG Embryology and TF Basic Science on epigenetics was of prime interest in the treatment of subfertility. It was reported that the disturbances in the epigenome may relate to lifestyle, nutrition, environmental disorders and exposures in utero. Experimental studies and observations in the human suggest that an altered phenotype can also be due to disturbed control of gene expression by direct and indirect epigenetic mechanisms - related for example to culture and cryopreservation.

A Campus **Update on PGS** on 12-13 March in Rome organised by the SIG RG and PGD Consortium is now open for registration; it will provide an overview of results from RCTs and critically discuss the new technologies in PGS .

Precongress courses

Our PCC in Munich on **The current status of PGD and PGS** organised with the PDG Consortium attracted a large audience. Controversies on improving outcomes by PGS and ethical dilemmas in PGD were discussed. Further developments in analysis, safety, efficiency and outcome will be covered by the Campus workshop in Rome.

The PCC in Lisbon will cover topics related to **Genetic and genomic mechanisms and markers associated with gamete and embryo quality**. There will be contributions on chromosome-associated mechanisms and markers in germ cells, and genetic mechanisms and markers in embryos, followed by the business meeting at the end of the PCC.

STEERING COMMITTEE

Ursula Eichenlaub-Ritter (DE), Co-ordinator
Claudia Spits (BE), Deputy
Tania Milachich (BG), Deputy
Georgia Kakourou (GR), Junior Deputy
Joyce Harper (GB), Past Co-ordinator

E-learning

Lectures from last and this year's PCCs (on epigenetic mechanisms and genome scanning, and on the current status of PGD and PGS) will eventually be viewable on the ESHRE website. Educational presentations by members of the SIG and PGD Consortium are also available for ESHRE members, including an update of the PGD Consortium (Jan Traeger-Synodinos), accreditation of a PGD centre (Sioban SenGupta and Mike Morris), an introduction to genetics (Joep Geraedts) and embryo biopsy (Georgia Kokkali). The SIG and PGD Consortium held a second webinar in autumn 2014.

Publications

The joint paper by ESHRE and the European Society of Genetics on **Current issues in medically assisted reproduction and genetics in Europe** was published in the August issue of Human Reproduction (Hum Reprod 2014; 29: 1603-1609). A paper on the **Genetic screening of gamete donors** from ESHRE's TF Ethics and Law with input from the SIG RG was recently published (Dondorp W, De Wert G, Pennings, etal. Hum Reprod 2014; 29: 1353-1359). A paper on **testicular tissue cryopreservation in prepubertal and adolescent boys** with input from SIG RG members initiated by the TF Fertility Preservation in Severe Disease has been submitted.

Ursula Eichenlaub-Ritter
Co-ordinator SIG Reproductive Genetics

Certification: first exams in Lisbon, log book submission by 15 February

The Paramedical Board is now finalising the first nurse and midwives certification exam. The steering committee meets this month to set the exam questions and the exam itself will be held in Lisbon on Saturday 13 June. The deadline for completed log books has been extended to 15 February. Please check the ESHRE website for details.

We would like to remind paramedical members that we are running another of our **Basic training course for paramedics working in reproductive medicine** in Lisbon from 19-21 March 2015. This is an ideal course for nurses, midwives and lab technicians who might be new to the field, and also for those who might feel the need to update their skills and knowledge.

We are also announcing a vacancy for an enthusiastic nurse or midwife to join the Paramedical Board. Current board member Jolieneke Schhoonenberg-Pomper will complete her term of office in June. Applications are welcome from ESHRE paramedical nurses/midwives who can make a commitment for an initial term of four years, with possible re-election for a second four-year term. Applications should be sent to info@eshre.eu by 16 January. Board meetings are held three times a year - one in the Spring, one at the Annual Meeting and one in the Autumn. If you would like some informal information about the position or have any other comments or queries about the Paramedical Board, please contact me directly.

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

New ideas and proposals welcome for future events and e-learning

It is important that members tell us their views on the work carried out by the SIG SQUART and provide us with new ideas. We hope to involve our members more by sending e-mails and short questionnaires. We also welcome members to attend our annual committee meeting held during the Annual Meeting.

Recent events

Our precongress course **Seeking and finding the evidence** in Munich, which was staged in collaboration with the SIG Psychology & Counselling, proved very interesting and well attended. Our latest collaboration, with the SIG Ethics & Law, produced an original article, 'Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment' published in *Human Reproduction* last year (2014; 29: 413-417).

The manual of the ESHRE guideline programme has been revised and is now available for use. The clinical guideline on endometriosis, developed in line with the manual, also included an app to help implementation.

A well attended Campus meeting on **Fertility preservation: from technique to implementation in clinical practice** organised in collaboration with the SIGs Ethics & Law, Psychology & Counselling, the Paramedical Group and Task Force Fertility Preservation was held in Amsterdam (14-15th March 2014).

The SIG SQUART's participation in the open EIM meeting held in Leuven in November 2014 (see page 18) considered the core factors in quality and safety in ART using a Wordle approach. A Wordle, or a word cloud, is a very attractive tool to visualise data and, in this graphic way, the core factors truly looked at the audience as they looked at them. Slides from our lecture, delivered by Kelly Tilleman, will be on the ESHRE website from March. The meeting was very interactive, with much time for stimulating discussions. The EIM and PGD Consortium registries both illustrate the power of huge datasets. Improvements can still be made and the importance of good data validation and completeness of registries was pointed out.

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Future events

After the great interest shown in Maribor (Slovenia) in the first Campus course on ultrasound in 2013, our precongress course this year has been organised in collaboration with the SIG Andrology on **Quality assurance of ultrasound in medically assisted reproduction**. The course aims to examine what is already available, standardised and regulated, and what is needed to make sure that ultrasound is safe and reproducible in current practice.

New e-learning modules will be developed to offer case studies on ultrasound and OHSS as a tool for practical learning. If you have additional ideas or needs for e-learning, please let us know. We welcome any further collaboration ideas and proposals.

Willianne Nelen
Co-ordinator SIG Safety & Quality in ART

Stem cell therapies in reproduction: a journey just begun

With the deadline for submission of abstracts brought forward this year to mid-January, we hope that all members with an interest in stem cell biology are able to submit their work: we love to hear about new and exciting research! And keep in mind our excellent precongress course in Lisbon on **Early pregnancy and the role of stem cells**, as you can guess, jointly organised with the SIG Early Pregnancy. The programme will highlight the possible roles for stem cells in modelling implantation, understanding its alterations, and proposing future therapies in this very complex field. Don't worry about the course being too basic and technical - it offers a nice balance of basic science and clinical application, and will thus be appealing to a wide range of ESHRE members.

The reality of stem cell therapy

Now that the first clinical trials with pluripotent cells are out of the blocks and running, interest is now turning to stem cell therapy in reproduction. To clarify which treatments are currently available and effective, we have prepared a review of current knowledge in which we address in vitro gamete formation, germline stem cells and regenerative therapies of the reproductive tract. The paper has been presented to the Executive Committee, and will soon be available to all ESHRE members for comment before publication in *Human Reproduction*.

Steering committee

'No man ever steps in the same river twice,' said the Greek philospoher Heraclitus, and we too must renew to promote enthusiasm and commitment. Filippo Zambelli, our excellent Junior Deputy, will complete his two years mandate in Lisbon and will continue as Deputy. As a result, elections will soon be announced for a new Junior Deputy to join our group. So we're looking for young, motivated, and energetic candidates, with an interest in stem cell research and a commitment to give a little of their time to ESHRE. Start preparing your CVs!

Rita Vassena
Co-ordinator SIG Stem Cells

Exciting times for andrology, as scientific developments move to the clinic

'Andrology has never been more exciting,' said Chris Barratt in concluding his Human Reproduction keynote lecture in Munich. His enthusiasm followed breakthroughs in the functional characterisation of sperm by calcium channels and future applications for sperm selection for assisted fertilisation. Such excitement has also been reflected in the recent presentation of other new findings - on genetic causes of male infertility, strategies for male fertility preservation in severe diseases, or the importance of DNA integrity in sperm. At the ASRM meeting in Hawai, plenary lectures on Klinefelter patients by Ron Swerdloff and on sperm cell biology by Jon Aitken were considered scientific highlights.

These developments have been well recognised by ESHRE's scientific committee and by the SIGA, and the upcoming Annual Meeting in Lisbon contains many outstanding andrological topics. The main programme will feature a plenary lecture by Niels Jörgensen on the importance of semen quality in ART, and a presentation on the risks and benefits of being male (why males die younger), which will provide insights into the sex specificity of meitotic failures and the consequences for DNA integrity in gametes. The ASRM exchange lecture will revisit environmental effects on male reproductive functions, while a symposium on fertility in ICSI boys will introduce RAMAN spectroscopy as a promising new tool for selection of live intact sperm.

Our precongress course, titled **Keep the sperm in mind when perfecting ART: News and perspectives in spermatology**, will begin with basic biology and end with future tools for generating artificial sperm. So we are proud to represent such an emerging field and provide a home to so many andrology-oriented scientists and clinicians. As recent scientific breakthroughs enter the clinic, they surely will have a strong impact on improvements in fertility treatment.

Stefan Schlatt
Co-ordinator SIG Andrology

Recurrent implantation failure on Lisbon agenda

The SIG Reproductive Endocrinology organised a very successful workshop in Thessaloniki in October last year titled **Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering.** More than 160 attended the workshop at which a distinguished group of experts discussed all aspects of OHSS prevention, focusing on its elimination with the use of agonist triggering for final oocyte maturation. There is a full report of this important meeting on page 7 of this issue.

Local faculty members Kostas Dafopoulos, Stratis Kolibianakis and Basil Tarlatzis with former SIG RE Co-ordinator Georg Griesinger in Thessaloniki in October.

Future events

Our precongress course in Lisbon is entitled **When IVF fails: optimal management of recurrent implantation failure**. The course will provide a critical appraisal of recurrent implantation failure (RIF), one of the most difficult problems in IVF for both patients and physicians. Focus will be given to the controversy surrounding the definition of RIF and the role of lifestyle modification in its management. By critically appraising the existing literature, the course will provide answers to clinically important issues, such as the value of genetic embryo selection, and assessment of the the peri-ovulatory endocrine environment prior to oocyte retrieval. The course will examine how relevant to RIF is the presence of endocrine disorders or thrombophilia prior to treatment and the importance of optimising embryo transfer technique, the role of surgery in the management of RIF and paternal contribution. The course will also ask if RIF can be managed by manipulating the endometrium or, if all else fails, whether oocyte donation is efficient in these patients.

In the meantime, everything is now ready for our next ESHRE Campus course. **Old and new in reproductive endocrinology** will take place in Helsinki, Finland, on 24-25 April. The programme will cover the hormonal environment during pregnancy and early stages of reproductive development from the fetal period to adulthood, with a focus on developmental disturbances of reproductive organs during early and late reproductive life. State-of-the-art diagnostics and some aspects of the long-term health consequences of these conditions will also be presented. A further series of lectures will be dedicated to testicular and ovarian endocrinology, including ART-related topics on ovarian stimulation, response patterns, and corpus luteum formation and maintenance. The workshop will also give special attention to extra-gonadal factors with a role in reproductive functions, eg, pituitary, thyroid, adrenals, fat tissue and vitamin-D. This Campus event will provide an excellent opportunity to update the 'old and new in reproductive endocrinology' and to meet the experts in the field.

For 2016 we are preparing our PCC in Helsinki on **Managing the difficult IVF patient: Facts and fiction** and a Campus workshop in Istanbul on **The ageing women and her ovary**. In addition, it has been agreed that for 2016 the SIG RE and the SIG Reproductive Surgery will develop a programme for a joint Campus workshop for which more details will be given in the next issue of *FoR*.

Stratis Kolibianakis
Co-ordinator SIG Reprodcutive Endocrinology
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Special session on myoma morcellation - with interim consensus - added to endoscopic surgery Campus

The SIG RS hosted yet another enjoyable endoscopy workshop in October in Leuven, under the direction of Stephan Gordts. A diverse group of participants (from UK, Latvia, Poland, Turkey, Greece, South Africa to mention a few) gave a particularly interesting flavour to discussions during the several hours of live surgery sessions. Delegates also practised laparoscopic suturing and knot tying for over five hours during the three days of the course.

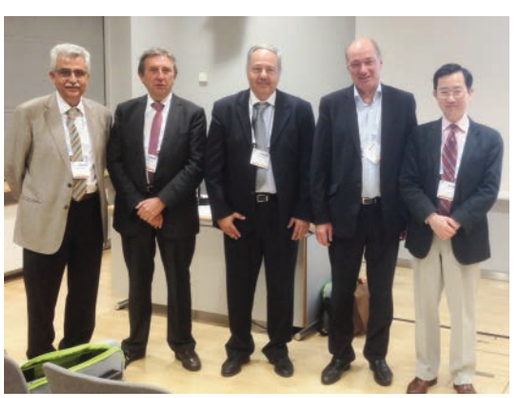
Our SIG is also continuing its friendly ties with the other SIGs, having hosted a successful joint Campus symposium in Liege, with the Endometriosis and Endometrium group. The topic was **Controversies in endometriosis and adenomyosis**, and participants had the opportunity to follow and discuss topics ranging from genetics-epigenetics to diagnosis and surgical management.

Future activities

The biannual endoscopy course in Leuven will take place as planned on 18-20 March this year. The course is designed for specialists with an interest in endoscopic reproductive surgery, and caters for candidates of all range of endoscopic skills.

We are also looking forward to our Campus workshop in Lyon on **Complications in endoscopic surgery**, a topic guaranteed to draw a lot of debate and discussion. This will take place on 17-18 April and is being organised by Antoine Watrelot. Sessions will include the incidence, prevention and management of different types of complications.

Finally, looking ahead to the Annual Meeting in Lisbon, we will be hosting a precongress course on **Challenging reproductive surgery**. The focus will be on how to deal with difficult cases, such as adenomyosis, massive cysts, severe Asherman's syndrome and deep endometriosis. In addition to lectures from distinguished guests, there will be a presentation of selected cases, which will be up for interactive discussion and debate.



Former and present SIG steering committee members, from left, Grigoris Grimbisis, Stephan Gordts, Vasilios Tanos, Antoine Watrelot, and Co-ordinator TC Li.

Hot topic

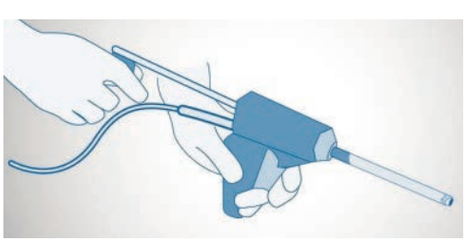
Following the recent controversies surrounding the use of the morcellation during laparoscopic myomectomy and the risk of leiomyosarcoma dissemination, the SIG is delighted to announce that a special interactive hot session and panel discussion will be added to the programme of the Lyon Campus workshop - entitled **The obituary of myoma morcellation?** The session will include hot-off-the-press data from a survey on gynaecological morcellation and specialist presentations on the incidence, risk factors, imaging and pre-operative diagnosis of leiomyosarcomas. Most importantly, a panel discussion will be held with the aim of producing an interim consensus statement on the use of laparoscopic myoma morcellation in reproductive surgery.

Training and education

Following the first ESHRE certifications for the Bachelor in Endoscopy (Level 1) and the ECRES Reproductive Surgeon accreditation (Level 2) in Munich, new candidates continue to enrol in the certification programme. Next round of examinations and certifications will be taking place at the Annual Meeting in Lisbon.

Sotirios Saravelos
Junior Deputy, SIG Reproductive Surgery

Hot topic. Morcellation during laparoscopic myomectomy will be the subject of a special late session during the SIG's next Campus meeting in Lyon in April. Pictured right are the morcellator used for laparoscopic myomectomy, and myoma tissue after laparoscopic morcellation.



Emancipation or corporate constraint?

Corporations great and small offer oocyte cryopreservation as a perk of the job

Employee benefits usually range from the dull to the very dull: pension payments, health insurance, a car, dry-cleaning . . . but who would ever have added egg freezing to the list? Yet that apparently is just what the tech giants Apple and Facebook have done in the cool of their Silicon Valley offices.

Facebook began covering up to $20,000 in egg freezing expenses a year ago, while Apple says it will start this month. According to reports, the fertility preservation offer is a return to its female staff for giving up so many of their childbearing years to the company - 'payback for commitment' said NBC News. 'Freeze Your Eggs, Free Your Career', claimed *Bloomberg News*.

And jumping on the bandwagon were several banks - and even Virtus Health, Australia's first publicly listed conglomerate of IVF clinics. 'We thought, if it's good enough for Apple and Facebook, it's good enough for us,' said the medical director at Queensland Fertility Group, part of Virtus.

Back in the USA oocyte cryo-preservation took on new life after the ASRM removed the 'experimental' label in 2013 - despite adding cautiously that it could not yet be recommended for 'circumventing reproductive aging'.[1] NBC nevertheless reported that clinics in New York and San Francisco 'have nearly doubled' their egg freezing cases over the past year.

Few clinics in Europe would go that far, though Dominic Stoop, who runs the cryopreservation programme at the VUB in Brussels, told *Focus on Reproduction* that around 120 women a year are now enquiring about 'AGE banking' (anticipation of gamete exhaustion), most of whom would eventually start the programme. Costs, said Stoop, would be around €2500 per cycle, covering oocyte retrieval, vitrification and cryo-storage for ten years (but not the cost of medication).

Stoop's estimate was that women who started egg banking under the age of 35 would need at least a 20-25 oocytes in storage. 'That would offer her three future thawing cycles,' he said, 'but beyond 35 it's much harder to say. From 38 years on it's probably impossible to collect a reassuring number of oocytes from a reasonable number of cycles.'

In a study reported at last year's Annual Meeting, Ana Cobo from IVI Valencia calculated from a huge series of vitrified donor oocytes (3400 patients and 40,000+ oocytes) that cumulative live birth rate was 39.4% when a total of ten oocytes were used in the treatments, and 75.9% when 20 were used.

Inevitably, the job perk news was greeted with a variety of responses, particularly from female news columnists, many of them sceptical. The move would, in the words of Sheryl Sandberg, Facebook's CEO, enable women to be as ambitious as they like in their careers. But others, like US lawyer Seema Mohapatra in an opinion for the *Harvard Law & Policy Review*, seemed more cautious, worried that an egg-freezing option will define the committed and less committed careerists, and benefit the well educated more than lower income workers.[2]

Veerle Provoost, Co-ordinator of ESHRE's SIG Ethics & Law, asked: 'Do these initiatives show that the companies support women trying to align career with plans for a family? Do they increase gender-equality by buying more time for women? Or is the underlying message that (aspiring) mothers do not belong in the board room?' Other questions raised by Provoost were the reliability of the information, the 'coercive' nature of the offer, and the weight of obligation felt by those who accept it.

In a letter to *The Times* newspaper in the UK, Lord Robert Winston, Emeritus Professor of Fertility Studies at Imperial College, described the many press stories in support of egg freezing as 'likely to mislead women'.[3] He cited recent HFEA data showing that only 21 pregnancies from 243 cycles of thawing and IVF had been reported.

Simon Brown
Focus on Reproduction

1. The Practice Committees of the ASRM. Fertil Steril 2013; 99: 37-43.
2. Mohapatra S. Using egg freezing to extend the biological clock. Harvard Law & Policy Rev 2014: 8: 381-411.
3. Lord Winston. Freezing eggs. The Times, 28 October 2014.

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