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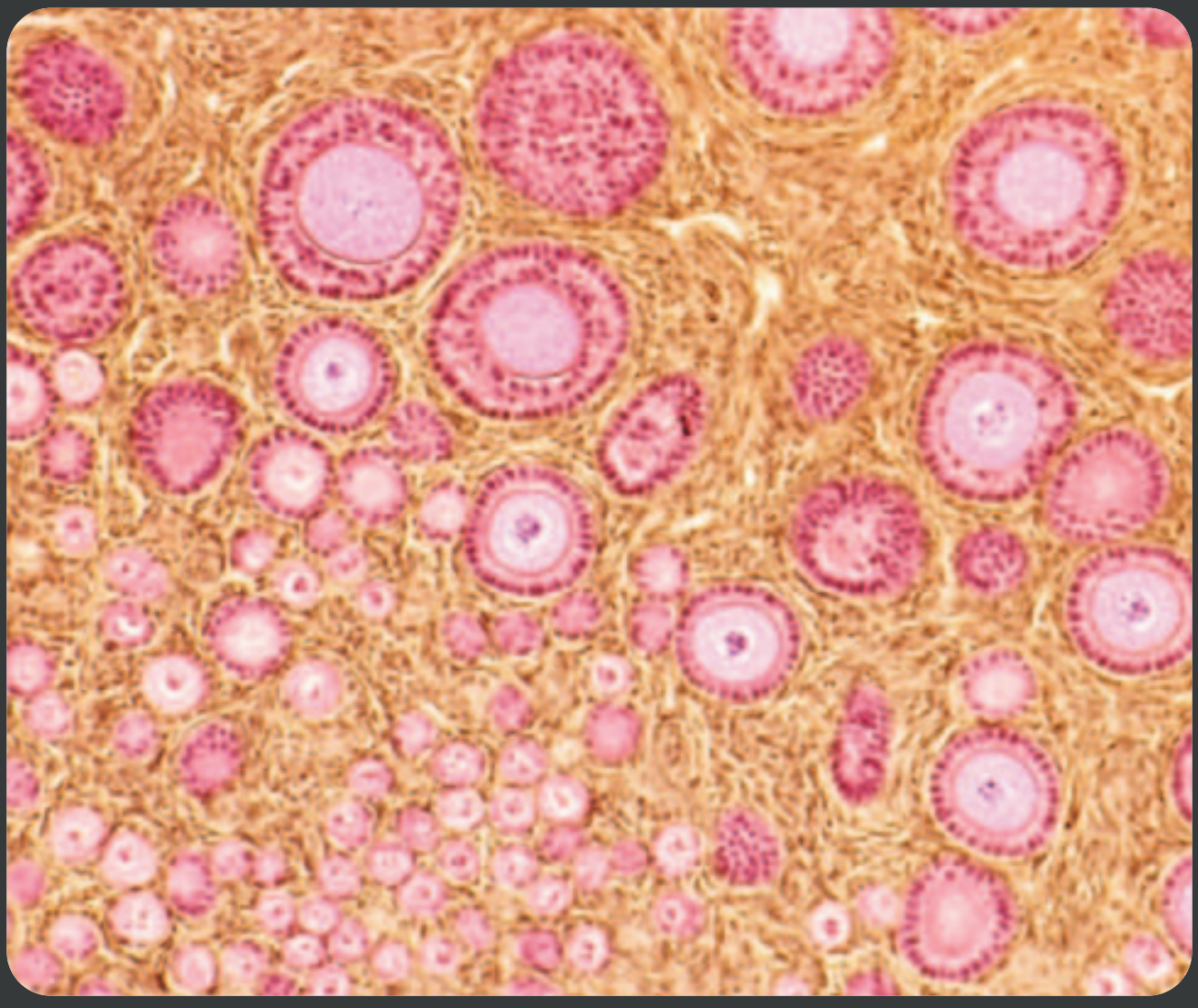
SCIENCE MOVING PEOPLE MOVING SCIENCE

focus on REPRODUCTION



Anti-Mullerian hormone

More than just a guide to stimulation response

// MAY 2014

- Look ahead to Munich
- ESHRE research grant
- Best of ESHRE-ASRM 2014
- Nurse certification

Cover picture: STEVE GSCHMEISSNER/SCIENCE PHOTO LIBRARY
MAY 2014

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CHAIRMAN'S INTRODUCTION

The 30th anniversary of ESHRE's founding was marked at one of the Society's youngest events, the third 'Best of' ASRM/ESHRE meeting in Cortina, Italy. Once again it was a well attended event, with another quality programme of lectures and debates, and, for our sister society the ASRM, a celebration of 70 years in existence. Our next meeting will be held in New York in March 2015.

As reported on page 9, ESHRE is introducing a research grant of up to €150.000, to be spread over a period of one to three years. The deadline for applications for the first round is 15 May, and the final decisions will be made in the autumn - so that the grant can be activated in 2015. News of the grant has aroused much interest among members already, and we expect to receive numerous applications.

The first exam for ESHRE's Certification for Nurses and Midwives will take place at next year's Annual Meeting in Lisbon. The working group is on schedule to have everything in place, with logbooks and reading lists already available. The current Chair of the Paramedical Board, Helle Bendtsen, will step down in Munich and Helen Kendrew from the UK will take over.

ESHRE is increasingly taking an active role in discussions on the politics of science and medicine, with statements on a number of recent issues. One which has concerned many other societies as well as ESHRE has been the 'One of Us' European Citizens Initiative encouraging the EU to ban the financing of activities which presuppose the destruction of human embryos. This would be a major threat to stem cell research and progress in infertility treatments. The public hearing of the initiative was a few weeks ago at the European Parliament, and several Executive Committee and Special Interest Group members represented ESHRE. ESHRE produced a formal position statement, and let's hope that the European Commission makes wise decisions - to defend both the freedom of research itself and future developments in stem cell research and treatments in reproduction.

The Scientific Committee has now completed its programme for the Annual Meeting in Munich, and we are looking forward to another outstanding assembly of members and international guests. The social programme will be diverse and we will certainly enjoy the friendly and culinary Bavarian hospitality. Among many activities, participants this year are warmly invited to participate in our 30 years anniversary charity run. It will be for a good cause, and I am confident that the congress will be a great success.

See you all in Munich

Juha Tapanainen
ESHRE Chairman 2013-2015

// MAY 2014

Another bumper crop of abstracts for Munich

ESHRE Annual Meeting broadens its international appeal; abstract acceptance rate around 20% for oral presentation

Another congress of high quality original research and invited reviews is promised for Munich in June and July. More than 1450 abstracts were submitted before the 1 February deadline, around 100 fewer than submitted for London last year. But as has been the rule in the past few years, the selecting International Science Committee found a wealth of new developments which have now been scheduled for free communication, either as oral or poster presentation.

There were four non-European countries notable among the top ten submitting countries, with China listed for the first time. Indeed, the steady rise in the number of abstracts submitted from outside Europe increasingly marks ESHRE's Annual Meeting as a truly international event. The leading countries submitting abstracts this year (with last year's figures in brackets) were:

1. Spain	137 abstracts	(152)
2. Italy	123	(106)
3. United Kingdom	105	(162)
4. Japan	86	(87)
5. Turkey	83	(89)
6. USA	71	(69)
7. Germany	70	(37)
8. China	68	(52)
9. Iran	61	(27)
10. France	60	(61)

As ever, the greatest number of abstracts were in clinical science, of which embryology (286 abstracts) has now become by far the most prolific. Reproductive endocrinology (214 abstracts), andrology (163),

Above: Munich's Marienplatz, New Town Hall and Frauenkirche.

Fifteen precongress courses available; many will be fully booked.

All accepted posters must be submitted electronically, and on poster boards if investigators wish.

female infertility (162), endometriosis (112), reproductive genetics (105), quality and safety of ART (84) and early pregnancy (68) were the most popular.

All abstracts, which were submitted in the *Human Reproduction* format, were reviewed according to our standard procedure of screening and scoring. Screening aims to ensure that abstracts are designated to the correct topic category and to eliminate all submissions of obviously poor quality. Selection for oral and poster presentation was done solely on the basis of scores from three reviewers marking blinded abstracts. The International Scientific Committee finally selected 248 abstracts for oral presentation from a total of 1450 submitted.

As ever, around 600 abstracts have been selected for poster presentation. As before, all posters must be available in electronic format, but the highest scoring top 40 posters must also be presented in paper format on the poster boards. Twenty of these 40 selected posters will be considered for the two poster awards (in basic and clinical science).

Fourteen precongress courses will be staged on the Sunday preceding the Opening Ceremony. The majority are organised by ESHRE's Special Interest Groups, but there are additional courses run by the editors of the ESHRE journals on academic authorship, by the ASRM on the applications of genetics to reproductive medicine, on fertility preservation by the Middle East Fertility Society, and on the management of 'special patients' by the Paramedical Group.

The Opening Ceremony, to be held on Sunday 29 June at 19.00, is the first of the meeting's social events and will be followed by a welcome reception in the exhibition area. Admission to the Opening Ceremony, which will take place in the main hall of the congress centre, and welcome reception are complimentary.

The congress party will be held at the old Munich congress hall (www.altekongresshalle.de/en/alte-kongresshalle), close to the grounds of the Theresienwiese in the heart of Munich. Built in 1952/53 the restyled building has kept its characteristic award-winning retro architecture (with 1950s illumination) and is a popular venue for delicious Bavarian food, dancing and entertainment. The party, to be held on Tuesday evening 1 July, is optional, with tickets for this always popular event costing €143 per person.

Those without accommodation reserved so far should make hotel reservations through ESHRE's appointed agent MCI Stockholm via the ESHRE website, where online hotel reservation forms are available (http://www.eshre2014.eu/Plan-Your-trip/Hotel-accommodation.aspx).

AGENDA OF 2014 GENERAL ASSEMBLY OF MEMBERS

The Annual General Assembly of Members will be held on Tuesday 1 July 2014, from 18.00 to 19.00, at the International Congress Centre Munich (ICM), venue of the 30th Annual Meeting. The agenda will be as follows:

1. Minutes of the last meeting (held in London and published in *Focus on Reproduction*, September 2013)
2. Matters arising
3. Membership of the Society
4. Society activities
   - Annual meetings
   - Campus meetings
   - Special Interest Groups and Task Forces
5. *Human Reproduction* journals
6. Paramedical Group
7. Financial report
8. Composition of the Committee of National Representatives
9. Election of the Honorary Members for 2015
10. Any other business
11. Date of the next General Assembly of Members

GETTING TO AND FROM THE CONGRESS CENTRE

This year's Annual Meeting will be held at the International Congress Center Munich (ICM). For those arriving at Munich airport, a special shuttle service will be available for direct transfer to the ICM at a low fare of just €8 (one way) or €13 (round trip). The shuttles will run from Saturday 28 June (13:00-18:0) every 30 minutes, and on Sunday and Monday (29-30 June, 08:00-19:00) again every 30 minutes. On Tuesday 1 July the shuttle service will be available from 08:00-10:00 and from 16.00-18.00 every 30 minutes, and on the last day - Wednesday 2 July - from 08:00-13:00 every 30 minutes. For those attending sessions right up to the very last moment, there will be direct shuttles from the ICM to the airport from 13:00-19:00 every 15 minutes.

Participants can also take the direct fast train S8 (S-Bahn) from the airport straight into the city centre. An Airport-City Day Ticket (MVV Tageskarte) costs €11.70 and is valid from purchase to 06.00 next day for all inner city destinations.

The MVV logo will be printed on all delegate badges, thereby allowing participants the use of public transport within the inner district (MVV Innenraum) during conference days (29 June to 2 July). So a simple production of the delegate badge allows an unlimited number of journeys with all MVV transport (S-/U-Bahn, tram and bus) within the inner district.

Delegates will thus be able to travel from the ICM to the inner city and explore all the great sights and museums of Munich, including the Old, New and Modern Pinakotheks with their exquisite collections. And, of course, don't miss the city's many beer gardens and pubs, which can all be easily and safely reached by public transport.

The MVV logo printed on all delegate badges for use of inner city public transport.

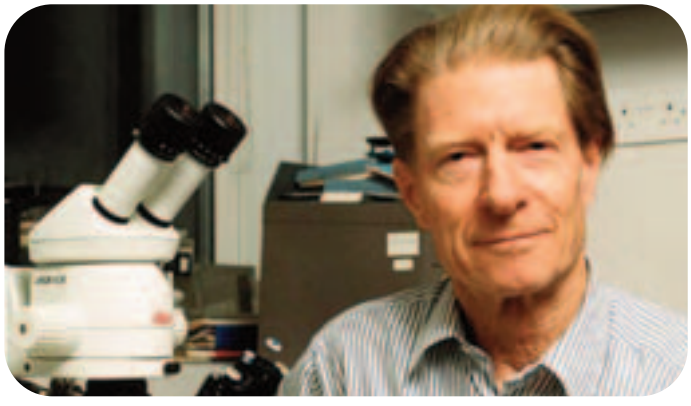
The Nympenburg Palace, currently home to fine collections of furniture, paintings and porcelain.

ESHRE'S 2016 Annual Meeting confirmed for Helsinki, Finland

ESHRE's Annual Meeting of 2016 - ESHRE's 32nd annual event - will be held in Finland's capital city of Helsinki from 3-6 July. Venue will be the Helsinki Exhibition and Convention Centre ('Messukeskus') in the east of the city, and well located for public transport. This is the first time that an ESHRE Annual Meeting has been staged in Finland, although it was in the city in 1984 (at the 3rd World Congress of IVF) that Robert Edwards and Jean Cohen first raised the idea of forming a European society for reproductive science and medicine.

A Nobel prize winner and a true ESHRE pioneer are awarded honorary membership for 2014

Stem cell scientist Sir John Gurdon and former ESHRE Chairman Klaus Diedrich will receive their awards at this year's Opening Ceremony



Professor Sir John Gurdon, the 'international' recipient of this year's honorary membership of ESHRE, was awarded the Nobel Prize in Physiology or Medicine for 2012 along with Professor Shinya Yamanaka for their ground-breaking work showing that mature cells can be reprogrammed to become pluripotent stem cells capable of developing into all tissues of the body. The Nobel Assembly stated that their work 'revolutionised our understanding of how cells and organisms develop' and that their discoveries 'have completely changed our view of . . . cellular specialisation'.

Sir John, after Sir Robert Edwards and Luc Montagnier, is the third Nobel laureate to be awarded honorary membership of ESHRE, and the second as a current Nobel prize winner.

Like Sir Robert, Sir John has spent the most of his working life in Cambridge. The Wellcome Trust/Cancer Research UK Institute – part of the University of Cambridge – where Gurdon was formerly chairman, was renamed the Gurdon Institute in 2004, in honour of his achievements in the field of developmental and cancer biology.

In Britain Sir John is not just acclaimed for his work on induced pluripotent stem cells, but also for his failures at the country's most celebrated 'public' (private!) school, Eton College. On a shelf in his Cambridge office, Gurdon kept a framed copy of a school report from Eton when he was 15 years old. His teacher described Gurdon's scientific ambitions as 'quite ridiculous', because 'he will not listen, but will insist on doing his work in his own way'. A poor academic record at Eton was evidently no hindrance to a later illustrious career.

The 'local' recipient of this year's honorary ESHRE memberhsip is the German gynaecologist Professor Klaus Diedrich, whose record with ESHRE stretches back to the very beginnings of the Society's history.

After qualifying in medicine in 1972 and military service, Diedrich was appointed consultant in ob/gyn at the University Women's Clinic of Lübeck. Lübeck's own IVF programme was approved in 1981 and achieved its first live birth the following year - just a few months after Siegfried Trotnow's group in Erlangen reported the birth of Germany's first IVF baby. In 1984 Diedrich moved to Bonn as consultant in ob/gyn and Professor at the University Hospital. He remained in Bonn until 1993, when he returned to Lübeck as head of the Department of Obstetrics and Gynecology.

Klaus Diedrich, along with Robert Edwards, Jean Cohen, André Van Steirteghem, Arne Sunde and Piergiorgio Crosignani, was a founding member of ESHRE and a member of the temporary and first Executive Committees. It was also Diedrich who, with German colleagues Al Hasani, Beier, Krebs and Van der Ven, organised ESHRE's first Annual Meeting in Bonn. Diedrich became Chairman of ESHRE in 1993.

Klaus Diedrich has published extensively in reproductive medicine and, through ESHRE's Campus workshop programme, established both Bonn and Lübeck as important training centres. In 1994 he was made secretary of the German Society of Obstetrics and Gynecology (DGGG), and in 2002 President. Diedrich retired from his post in 2012, and his retirement was marked in Lübeck by a valedictory symposium in his honour. His main field of interest was ovarian stimulation and Diedrich was among the first to introduce the GnRH antagonists (the 'Lübeck protocol').

Klaus Diedrich with the late Patrick Steptoe at ESHRE's first Annual Meeting in 1985, which Diedrich helped organise in Bonn.

Does calcium signalling hold a key to the medical treatment of sperm dysfunction?

Opening keynote lecture based on top downloaded paper


The clinical significance of calcium-signalling pathways mediating human sperm hyperactivation

The Human Reproduction keynote lecture which opens the Annual Meeting has quickly set a tradition of being the record-breaking presentation at any ESHRE event. Last year in London around 4000 packed the auditorium for Aisling Ahlström's presentation on the morphological parameters for predicting blastocyst viability. The year before in Istanbul a similar number heard Sonya Desmyterre's lecture on the safety of blastomere biopsy in PGD.

This year's Human Reproduction lecture returns to the IVF lab with a study from Wardah Alasmari and colleagues at the University of Dundee in Scotland on the clinical significance of calcium-signalling pathways in human sperm hyperactivation.[1] The paper had the highest number of full-text downloads during the first six months of publication of all original articles published in *Human Reproduction* between January 2012 and June 2013. The lecture will be given in Munich by principal investigator Chris Barratt.

ESHRE's opening keynote lectures have set a trend of attracting record-breaking audiences of more than 4000.

The study was a prospective investigation of defects in calcium signalling in 68 research sperm donors and 181 fertility patients for prevalence and for clinical effect. What we knew so far, explained Barratt, is that sperm motility and hyperactivation - both critical for sperm's ascent through the reproductive tract and penetration of the zona pellucida - were regulated and controlled by calcium channels, but little else was known about what exactly triggered hyperactivation in sperm.

'Previous studies had shown a significant relationship between basal levels of hyperactivation, calcium responses to progesterone and IVF fertilisation rates,' said Barratt. 'So in this study, we systematically investigated the ability or failure of human sperm to generate calcium signals and hyperactivation in response to a pharmacological challenge - and then related those defects in responses to IVF success. What we found is that calcium signalling is fundamental for sperm motility and I hope our results will lead to further assessment of these defects using other techniques.' One such technique is single-cell imaging and another patch clamping, which Barratt will describe in Munich.

In the keynote study calcium signalling was stimulated with targeted agonists and the response screened for hyperactivation and intracellular calcium signalling. This response was compared in three groups - the research donors, IVF patients and ICSI patients.

Response to the stimulus proved different among each of the three groups. For example, failure of hyperactivation was significantly more common in IVF patients than in donors, and failure of calcium signalling was a common observation in ICSI patients. However, the overall pattern of response showed emphatically that defects in calcium signalling leading to poor hyperactivation do indeed occur and that the (in)ability to achieve induced hyperactivation does affect fertilising capacity in IVF.

The data also confirmed that the release of stored calcium is the crucial component of calcium signals leading to hyperactivation and that defects in the calcium store may therefore underlie hyperactivation failure.

'Sperm dysfunction has consistently been identified as the single most common cause of male infertility,' said Barratt, 'but there are no drugs a man can take to treat it. ART is the only option. So I hope that studies like this will act as a platform for a potential drug-based screening programme to modulate calcium mobilisation as a possible rational treatment for sperm dysfunction.'

● Chris Barratt in profile. The editor of *Molecular Human Reproduction* talks about basic science in ESHRE and reproductive medicine. Page 18.

1. Alasmari W, Barratt CLR, Publicover SJ, et al. The clinical significance of calcium-signalling pathways mediating human sperm hyperactivation. Hum Reprod 2013; 28: 866-876.

ESHRE unveils research in reproduction grant scheme

- Up to €150,000 funding available spread over one to three years
- Grant awarded on basis of 'scientific excellence, originality and feasibility'

An ESHRE research grant of up to €150,000, with funding spread over one to three years, will be available from this year. The scheme, approved by ESHRE's Executive Committee in February, is designed to support scientists and clinicians in basic and clinical research in reproductive medicine.

The deadline for proposals this year will be 15 May, with subsequent May deadlines scheduled every two years. Proposals will be evaluated over two rounds, first by the ExCo and SIG Co-ordinators, and secondly by a committee of independent reviewers.

Because the grant scheme will provide limited funding over a short period of time, eligible projects include, but are not limited to, pilot or feasibility studies, collection of preliminary data, secondary analysis of existing data, small/self-contained research projects and development of new research technology. The evaluation of proposals, however, will give emphasis to originality, design, feasibility, quality of the consortium, and expected impact.

The grants will range from €50,000 to €150,000 and will be awarded to projects running between one and three years. 'The total requested grant should reflect a realistic estimation of the project needs and be fully justified,' says ESHRE Chairman Juha Tapanainen. 'The overall level of the grant offered will be determined on the basis of the needs of the project.'

Applications can be submitted only in response to a 'call for proposals' published every second February on the ESHRE website. Applications can thus be made between the end of February and 15 May of the same year, with the grant awarded in December.

- Full details of how the scheme will work and how applications should be made are on the ESHRE website.

PRINCIPLES OF ELIGIBILITY

- Projects for funding will be selected based on scientific excellence, originality and feasibility.
- Projects in reproductive medicine.
- The co-ordinator of the project should be an ESHRE member.
- The applicants (co-ordinator and associated investigators) should be from at least two different legal entities/institutions - public and/or private.
- Grants are awarded to the host institution which engages and hosts the co-ordinator of the project and which will distribute the funding to the associated investigators.
- The host institution guarantees the co-ordinator's independence and provides the research environment to carry out the project and manage its funding.

Italian court finds Law 40 ban on gamete donation 'unconstitutional'

It has taken ten years of legal challenge to dismantle the legislation of Italy's infamous Law 40, but in April the last of its draconian restrictions was finally removed when a court ruled that the Law's ban on gamete donation was unconstitutional.

Lawyers working on the case said the ruling would be immediately effective, although the health minster, from the socially conservative New Centre Right party, said Parliament would have to debate how the court order could be applied.

Law 40, introduced in 2004, became Europe's most restrictive legislation in ART, not only banning embryo freezing, PGD and gamete donation, but also requiring the transfer of every oocyte fertilised up to a maximum of three. The result was an increase in multiple pregnancies, and a mass exodus of patients in a search for cross-border treatments.

Many of Law 40's provisions were overturned after legal challenges in 2008 and 2009, although the restrictions on PGD remain subject to further Constitutional Court decision - despite a European Court of Human Rights ruling in 2012 that the ban breached the right to respect for family and private life.

Former ESHRE Chairman Luca Gianaroli, who has campaigned continuously against Law 40, described the removal of restrictions on gamete donation as 'great news' and 'the best possible reward for all the hard work we have done so far'. Indeed, ESHRE itself, under the chairmanship of Arne Sunde in 2004, formally campaigned with Gianaroli against what were then legal proposals, but at the time to no avail.

'Many of my Italian colleagues and the patient associations always considered the law unfair and harmful,' said Gianaroli. 'But we never lost hope and now the substance of our position has been officially acknowledged. The ending of the ban on egg donation will mean that Italian couples can get the treatments they need in their own country, without having to go abroad.

'The verdict finally marks the end of Italy's odious discrimination against infertile patients and it emphasises yet again the importance of the patient's right to fair and adequate treatment.' Research performed by ESHRE's Task Force for Cross-border Reproductive Care in 2012 found that gamete donation was the main treatment sought by Italians overseas.

Endometriosis guideline goes mobile

A decision-aid app now available for tablets and phones

ESHRE's latest guideline - on the *Management of Women with Endometriosis* - was a highlight of 2013. But, with 83 recommendations spread over eight chapters, it was no easy read. So now, to improve implementation and thereby both quality of care and quality of life in women with endometriosis, ESHRE has developed a decision-aid app based on new technologies and accessible to mobile devices (tablet and smartphones) and via the internet.

This new endometriosis app provides evidence-based advice for the diagnosis and treatment of endometriosis. Doctors are guided through questions whose answers will conveniently lead them to the appropriate evidence-based recommendation of the guideline.

In March, ten young gynaecologists from Maastricht University Hospital tried out a test-version of the app. Different clinical scenarios were proposed and the gynaecologists had to find management recommendations for the suggested cases. Jonas Ellerbrock, a gynaecologist in training in Maastricht, said: 'I found the app very helpful for decision-making. It's user-friendly and I am sure I could use it quite regularly with my patients.'

Medical students test-drive the endometriosis app in Maastricht.

The app is downloadable from the App Store and Google Play. A web-based version has also been developed and can be found at www.eshre.eu/guideline/endometriosis.

The app is only accessible and available for download to ESHRE members.

Two further ESHRE guidelines for Munich presentation

Premature ovarian insufficiency

ESHRE's POI guideline has been developed by a multidisciplinary group (gynaecologists, endocrinologist, psychologist, cardiologist and neurologist). The development group is chaired by Melanie Davies and Lisa Webber. Dr Davies will present the draft of the guideline in Munich, after which it will be published on the ESHRE website for review and comment. The final text should be ready by the end of 2014.

Psychosocial care in infertility and medically assisted reproduction

The ESHRE guideline on psychosocial care in infertility and medically assisted reproduction has been mainly developed by a group of psychologists whose aim was to raise awareness of psychosocial health in infertility and ART and how it might best be supported. The draft of the guideline will be presented in Munich by Sofia Gameiro, chair of the guideline development group and currently Deputy Co-ordinator of ESHRE SIG Psychology & Counselling. After the Annual Meeting, the guideline will be open for review on the ESHRE website. The final guideline, incorporating all comments, should be finished by the end of 2014.

Hit surge on ESHRE website just days before 1st February abstract deadline

Use of ESHRE's website is usually steady at around 1500 hits per day, with use clearly higher during the week than at weekends. www.eshre.eu is certainly a working site, and not a place for leisure-time surfers!

But in the week preceding the deadline for abstract submission on 1 February, usage built up towards a surge of almost 4000 hits on 31 January, the final day for abstract submission to this year's Annual Meeting. Thereafter, usage reverted to its usual weekly pattern.

In the two weeks preceding the abstract submission deadline website use built up throughout both weeks towards a Friday peak, suggesting not only that many abstracts are completed for submission at the end of the week - and most on the last day possible. Abstract submission can only be completed online.

$1000 genome sequencing a step closer to reality

How much to sequence the average human genome? At last year's Annual Meeting in London, Oxford geneticist Dagan Wells made claims for next generation sequencing as a technique of embryo screening not just because of its real time accuracy but also because of its ever declining cost. But how low can sequencing go?

In the past six years the cost of sequencing a whole human genome has skydived from around $10 million to just a few thousand. According to the journal *Nature*, the price is now hovering at around $5000, 'and is expected to drop even lower'.[1]

One explanation for the drive towards loose-change sequencing is the grant scheme run by the US National Human Genome Research Institute (NHGRI). Officially called the Advanced Sequencing Technology awards, the challenge scheme is more widely known as the '$1000 genome programme'. Started in 2004, the scheme has so far awarded grants to many groups of academic and industrial scientists, with a single and quite simple aim: a genome sequencing test which can be run for $1000.

According to *Nature*, the programme is now quite close to achieving its goal, and thus seems likely to end its funding of genome sequencing research - though not without a ring of success almost unprecedented elsewhere. Can such a winning formula be applied elsewhere, asks *Nature*.

Meanwhile, the promise of next generation sequencing (also known as massive parallel sequencing) raised last year in London as a technique for affordable preimplantation genetic screening now looks set to be taking another step even closer.

1. See http://www.nature.com/news/technology-the-1-000-genome-1.14901?WT.ec_id=NATURE-20140320#/falling

IVF continues to thrive in USA

Number of cycles, success rates, eSET all increase

The number of multiple IVF pregnancies have continued their inexorably slow decline in the USA, while overall success rates have climbed yet a little higher. Data released in the latest SART report (for 2012) show that the country's 379 member clinics (around 90% of the total) reported 165,172 IVF/ICSI cycles in 2012, around 2000 more than in the previous year. IVF newborns accounted for just over 1.5% of the US total of 3.9 million, more than ever before.

The latest figures show that in patients who were 35 and under 14.8% of cycles were elective SET, against 11.7% in 2011. However, the proportion of twins remained high - 29.5% twins in 2012 and 30.8% in 2011. Live birth per cycle was 40.7% in 35-and-unders in 2012, and 40.1% in 2011. The figures yet again emphasise the effect of age on success rates, with a live birth rate of just 4% in those aged 42 or over.

Egg donation, despite its likely use in an older population, continued to report high success rates, with a live birth rate of 56.6% (per transfer) in fresh cycles and 37% in frozen.

Around two-thirds of all cycles reported were ICSI, and 'diminished ovarian reserve' along with male factor the most frequent diagnoses (each 17% of cases).

Age range	**<35**	**35-37**	**38-40**	**41-42**	**>42**
Cycles	38662	19599	18410	10167	6224
% pregnancies/cycle	46.7	37.8	29.7	19.8	8.6
% LBR/cycle	40.7	31.3	22.2	11.8	3.9
% LBR/transfer	47.1	37.9	28.5	16.3	6.1
% eSET/cycle	14.8	8.9	3.0	1.2	0.6
% cancellations	6.3	9.2	12.7	15.8	21.5
Implantation rate	37.5	27.6	18.4	9.8	3.8
Average no. embryos /ET	1.9	2.0	2.4	2.9	2.9
% twin LBR	29.5	25.0	20.3	13.4	9.0
% triplet+ LBR	1.1	0.7	0.7	0.7	0.4

Britain publishes first draft regulations on mitochondrial replacement techniques

Draft regulations as part of a national consultation on mitochondrial replacement were published by Britain's Department of Health in February. If accepted by Parliament, the UK would become the world's first country to allow the procedure for the prevention of mitochondrial disease.

The technique - dubbed 'three parent IVF' by Britain's ever inventive press - aims to prevent mitochondrial diseases by replacing the mother's mitochondria with healthy cells from a donor, either through nuclear or spindle transfer. The resulting child would thus have the genetic material of three people - the majority as normally from the mother and father, but with around 1% from the mitochondrial donor.

The draft regulations would require Britain's regulatory authority, the HFEA, to decide that 'there is a particular risk that the egg or embryo of the patient has a mitochondrial abnormality'. Such diseases are thought to affect around one in 6500 people, and only around 10-20 cases per year are expected to be treated.

Britain's Chief Medical Officer said that enactment of the legislation would 'keep the UK at the forefront of scientific development in this area'.

ESHRE and ASRM back in Europe with a third high quality meeting

Details of uterine transplantation programme disclosed in debate

While attendance at this year's 'Best Of' meeting was not quite as high as at the first European event, many countries were well represented and post-presentation discussion enthusiastic.

This was only the third 'Best Of' meeting hosted jointly by ESHRE and ASRM but already the project has established a recognisable blend of lectures, back-to-back sessions and debates devised from both sides of the Atlantic. The presentations can be at once informative, provocative and enjoyable - and everyone taking part seems to have fun.

This year the meeting was back in the Italian ski resort of Cortina d'Ampezzo, following last year's ASRM venture in the Bahamas. The mornings in Cortina are taken up with skiing and walking, while the scientific programme fills the afternoons and early evenings.

Thirty presentations were made during the three days of this year's meeting, with several themes explored from both the US and European perspective. Indeed, it was in a debate session (on the preference of uterine transplantation or surrogacy for the treatment of women with uterine factor infertility) that the meeting's news highlight emerged - from the Swedish gynaecologist Mats Brännström with an update on the first series of nine women to receive a donor uterus at the Sahlgrenska University Hospital in Gothenburg. A report on progress appeared in *Fertility and Sterility* on the very day after Brännström's presentation, with - not surprisingly - considerable press coverage a few days later.[1]

With many countries denied surrogacy by law, and others facing complex challenges over citizenship (to say nothing of cost), the session hardly took off as a debate. But there was no denying the magnitude of what Brännström and his colleagues had achieved.

The series, he said, comprises nine women who had an absent or dysfunctional uterus - by far 'the biggest group in existence, if it works'. Two earlier cases have 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, allowed no risk of such accusations, with a painstaking ten-year research approach progressing from mice to non-human primates. The work was also funded by private research foundation, with the multinational surgical team giving their time freely at weekends.

Brännström described the transplantation surgery as 'difficult', with each case requiring between ten and 12 hours - substantially longer than the three or four hours first estimated! No donors or recipients required blood transfusion or ICU care, and hospital stay was over in five or six days. The work was based on a live donor concept, with all donors healthy and closely related to their recipients (only one was a friend).

The University of Gothenburg released pictures from the operating theatre during one of the uterus transplantation procedures. Brännström estimated that each would take three or four hours, but admitted that, even with experience, it still lasts between ten and 12 hours.

ESHRE BACK ON TOP IN SKI CHALLENGE

During a weekend of heavy snow in Cortina, the men's skiing competition was won by the Polish gynaecologist Grzegorz Ziolkowski, with ESHRE's own Chairman Juha Tapanainen taking the runner-up spot from Frederick Licciardi of the USA. The challenge trophy, won last year in the Bahamas by ASRM, was received by ESHRE's present and two Past Chairmen.

The programme is aiming for subject anonymity and a minimal disclosure of information, but Brännström said that seven of the nine recipients began menstruating from the second month, with viable uteri at six months. Subsequent press reports indicated that embryo transfer had been performed in four cases. Should any pregnancies develop and progress to term - which of course will be the real test of uterine function - delivery will be by caesarean section. Hysterectomy is planned after one or two deliveries to minimise the period of immunosuppression.

'One or two more will perhaps get pregnant and miscarry and one or two won't be able to get pregnant,' he told reporters a few days after the meeting.

Implantation failure

Implantation failure and miscarriage were recurring themes of the meeting. US gynaecologist Ruth Lathi from Stanford defined 'early' miscarriage as occurring within ten weeks, and 'late' between ten and 24 weeks. Following the American College and ASRM recommendations, she proposed that 'no discussion on diagnosis is complete' without antiphospholipid antibody testing, uterine cavity examination and parental karyotyping.

The origins of miscarriage, she added, may be sporadic, or of maternal or paternal cause. However, despite such evaluation, Lathi reported that 40-70% of cases will remain unexplained, 'often due to a combination of random unrelated causes'. Prognosis and counselling are thus important to couples.

However, recent studies confirm aneuploidy as an 'important' cause of miscarriage, with one study of embryonic karyotypes in miscarriage patients reporting chromosomal abnormality as the most common explanation. Almost 100% of these abnormalities are maternal in origin, said Lathi, and of these single autosomal trisomies account for 74%. Thus, as she and fellow US presenter Mina Alikani proposed, preimplantation screening has the potential to decrease the rate of miscarriage for women at risk of both miscarriage itself and aneuploidy; maternal age remains a strong predictor of this risk.

Alikani, from North Shore University Hospital in New York State, also described aneuploidy as the leading cause of embryonic loss both post- and preimplantation. A very recent study from the group of Dagan Wells found that 75% of oocytes, 83% of cleavage stage embryos and 60% of blastocysts were aneuploid when assessed by array CGH (though these rates were lower in women under 36 years). Thus, said Alakani: 'Aneuploidy of mitotic and meiotic origin in embryos is the most likely cause pre-and post-implantation loss,' while adding the caveat that even well developed euploid embryos still fail to implant. Thus, failed or abnormal blastulation, incomplete hatching from the zona pellucida or a breakdown in the cross-talk between embryo and uterus may all provide an aneuploidy-independent reason for implantation failure.

The prediction of aneuploidy by morphology at the cleavage stage is 'very difficult', she said, citing a 2014 study from the Wells group, while the relationship with blastocysts seems 'more solid'. This same study, she reported, had found that aneuploid embryos had good morphology as often as euploid embryos, and more than half the complex abnormal embryos (with three or more confirmed chromosomal errors) also had good morphology.

There are similar discrepancies, she added, in

morphokinetic screening, with no agreement yet on which parameters are central for the confirmation of abnormality.

There are, of course, other physiological factors in implantation failure and pregnancy loss, yet Dolores Lamb, a former President of ASRM, noted that the male contribution at the sperm chromosomal level is 'not always considered' in the affected couple, especially if the male is normospermic. Sperm aneuploidy, she said, is most commonly detected by FISH, and infertile men have a ten-fold greater incidence of sperm-specific chromosomal abnormalities. An incidence even two or three times higher than normal may be clinically significant, she said. Oligospermic and oligoasthenozoospermic men, and the male partners of women with recurrent pregnancy loss are all candidates for testing.

Non-invasive prenatal testing

Joe Leigh Simpson, Senior Vice President for Research at the March of Dimes Foundation, described prenatal genetic diagnosis by cell-free fetal DNA in maternal blood as 'transforming technology', a 'near definitive' non-invasive test which now approaches the ideal and offers an alternative to the invasive procedures of amniocentesis and CVS. The concept, said Simpson, relies on the fact that in pregnancy cell-free DNA from both the mother and fetus are present in maternal blood - and that these short DNA fragments are not housed within the nucleus of a cell. Moreover, the new DNA sequencing technologies now make possible the very precise relative quantification of DNA fragments - and thus the reliable detection of any fetal chromosome abnormalities. Studies so far have found detection rates of over 99% for trisomy 21, and much lower false positive rates (<1%) than serum analyte/ultrasound screening. The test, added Simpson, is applicable from ten weeks' gestation. Different tests, with different approaches to detect chromosomal abnormality (either targeted or shotgun via next generation sequencing) are available and in development, and studies with massively parallel sequencing have already demonstrated significantly lower false positive rates and higher positive predictive values for detection of trisomies 21 and 18 than standard screening.

Following a relatively cautious American College comment in 2012 (should not be offered to low risk women), a more recent statement from the American College of Medical Genetics said there should be no restrictions on indication (ie, extended to low risk women and for sex chromosome abnormalities). Simpson too said that cell-free fetal DNA screening is 'likely' to replace serum analyte screening in the US obstetric population in the near future.

Comment from the floor in Cortina suggested that Europe was a little more cautious. Indeed, a report from the UK's Royal College of Obstetricians and Gynaecologists (RCOG) published in March noted that there are still 'technical, financial and ethical issues'.[2] Nevertheless, the RCOG acknowledged that 'in time, this technology is likely to become the primary screen for chromosomal abnormalities in pregnancy'. Non-invasive testing, said the report, 'avoids the risk of miscarriage associated with invasive testing procedures, and the sensitivity and specificity of NIPT approaches 100% for detecting Down syndrome, providing the sequencing is successful'.

Miguel Angel Checa: 'Vitrification permits embryo development comparable to that of fresh embryos.'

Freeze all embryos

A policy of freezing all embryos for the prevention of OHSS is already well established. Now, however, Miguel Angel Checa, from the Hospital del Mar, Universitat Autonoma de Barcelona, proposed that this same freeze-all policy would also have outcome benefits in a far broader population of IVF patients. Behind his claim lay findings from randomised trials (showing that delayed embryo transfer can increase delivery rates) and the indisputable fact that vitrification 'permits embryo development comparable to that of fresh embryos'.

Checa conceded that there is not yet enough data to change policy, but from his limited systematic review of three randomised trials there seemed an indication that endometrial receptivity was indeed impaired in stimulated cycles, and delivery rates improved by delayed transfer. Uterine receptivity is better in natural or HRT cycles than in stimulated cycles, said Checa, with some evidence that high estradiol levels may inhibit endometrial maturation and implantation. He added that endometrial gene expression may also be affected in stimulated cycles. However, questions from the floor reaffirmed the concern of limited data (with one of Checa's three RCTs - Aflatoonian A, et al, 2010 - apparently retracted) and the possibility of bias in the selection of embryos for freezing.

However, there was little dispute over the safety of the policy, with most reviews confirming that OHSS can be virtually eliminated, especially when the policy is linked to an antagonist programme with agonist triggering.

Too old for ART?

It was appropriate that the case for postmenopausal egg

donation was made by one of the US practitioners who first made the headlines in California. For it was the gynaecologist Richard Paulson and colleagues at USC who reported the first series of over-50 egg recipients in the *New England Journal of Medicine* in 1990 - 21 transfers in 14 couples resulting in seven live births, a rate of 33%. And what this and other reports would confirm beyond doubt was that success would depend not on the age of the recipient, but on the age of the donor. A later review by Paulson showed that cumulative pregnancy rates in egg donation cycles were the same whatever the age of the recipient; crucial was the hormonal synchronisation between donor and recipient and the viability of the egg.

Of course, despite the framework of this lively debate in Cortina, Paulson was well aware of the obstetric complications of postmenopausal pregnancy and motherhood. A retrospective analysis of his own cases from 1991 to 2001 (77 women aged over 50) revealed relatively high rates of gestational diabetes (20%) and pre-eclampsia (35%) - between two and three times higher than usually found in 40-year-old patients. However, a study by one of Paulson's own students found that 'parenting stress' was lower in the older mothers - and indeed an ASRM opinion in 2013 reaffirmed that 'some women' over the age of 50, particularly in the age range 50-54, who are healthy and well prepared for parenting, are candidates to receive donor eggs.

With an ever changing perception of ageing, Paulson appeared to accept a cut-off of 54 years as appropriate for postmenopausal egg donation - at least for the purposes of this entertaining debate. His opponent on the platform, the UK gynaecologist Adam Balen, was a little more cautious, despite acknowledging the changing demographics of female ageing. Balen unearthed salutary examples of elderly mothers whose ventures into late motherhood rarely turned out as anticipated, and warned that a mother's declining energy levels 'leave her ill equipped to cope with the demands of young children'. He also proposed that a lengthening age gap between mom and the kids may well be the cue for 'dysfunctional family dynamics' - and finally settled for a conservative cut-off age of around 50.

Gynaecologists Richard Paulson (top) and Adam Balen were in rough agreement that egg donation should be restricted by age - Paulson to 54, Balen to 50 years.

US and European perspectives on fibroids

There was little at this meeting to suggest any huge discrepancy between US and European approaches in the many techniques explored. The US perspective in the treatment of uterine fibroids, presented by Elizabeth Stewart from the Mayo Clinic, began with the premise that any strong grade A evidence of any single approach was hard to find and that even the latest guidelines were subject to some doubts. Thus, based on a premise that treating the fibroid may in itself affect subsequent fertility adversely, Stewart said there was a view in the US that the less invasive the treatment, the more beneficial the outcome. However, trials of uterine artery embolisation - while demonstrating safety and patient acceptability - were inconclusive in their effect on fertility outcome.

Vasilios Tanos, a former Co-ordinator of ESHRE's SIG Reproductive Surgery, proposed that both intramural and submucous myoma were indeed amenable to surgical treatment when the aim was to preserve fertility. He said that the laparoscopic/hysteroscopic approach is preferable for myomectomy, although the data are 'controversial' with respect to small intramural myomas, with doubts over benefit. However, he said that 'serious consideration' of myomectomy for both intramural and submucous myomas in women having IVF 'is justified'.

1. Brännström M, Johannesson L, Dahm-Kähler P, et al. The first clinical uterus transplantation trial: a six-month report. Fertil Steril 2014. doi: 10.1016/j.fertnstert.2014.02.024.
2. http://www.rcog.org.uk/files/rcog-corp/SIP_15_04032014.pdf.

'BEST OF' 2015 HEADS FOR NEW YORK

Next year's 'Best of ESHRE and ASRM' meeting will be held in New York from 5-7 March, with ASRM as the local hosts. The format of the meeting - the societies' fourth - will retain its now familar mix of lectures, back-to-back sessions and debates. The aim will be to explore emerging clinical and scientific themes from a US and European perspective.

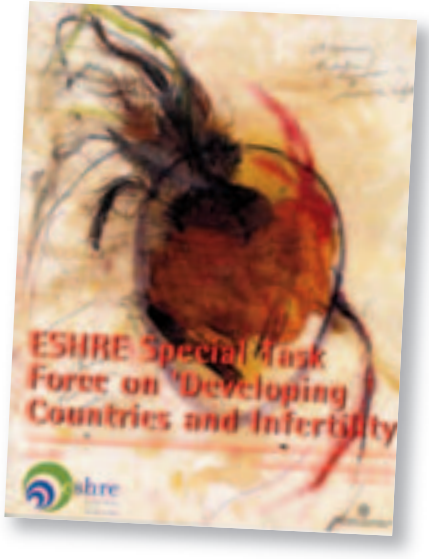
Venue for the meeting will be the New York Marriott Marquis, a modern hotel located in Times Square well equippped with substantial meeting space and facilities. Within easy reach are most of Manhattan's celebrated attractions - and of course the midtown shopping districts. No challenge activity between the two societies has as yet been selected.

Low-cost IVF centres aiming for 2015

Following encouraging results reported last year from a simplified laboratory procedure, emphasis moves to the clinic

It was in 2001 that the WHO organised its first meeting on the 'Medical, Ethical and Social Aspects of Assisted Reproduction' and for the first time in history raised the implications of childlessness in developing countries. However, although a consensus was reached resulting in many different recommendations, no real progress was made in the next few years, probably because of a lack of budget and moderate interest among those in the field of reproductive health.[1]

The foundation of ESHRE's Special Task Force on Developing Countries and Infertility in 2006 was an important step forwards, especially to convince many infertility specialists of the need for affordable infertility care in developing countries. An expert meeting held in Arusha, Tanzania, in December 2007 was the first project of the Walking Egg non-profit organisation in co-operation with the Task Force. From the beginning, the Walking Egg and Task Force have opted for a multidisciplinary and global approach towards the problem of infertility in developing countries - with a goal of making infertility care in all its aspects universally available and accessible. This will only be possible if we change and optimise the whole set-up of fertility care in terms of availability, affordability and effectiveness.



A supplement to Human Reproduction from the 2007 Arusha meeting set out the main principles of fertility care in developing countries.

In March this year the first national congress on infertility and childlessness was organised by the Association of Childless Couples of Ghana (htpp://accog.com.gh) in Gommoah Fetteh, Ghana. More than 1500 took part, most of them infertile couples. Among other speakers, Willem Ombelet described the Walking Egg Project.

As a result of the Arusha meeting the cornerstones for successful implementation were reported in a supplement to *Human Reproduction*.[2] And among them was the most important objective of the Task Force - to perform ART at a much lower price by simplifying the stimulation protocols and modifying IVF laboratory procedures.

A simplified laboratory method

A trial to examine the value and effectiveness of a new 'simplified' laboratory method was started at the Genk Institute for Fertility Technology in 2012. The method had to be independent of logistical support (eg, medical grade gases, reliable clean electricity), complex equipment (eg, microprocessor controlled incubators including the triple gas type), and costly disposable culture which were commonly used in high resource settings.

We have recently described this simplified (low-cost) IVF culture method - a closed system in which pure CO_2 is generated in a vacutainer tube containing predetermined amounts of sodium bicarbonate, citric acid and water.[3] This tube is connected to another tube containing sodium bicarbonate-buffered media. We found that optimal conditions for pH, O_2 and CO_2 could be consistently reproduced and that both the appropriate

atmosphere and medium equilibration remained stable for at least two weeks.

For insemination, 1000-5000 motile washed spermatozoa and intact oocytes are separately injected into the equilibrated medium tubes. Pronuclear visualisation and assessments of cleavage on days 1-3 are made by holding the tube horizontally in either a standard dissecting or inverted microscope. Development from insemination is undisturbed and remains in the same tube until embryo transfer.

The first results of our prospective study were presented at the 2013 ESHRE annual meeting in London. These results showed that fertilisation and embryo implantation rates were similar to those reported by high resource IVF programmes. Up to May 2013 12 healthy babies had been delivered - and the interest of the international press was huge.

Because of the very reassuring and promising results of this proof-of-principle study, further studies on the combination of this simplified method and minimal ovarian stimulation are now planned in Belgium, the UK and South Africa in 2014 and 2015. Previous studies have shown that the cumulative pregnancy and live birth rates after modified natural cycle IVF or mild ovarian stimulation are reassuring making it a cost-effective, safe and patient-friendly option.[4,5]

CONDITIONS FOR WALKING EGG CENTRES

The Walking Egg centres should honour the following conditions:

- Good quality family planning available. Ideally, infertility management should be integrated into sexual and reproductive health care programmes
- Good quality mother care facilities present.
- An endoscopic surgery unit available in the neighbourhood
- At least two dedicated specialists are available (gynaecologist, embryologist)
- Training, quality control, regular audit and systems of accreditation and registration implemented in order to maintain appropriate standards of care
- Affordable infertility care is provided according to the philosophy of the Walking Egg with respect to diagnostics, therapeutical procedures and data registration:
  - TWE promotes mild, safe and more physiological ART
  - Actions to prevent the most common complications of ART are obligatory
  - Single embryo transfer recommended to prevent multiple pregnancies; double embryo transfer is allowed in selected cases
  - The use of natural cycle/modified natural cycle protocols or mild ovarian stimulation protocols to prevent OHSS
  - A strict flowchart for the diagnostic phase will be implemented in all Walking Egg centres
  - Only IVF (and not ICSI) to be performed because of the characteristics of the simplified IVF system itself
- Focus on childless couples in a current relationship
- If HIV-positive, ART only performed if anti-HIV medication is freely available.

More information on the Walking Egg can be found at www.thewalkingegg.com.

The demand for a low-cost programme like this is immense, not only from developing countries but also from the developed world. However, funding for such a project remains very difficult. International societies, NGOs and foundations show some interest, but this is where the story ends. Although the consequences of involuntary childlessness are dramatic in most developing countries, and despite the fact that, according to the WHO, between 100 and 200 million couples are affected, infertility care is non-existent in nearly all reproductive health centres, which focus exclusively on contraception, prevention of sexually transmitted diseases and prevention of HIV. Overpopulation, limited resources and high costs associated with infertility remain the most common arguments against the implementation of infertility care services.

Nevertheless, it is our aim to set up low-cost IVF centres in developing countries in 2015. These Walking Egg centres should honour certain conditions (see box above).

From an economic point of view a substantial reduction in laboratory costs is only possible if IVF alone is offered. In all cases where the surrounding air quality of the laboratory is important (ICSI, PGD, etc) the cost reduction is minimal.

Willem Ombelet
Co-ordinator
Task Force Developing Countries and Infertility

Results from the proof-of-principle study of the simplified laboratory method were published in March.[3]


First births with a simplified culture system for clinical IVF and embryo transfer

Jonathan Van Blerkom [a,b,*], Willem Ombelet [c,d], Elke Klerkx [c], Mia Janssen [c], Nathalie Dhont [c], Geeta Nargund [d,e], Rudi Campo [c]

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1. Ombelet W. Is global access to infertility care realistic? The Walking Egg Project. Reprod Biomed Online 2014; 28: 267-272.
2. ESHRE Monograph. ESHRE Special Task Force on Developing Countries and Infertility (Eds. Ombelet W, Devroey P, Gianoroli L, te Velde E). Hum Reprod 2008.
3. Van Blerkom J, Ombelet W, Klerkx E, et al. First births with a simplified culture system for clinical IVF and ET. Reprod Biomed Online 2014; 28: 310-320.
4. Nargund G, Waterstone J, Bland JM, et al. Cumulated conception and live birth rates in natural (unstimulated) IVF cycles. Hum Reprod 2001; 16: 259-262.
5. Verberg MF, Macklon NS, Nargund G, et al. Mild ovarian stimulation for IVF. Hum Reprod Update 2009; 15: 13-29.

Standing up for the basic science of reproduction

'Science is fundamental to what we do and to the development of the Society.'

The UK scientist Chris Barratt took over the editorship of *Molecular Human Reproduction* two years ago. He talks to *Focus on Reproduction* about his responsibilities as editor-in-chief and the place of basic science within the interests of ESHRE.

FoR: As the editor of MHR you're probably ESHRE's most visible representative of basic science. Do you recognise that as a responsibility?
CB: Yes, it's a fundamental responsibility. It's one reason why I do the job. It's critical to try and develop basic science in reproduction.

And do you think ESHRE is a reasonable place for basic science to be represented?
The annual meeting of ESHRE is a fantastic event and a great vehicle for interaction. But is the Society a worthy representative of basic science? I believe the answer is no. It is not the premier society for people in basic reproductive science. ESHRE as a society *should be* representative of basic science. There's a Task Force devoted to this, but at the moment I still feel that basic science is ESHRE's weakest area of expertise and influence.

Of course, Bob Edwards in founding the Society had a vision of equal representation between science and clinical medicine. Presumably, you don't see that equal representation?
No. They are not equally represented and the mission of ESHRE should be to develop its interests in basic science further. Right now I don't think the Society is doing that.

So what more could ESHRE do?
There's no simple or single answer. But one possibility is to extend the political base. For example, there's more that ESHRE could have done in the formulation and execution of Horizon 2020. ESHRE could also take on a strong political role at an intellectual level of response to the problems we now face in basic science and how they get translated.

But won't that mean a different kind of membership in ESHRE . . . different sorts of people at the heart of ESHRE?
It would only mean a minor shift in the character of the Society, but there does need to be a shift - a realisation that basic science is fundamental to what we do and to the development of the Society. That's how you win the Nobel Prize. So it's critical that ESHRE takes this aspect of its mission seriously. But it will require other influences and a little rebalancing. Most people I talk to in the Society would welcome that.

So the journal, *MHR*, is not enough for ESHRE as a stand-alone representation of science?
No. In fact the profile of *MHR* even among basic scientists in reproduction is still quite low, despite the impact factor. I was recently at a Gordon research congress on fertilisation in the US and I was surprised how many people there were unaware of *MHR*.

How can that be? I would imagine that any journal with an impact factor over 4 would be widely known.
Well, they may have misunderstood the journal's title, or misunderstood me, but there were a number who did not know about *MHR* as a journal of basic science in reproduction - which is ironic in the light of Bob Edwards's Nobel Prize in 2010. It just makes no sense.

So what can you do the raise the profile?
We have to look at promotion, the involvement of young scientists, leading scientists, and the scope of the journal. We are emphasising animal studies now - *MHR* is not just 'human'. We're doing a whole issue on sperm competition, and that begins with the very lowest order of animals. So there are gaps that we must face and bridge. It a long-

Molecular Human Reproduction now boasts an impact factor above 4, not far behind that of its better known parent journal.

term project, but necessary if *MHR* is to continue its progress.

But there's still an objective to keep the impact factor moving forward?
Impact factors are not everything, but they are important. So our objective was always to get *MHR* to an impact factor in the region of 4 - and we've done that. Ultimately, keeping the impact factor at this level will all depend on the quality of the papers and the quality of the science.

Is there a danger, do you think, that generally in reproduction science is becoming a poor relation?
Yes, I do. I think basic science is struggling to make its voice heard in reproduction - to explain and emphasise its role, and to get funding. In IVF, of course, I agree that the lab has always been relatively strong. And certainly, most of the big moves in IVF have been because of laboratory science.

Hasn't that always been true - that most of what's exciting in IVF has actually come out of the lab?
Yes. But most of those develeopments are testament to the strength of translational medicine in reproduction. Very few of them are the result of pure basic science. Nevertheless, it is fair to say that translational science is very strong in reproduction. Indeed, I think this area of medicine is one the fastest moving disciplines there is, where an idea can quickly take shape as a working application. Of course, some of these can be introduced on a whim, but this is still an area of medicine where a good idea can be translated incredibly quickly.

You began your career at the University of Wales with a degree in zoology. How did that take you to Professor of Reproductive Medicine in Scotland?
After my first degree I did a PhD in zoology at the University of Birmingham under the supervision of Jack Cohen, and that really stimulated my interest in reproduction and embryology. So when I finally began work - with Ian Cooke in Sheffield - it was in male germ cells in Ian's natural cycle IVF programme. So my interest was male gametes in reproduction, but my intellectual specialty is sperm biology and fertilisation. So currently, I am a scientist involved in reproduction, particularly sperm transport. My main role now is teaching and research.

And in reproduction generally is the sperm cell as well studied as the oocyte?
No. Most people consider the egg much more important than sperm, and that's because there are so few eggs. But the fact is that embryo quality is just as dependent on paternal gametes as maternal. Just because there's a difference in number doesn't dilute the importance of the sperm cell.

And sperm quality today?
Well, for a grant application it's essential to say that there's controversy in this area. But even scientifically there is still enough evidence for concern about a decline in sperm quality. There are indicators pointing that way - men with oligozoospermia, the need for ICSI - but I think we still have to be cautious in drawing conclusions. The male does seem to be a more prominent cause of infertility, but that may just be that we didn't look hard enough before.

So no patterns of morphological change?
Well . . . all sperms look different to me. If we have ten people reading ten slides we'll get many different answers - and this is a situation which must change. So it's difficult to identify trends - and essential that we try these tests for sperm function, such as DNA damage, even if the evidence right now is not as strong as it could be. DNA damage does seem to have a relationship with a pregnancy carried to term, so it's important that we look at these findings. But it's a fact that nothing major has happened in the diagnosis of male infertility for 80 years. We still relay on semen analysis, and there has been no progress whatsoever in doing that. The crazy thing is that we're doing the same things as we've always done before but getting different answers.

Continued on page 23

PROUST QUESTIONNAIRE*

- **Your greatest strength?**
  Saying it as it is
- **And greatest weakness?**
  Saying it as it is
- **Herbal tea or a wee dram of whisky?**
  Whisky

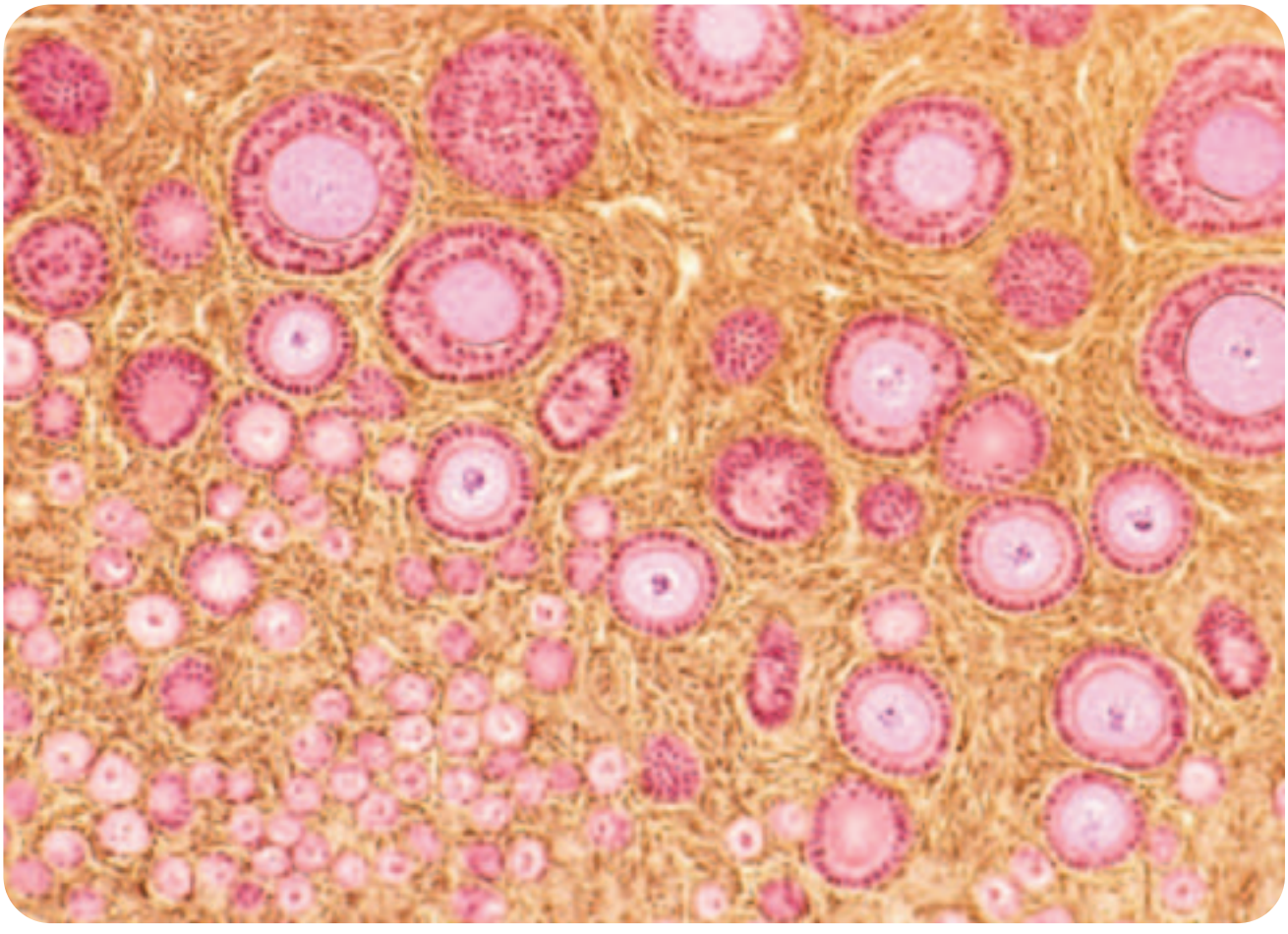
- **The last book you read?**
  Guns, germs and steel
  by Jared Diamond
- **And the last film you saw?**
  Rush – on the rivalry between F1 drivers James Hunt and Niki Lauda. Excellent
- **Which living person do you most admire?**
  The Welsh rugby player Gareth Edwards
- **Do you have a favourite composer?**
  Angus Young

- **And a favourite novelist?**
  No
- **Great Britain or an independent Scotland?**
  Great Britain!
- **If not Scotland, where would you most like to live?**
  Wales
- **What natural gift would you most like to possess?**
  Diplomacy
- **When not working and editing, what's your favourite occupation?**
  Walking in the mountains, particularly in the snow
- **Where did you spend your last vacation?**
  Clackmannanshire, Scotland
- **Your favourite dinner?**
  Chicken curry and chips
- **And your greatest extravagance?**
  Wife

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

Anti-Mullerian hormone

Still shrouded in mystery



Although the measurement of AMH routinely precedes almost every ART cycle today, there is more to AMH than just the prediction of ovarian response. Indeed, writes Roy Homburg, there is much of AMH's role in ovarian pathology which is yet to be fully defined.

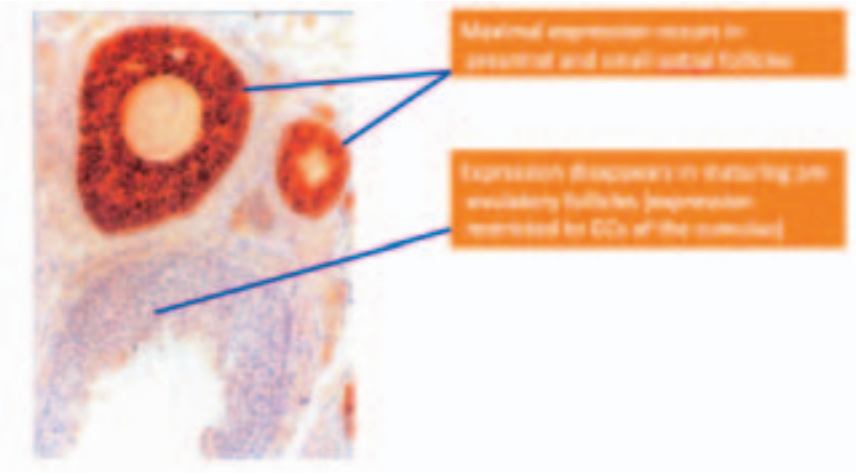
Any hormone that can convert a basically female foetus into a male within a few weeks of conception must be a focus of great fascination - and not only for embryologists. Anti-Mullerian hormone (AMH) derives its name from its function of causing regression of the Mullerian duct, the female reproductive tract. AMH is the first molecule to be synthesised and secreted by Sertoli cells at the time of seminiferous tubule organisation. Sexual dimorphism occurs at 6-8 weeks of gestation in the human and nothing remains of the Mullerian duct at 10 weeks, although secretion of AMH persists until

puberty in the male. Between the time of sexual dimorphism and puberty, the function of AMH remains a mystery.

It would have taken a prophet of biblical proportions to foresee that AMH would become such a leading predictor of ovarian reserve many years after its discovery as an 'anti-feminine' hormone. Its functions in the female are now being intensively investigated and a few more surprises are probably yet in store.

AMH, a dimeric glycoprotein and member of the transforming growth factor-beta family, is produced by ovarian follicular granulosa cells in late preantral and small antral follicles. It seems to have a role in the regulation of folliculogenesis at the two extremes of this process: a) by restricting the progression of primordial follicle development, and b) by an inhibition of the sensitivity of antral follicles to FSH and inhibition of aromatase activity during an ovulatory cycle.

Production of AMH is not seen in a maturing pre-ovulatory follicle, leaving an uninhibited FSH to carry the process further forward. These roles of AMH suggest not only that it plays an important function in the regulation of folliculogenesis but also that its concentrations are able to reflect ovarian reserve or, more practically, the number of small antral follicles in a cohort available for ovarian stimulation. The age-related decline in ovarian reserve is mirrored by serum AMH concentrations, which can also reliably predict the number of oocytes collected following ovarian stimulation or, at the least, enable a prediction of low, normal and high responders.



AMH is produced by ovarian follicular granulosa cells in late preantral and small antral follicles, but is not expressed in pre-ovulatory follicles.
(Reproduced with kind permission of Hamish Fraser and Richard Anderson.)

Response to stimulation

The ability of AMH to predict ovarian response enables planning of the stimulation protocol, in particular, whether with a GnRH agonist or antagonist and at what starting dose. Richard Fleming and Scott Nelson were the first to suggest recommended protocols for each range of AMH values, the purpose being to minimise the risk of ovarian hyperstimulation syndrome, maximise efficiency and patient comfort, and support the counselling of patients.[1] Clearly, patients with the very high and very low concentrations of AMH are those who demand the most attention. For example, the predicted high responders in our unit are given an antagonist protocol with a GnRH agonist trigger of ovulation and a maximum starting dose of 150 IU FSH. Predicted low responders are firstly counselled about their prognosis and given a flare protocol of GnRH agonist with a starting dose of 300 IU FSH - as in the table below. These are merely examples but they illustrate the usefulness of the predictive value of serum AMH concentrations.

Other predictors of ovarian response are well documented but AMH has definite advantages. Female age is fairly reliable, but serum concentrations of FSH measured on day 2-4 of the follicular phase should probably now be discarded and replaced by AMH. FSH concentrations, measured only in the early follicular phase and combined with an estimate of estradiol levels vary notoriously from cycle to cycle and are particularly unreliable in those under 40 years old. AMH, in contrast, is more reliable and varies very little throughout the cycle, and can therefore be measured at any time.

The antral follicle count has an equally good predictive value as AMH but, as well as needing good equipment, significant intra-observer differences and cycle-to-cycle variations have been reported.

Generally, the prognosis for achieving a pregnancy is influenced by the ovarian response to stimulation. However, this is far from being a *sine qua non*. The prognosis for pregnancy predicted solely by AMH levels has proved much less accurate than the

AMH (pmol/l)	FSH starting dose (IU/l)	GnRH Agonist/antagonist	Ovulation trigger
<5	300	Agonist flare	hCG
5 – 20	150 – 225	Antagonist	hCG
20 – 40	150	Antagonist	Agonist +1500 IU hCG on day of OPU
>40	Maximum 150	Antagonist	Agonist + freeze all

A suggested treatment plan according to serum AMH concentrations. This will vary according to personal preferences of the department but illustrates the possibilities involved. AMH – assayed with Beckman-Coulter Gen II kit.

prediction of ovarian response - perhaps understandably as so many other factors are involved. Although those with the higher levels of AMH clearly have a higher chance of success and those with lower levels a much lesser chance, pregnancies are not infrequently attained with very low concentrations of AMH.[2] This latter fact has been repeatedly reported, and the latest of these reports confirms that, although cancellation rate due to very poor response will be high with very low concentrations of AMH, pregnancy rates are far from negligible.[3] Presently, it cannot be recommended to deny treatment solely on the evidence of a low AMH concentration. A combination of age and AMH concentrations improves the prediction of a successful outcome but still leaves a lot to be desired.

Menopausal age

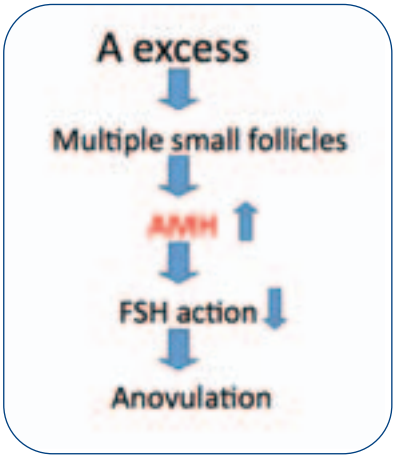
As AMH accurately reflects ovarian reserve, it was reasonable to assume that it could also predict the individual age at which the menopause would occur. There is growing evidence that this is indeed possible using a model built on age and AMH concentrations.[4] What does seem to be now well established is that AMH levels become undetectable approximately five years before the occurrence of menopause.

Prediction of the age of onset of the menopause should be especially useful for those attempting to plan their pregnancies, particularly as it may sound alarm bells if an earlier than usual menopausal onset is predicted, indicating the need for early intervention. A model to include mother's age at menopause, smoking and BMI, all factors known to influence the age of menopause, should narrow down the range of the prediction.

Accuracy of the assay

The development of an accurate assay for AMH has had a number of teething problems. Much confusion existed initially when two assays were available but, when the two were combined into a single assay (the Beckman-Coulter Gen-II enzyme-linked immunosorbent assay kit), it was hoped that a normal range of values according to age could be formulated more easily for clinical interpretation. However, a few hiccups in development of the assay remained. Now, a new method of pre-mixing the sample with a highly anionic assay buffer before plating will prevent complement interference and is said to improve stability. It is thus believed that the inconsistencies have been eliminated and, at last, an age-related standard normogram of AMH values can be accurately formulated for clinical application.[5]

A possible role for AMH in the anovulation associated with PCOS.



Polycystic ovarian syndrome

If I have described AMH as a mysterious hormone, then polycystic ovary syndrome (PCOS) can certainly be described as a mysterious syndrome whose aetiology remains unexplained. When the two become intertwined, it poses some intriguing questions.

As AMH reflects the number of small antral follicles and the polycystic ovary has these in excess, it is no surprise that women with PCOS have high serum concentrations of AMH. However, this is not the whole story, as the individual follicles of the polycystic ovary also produce more AMH than their size-matched counterparts in a normal ovary. Whether this is due to a genetically intrinsic property of polycystic ovary follicles or to the influence of androgens, LH or insulin is not known. It does, however, suggest that AMH may well be involved in the pathophysiology of PCOS.

The severity of the symptoms of PCOS is directly related to the number of small follicles present in the ovary, which in turn is reflected by AMH levels. Serum AMH concentrations are thus able to distinguish between women with normal ovaries, with polycystic ovaries but ovulating, with oligomenorrhea and amenorrhea in ascending order of AMH levels.[6] Reduction in the number of follicles in the polycystic ovary, by wedge resection, laparoscopic ovarian drilling or simply by aging, frequently restores ovulation.

A key role of AMH in the aetiology of anovulation associated with PCOS is suggested by its known function in the inhibition of FSH action in promoting follicle growth, possibly by inhibition of FSH-stimulated FSH receptor production. The possible role of AMH in the pathophysiology of PCOS is

ROY HOMBURG: 'SERUM CONCENTRATIONS OF FSH MEASURED ON DAY 2-4 OF THE FOLLICULAR PHASE SHOULD PROBABLY NOW BE DISCARDED AND REPLACED BY AMH.'

hypothesised in the figure above.

It is reasonable to assume that AMH serum concentrations could provide a cut-off level for the diagnosis of PCOS, but vagaries of the different assays so far used for this purpose and unconvincing values for specificity and sensitivity have made this difficult. Presently, PCOS is probably still best diagnosed on clinical criteria outlined by the Rotterdam consensus.

In summary, the emergence of the ability to measure AMH has added a great deal of spice into our daily practice and research. Its ability to indicate ovarian reserve and predict ovarian response to stimulation has distinctly improved our planning of ovarian stimulation protocols and so increased safety and efficiency as well as aiding in the counselling of patients. Refinements will be forthcoming, further enhancing intelligently planned individual treatment for IVF and the role of AMH in ovarian physiology and pathology has still to be completely defined. Revelation of the functions and possible further clinical applications of this initially mysterious hormone present an ongoing challenge for the clinician and researcher alike.

Professor Roy Homburg is a specialist in gynaecology and fertility at the Homerton University Hospital and Queen Mary, London, and Maccabi Medical Services, Israel.

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IN PROFILE Chris Barratt, continued from page 19

So why do you think the male has been so neglected?

One of the difficulties is the techniques of diagnosis. For example, most people can't actually count sperm. It's a statistical fact. You can train them to count sperm and then they will do it much better. Yet that rarely happens. In fact, the only thing you can guarantee are different results from the same sample. That's a crazy situation, so how can we ever make progress when we can't even perform the basics of sperm counting? ESHRE has been running semen analysis courses for years and they all show the same thing - if done well, if done properly, the answers are reliable, but mostly that's not the case. That's why in male infertility the area of weakness is diagnosis. We know how to do it, but we're not actually doing it. And that is fundamental to any progress. Another reason for the neglect is the perception that the sperm cell does nothing more than deliver DNA to the embryo - but it has to be delivered in the right way, packaged in the right way. There's a lot to come from the sperm cell to get the egg started in the right way. The contribution of male and female gametes is equal, but that's rarely the perception. The sperm cell is also much more difficult to study as a cell - it doesn't do transcription or translation, and it moves.

Finally, Chris, we're here in Scotland, where there's a great tradition of research in reproduction.

Well, I'm originally from Wales, but the tradition in Scotland is very strong and I'm glad to be part of that - but I'm also glad to be part of the bigger picture in the UK and Europe. But it is certainly true that we have high quality services in Scotland and very strong research centres - in Glasgow, Edinburgh, Aberdeen and of course here in Dundee. For a relatively small country it has made a huge contribution.

FISH-based PGD and PGS

A collaborative PGD Consortium evaluation

The latest published data collection by the ESHRE PGD Consortium recorded the outcome of 7912 FISH-PGD and 23,758 FISH-PGS cycles and reported seven and 12 adverse misdiagnoses in the respective groups.[1] These are cases in which there is the initiation of an affected pregnancy or the birth of an affected child. The number of reported misdiagnoses is probably an underestimate, as many embryo transfers have no follow-up (pregnancy or birth) and only a minority of PGD centres perform re-analysis of untransferred supernumerary embryos.

Here we report on a multicentre study whose main objective was to identify the validity of FISH-based PGD/PGS by comparing results at the time of PGD with the results of the embryo follow-up analysis in a cohort of samples. The secondary objective was to identify factors which may influence the validity of FISH-based PGD, including protocol-related parameters, embryo quality and embryo biology.

All ESHRE PGD Consortium centres were invited to participate in this retrospective study by completing a coded format database on PGD/PGS embryo (re)analysis using FISH. Initially, 18 centres showed interest, and ten actually submitted data which met the inclusion and data integrity criteria. With respect to embryo development, this comprised continuously developing embryos up until day 3 or day 4 post-fertilisation (pf), embryos reaching at least morula stage on day 5 pf or embryos reaching at least early blastocyst stage on day 6 pf.

The following data were requested: PGD indication; embryo morphology grade at day of biopsy; number of biopsied cells; multinucleation in biopsied cells; number of cells diagnosed/analysed; number of chromosomes analysed; result PGD/PGS analysis; 'no result rescue'(Y/N); day of re-analysis; embryo morphology grade at day of re-analysis; and result of re-analysis.

PGD/PGS analysis was coded 'euploid' (diploid, diploid male, diploid female, normal/balanced), 'aneuploid' (aneuploid, aneuploid male, aneuploid female, unbalanced), 'no result' or 'inconclusive'.

Result of re-analysis was reported as 'euploid' (diploid, diploid male, diploid female, normal/balanced), 'aneuploid' (aneuploid, haploid, aneuploid male, aneuploid female, unbalanced), 'mosaic' (diploid/ aneuploid mosaic, aneuploid mosaic, diploid/haploid mosaic, diploid/polyploid mosaic, chaotic),'no result' or 'inconclusive'.

Centres were asked to specify the abnormalities found both on the day of PGD/PGS analysis and on the day of re-analysis, as well as the number of cells with each abnormality (at re-analysis). The latter parameter was used to align the concordance criteria across all embryos from different centres. Re-analysis data further included the number of normal cells, number of cells with the same abnormality as on day of PGD and number of cells with an abnormality different from that on day of PGD.

In total, data from 1012 embryos were received. The number of cells diagnosed at re-analysis varied from two to 180. Cut-off values for data inclusion were based on mean cell numbers observed across centres. These included >10 cells on day 4 pf (120 out of 267

Results at PGD/ PGS analysis	Result at re-analysis	Category
Euploid (embryo not transferred, not cryopreserved)	All cells euploid	Concordant
	Mosaic - euploid >aneuploid	Concordant
	Mosaic - euploid <aneuploid	Discordant
	Mosaic – aneuploid	Discordant
	All cells same aneuploidy	Discordant
Aneuploid	All cells euploid	Discordant
	Mosaic - euploid >aneuploid	Discordant
	Mosaic - euploid <aneuploid	Concordant
	Mosaic aneuploid - identical to biopsy >other aneuploidies	Concordant
	Mosaic aneuploid - identical to biopsy <other aneuploidies	Discordant
	Chaotic	Concordant
	All cells other aneuploidy	Discordant

Table 1. Concordance criteria.

PGD/PGS analysis	Embryo re-analysis	Result 1-cell biopsy	Result 2-cell biopsy
Aneuploid	Aneuploid	Concordant 212/255 (83.1%)	Concordant 76/87 (87.4%)
Aneuploid	Euploid	Discordant 43/255 (16.9%)	Discordant 11/87 (12.6%)
Euploid	Euploid	Concordant 29/35 (82.9%)	Concordant 1/2 (50%)
Euploid	Aneuploid	Discordant 6/35 (17.1%)	Discordant 1/2 (50%)

Table 2. Impact of number of cells biopsied on level of concordance.

PGD/PGS analysis	Embryo re-analysis	Result grade 1 embryos	Result grade 2 embryos	Result grade 3 embryos
Aneuploid	Aneuploid	Concordant 184/218 (84.4%)	Concordant 86/104 (82.7%)	Concordant 18/20 (90%)
Aneuploid	Euploid	Discordant 34/218 (15.6%)	Discordant 18/104 (17.3%)	Discordant 2/20 (10%)
Euploid	Euploid	Concordant 17/19 (89.5%)	Concordant 12/16 (75%)	Concordant 1/1 (100%)
Euploid	Aneuploid	Discordant 3/19 (10.5%)	Discordant 4/16 (25%)	Discordant 0

Table 3. Impact of embryo grade at day of PGD/PGS analysis on level of concordance.

PGD/PGS analysis	Embryo re-analysis	Result grade 1 embryos	Result grade 2 embryos	Result grade 3 embryos
Aneuploid	Aneuploid	Concordant 107/132 (81.1%)	Concordant 121/140 (86.4%)	Concordant 60/70 (85.7%)
Aneuploid	Euploid	Discordant 25/132 (18.9%)	Discordant 19/140 (13.6%)	Discordant 10/70 (14.3%)
Euploid	Euploid	Concordant 12/14 (85.7%)	Concordant 12/14 (85.7%)	Concordant 6/9 (66.7%)
Euploid	Aneuploid	Discordant 2/14 (14.3%)	Discordant 2.14 (14.3%)	Discordant 3/9 (33%)

Table 4. Impact of embryo grade at day of reanalysis on level of concordance.

embryos), >27 cells on day 5 pf (256 out of 700 embryos), >22 cells on day 6 pf (15 out of 40 embryos) and >25 cells on day 7 pf (3 out of 5 embryos). The data from day 7 embryos were not further analysed.

In all, 394 embryos met the cell number criterion. They had been analysed for X-linked disease (n= 28), Robertsonian translocation (n=35), reciprocal translocation (n=102), aneuploidy (n=224) or other abnormality (n= 5). Of these 394, 379 gave informative results and were included for further analysis.

Large differences in embryo grading, number of cells biopsied and/or analysed and definition of mosaicism were observed, creating wide heterogeneity of the data, To enable data analysis, diagnostic concordance was based on the result observed in the majority of the cells at reanalysis (Table 1).

All embryos included in the study had either been diagnosed during PGD/PGS as chromosomally abnormal or were of poor quality and unsuitable for reproductive purposes. Overall, there was great heterogeneity of protocols appled: the cohort included cycles for a wide range of indications (chromosomal abnormalities) which were analysed using a wide variation of probe combinations, and the embryo samples included a varying proportion of cells. Thus, an assessment of the sensitivity and specificity of the FISH-protocols was not possible.

The impact of number of cells biopsied, embryo grade at day of analysis, embryo grade at day of reanalysis, and day of reanalysis on the level of concordance are presented in Tables 2, 3, 4 and 5, respectively.

Because of low numbers or the nature of the data, the results of this study do not reach statistical significance. However, certain trends are observed:

1. Concordance in aneuploid embryos seems to slightly higher when two cells are biopsied for PGD/PGS rather than one. This is to be expected given the high percentage of mosaic embryos on day 3 pf. No comparison can be made for euploid embryos due to the low number of embryos in the two-cell biopsy group.
2. Embryo grade at day of PGD/PGS analysis seems to

PGD/PGS	Embryo re-analysis	Result day 4 re-analysis	Result day 5 re-analysis	Result day 6 re-anlysis	Result day 7 re-analysis
Aneuploid	Aneuploid	Concordant 89/103 (86.4%)	Concordant 187/224 (83.5%)	Concordant 10/13 (76.9%)	Concordant 2/2 (100%)
Aneuploid	Euploid	Discordant 14/103 (13.6%)	Discordant 37/224 (16.5%)	Discordant 3/13 (23.1%)	Discordant 0
Euploid	Euploid	Concordant 6/8 (75%)	Concordant 21/26 (80.8%)	Concordant 2/2 (100%)	Concordant 1/1 (100%)
Euploid	Aneuploid	Discordant 2/8 (25%)	Discordant 5/26 (19.2%)	Discordant 0	Discordant 0

Table 5. Impact of day of re-analysis on level of concordance.

have little impact on level of concordance in embryos diagnosed as aneuploid, whereas the level of concordance in euploid embryos seems to decrease in embryos of less quality. This is in line with the many studies that have shown increased aneuploidy and mosaicism rates in embryos of poor quality
3. As could be expected, the level of concordance in embryos diagnosed as euploid decreases when embryos are of less quality on day of re-analysis. Likewise, fewer euploid embryos are found on re-analysis in the group of poor quality embryos compared to the group of good quality embryos when PGD/PGS analysis revealed an aneuploid result.
4. Data from Table 5 seem to support the hypothesis that the incidence of chromosomal abnormalities and level of chromosomal mosaicism decreases when cleavage stage embryos develop into morulae and/or blastocysts.

This report describes the results of a collaborative effort. Due to the many different conditions used by the participating centres (in vitro culture system, embryo grading system, biopsy strategy, PGD/PGS, probe strategy, mosaicism definition etc.) the data pool cannot be considered uniform and reliable enough to draw definite conclusions. As an observational study, it has confirmed the presence of chromosomal mosaicism at different stages of human embryo development, which is something that should be taken into account when designing a PGD/PGS test in order to optimise clinical PGD/PGS results.

Tugce Pehlivan, Edith Coonen and Joanne Traeger-Synodinos on behalf of the ESHRE PGD Consortium Steering Committee

● The authors greatly acknowledge the centres who provided data for this report:
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Working groups, e-learning and a new Steering Committee Chair

The following topics were reviewed at the PGD Consortium Steering Committee annual meeting in March.

Data collections

Data XII has just been published and the evaluation of data collections XIII, XIV and XV are on course. Céline Moutou and Martine de Rycke are working on finding a suitable online database which we hope will be available for the next data collection at the end of this year.

New technologies

The working group to monitor new technologies in PGD, chaired by Martine de Rycke, has completed its evaluation of returned questionnaires and initiated the writing of a paper. All participants will be informed of progress in due course.

HLA matching

The working groups to follow-up PGD cycles performed for HLA (to be chaired by Jan Traeger-Synodinos), and the other to look into collaborative working practices between genetics and IVF teams in the context of a PGD service (to be chaired by Sioban SenGupta) are planned to be launched in a few months.

Steering Committee annual meeting. From left, Ursula Eichenlaub-Ritter, Céline Moutou, Veerle Goossens, Joanne Traeger-Synodinos, Joep Geraedts, Martine de Rycke, Edith Coonen, and Sioban SenGupta.

E-learning

The topics of two interactive webinars for PGD Consortium members have finally been selected. The first, *HLA PGD and clinical utility: A discussion* is planned for the beginning of May and the second, *FISH or CHIPs – how to diagnose chromosome abnormalities in embryos by PGD,* is planned for the beginning of October.

All Consortium members will be notified of the exact date and time, along with instructions on how to register and take part.

Finally, Jan Traeger-Synodinos will be stepping down as Chair in Munich. Jan will stay on as Past Chair and Edith Coonen will become the new Chair. Members will soon be informed about elections for a new Steering Committee member. We look forward to seeing all PGD Consortium members at the annual PGD Consortium meeting, which will be held on Monday 30 June directly after the PGD Consortium presentation in the main programme in Munich. Details will be sent out to all PGD Consortium members in due time.

Jan Traeger-Synodinos
Chair Steering Committee

Combined Campus workshop on epigenetics for September

The report of a major expert meeting of ESHRE and the European Society of Human Genetics held in 2012 on **Current issues in assisted reproduction and genetics in Europe; research, clinical practice and policy** was published in the *European Journal of Human Genetics* in November.[1]

An approved paper on **Genetic screening of gamete donors: ethical issues** initiated by Task Force Ethics & Law with input from the SIG RG will be published soon in *Human Reproduction* as an ESHRE paper.

Forthcoming events

Because our Campus meeting in Prague last September on the **Application and challenges of emerging technologies in preimplantation and prenatal diagnosis** was so very well attended, we are now planning **An update on PGS** with the PGD Consortium on 12-13 March 2015 in Rome. This Campus workshop, organised by Joyce Harper, Ursula Eichenlaub-Ritter and Francesco Fiorentino, will provide an overview of results from the latest RCTs and critically discuss the new technologies in PGS.

A second Campus workshop in 2014 on **Epigenetics in reproduction** will take place on 26-27 September in Lisbon organised by Carlos Plancha. This meeting is hosted by the SIGs RG and Embryology and by the Task Force Basic Science. More details and registration formalities are on the ESHRE website. The workshop will provide an overview of epigenetics from gametes to embryo and beyond, with updated information on environmental effects and epigenetics in ART.

This year's Precongress Course at the Annual Meeting in Munich is a joint event of the SIG RG and PGD Consortium reviewing **The current status of PGD and PGS**. The course aims to attract a wide audience of those working in PGD/PGS and in embryology. It will hopefully open up new discussions on the outcomes of PGD/PGS, review developments in cell biology and the consequences of aneuploidy in the preimplantation embryo, discuss the relevance of mitochondrial disorders and consider ethical dilemmas in PGD/PGS.

The business meeting of the SIG RG take place on Tuesday 1 July during the lunch break.


Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy

The 20-page update report of the second expert meeting of ESHRE, ESHG, and EuroGentest2 on 'current issues' in assisted reproduction and genetics was published in November.

Recent events

A Campus workshop convened with the SIGs Stem Cells and Andrology and Task Force Fertility Preservation in Severe Disease took place at the end of April in Brussels under the guidance of Karen Sermon, Ursula Eichenlaub-Ritter, Stephan Schlatt and Helen Picton. **Stem cells: origins, genetics, properties and significance for fertility preservation** took place after *Focus on Reproduction* went to press and a full report will be included in the September issue.

E-learning

The SIG RG has been working with Central Office on the development of ESHRE's e-learning programme. Lectures from last year's Precongress Course on epigenetic mechanisms and genome scanning are already on the ESHRE website under Education. The first educational presentations by members of the SIG RG and PGD Consortium have been recorded and will soon be available to ESHRE members. These include an update from the PGD Consortium (Jan Traeger-Synodinos), accreditation of a PGD centre (Sioban SenGupta and Mike Morris), an introduction to genetics (Joep Geraedts) and a lecture on embryo biopsy (Georgia Kokkali). As reported opposite by the PGD Consortium, we are now planning two webinars for members of the PGD Consortium in 2014.

Ursula Eichenlaub-Ritter
Co-ordinator SIG
Reproductive Genetics

1. Harper JC, Geraedts J, Borry P, et al. Current issues in medically assisted reproduction and genetics in Europe: research, clinical practice, ethics, legal issues and policy. Eur J Hum Genetics 2013; 21: S1–S21.

Certification moves towards Lisbon

AGM agenda for Munich, with new Chair of the Paramedic Board

Nurse and midwives certification

Following progress reports in previous issues of *Focus on Reproduction*, the certification working group continues to move ahead towards the first certification exam in Lisbon in 2015. In January this year the log book and first draft of the reading list were introduced as the first practical step in this long process. We are now finalising the reading list and developing the examination questions for Lisbon. All nurses and midwives who are contemplating sitting the exam in Lisbon can start today with the log book. The log book is downloadable from the ESHRE website (under 'Accreditation and Certification') and must be completed over a maximum period of two years. The log book must provide the name and city of your clinic, the name and e-mail address of your supervisor, and record your involvement in the diagnostic, information and clinical consultations in which you have observed, assisted or performed.

Basic training

Our popular basic training course will be held for the fifth time in Paris from 15-17 May 2014. We are happy to organise this course in Paris and would like to thank the local organising committee and especially Valérie Blanchet de Mouzon for all their work. The course will a great opportunity for nurses, midwives and lab technitions (especially from France) to see how ESHRE can help develop their skills - and to meet paramedics from other countries. The course is not only interesting for nurses, midwives and lab technicians new to the field but also for those wishing to refresh their basic knowledge in preparation for the Clinical Embryologist Certification test in Munich.

The course will cover anatomy, diagnosis, lifestyle factors affecting infertility, counselling and communication skills, andrology, embryology and cryopreservation, fertility drugs, EU directives in daily practice, and treatments. Participants and speakers also have the opportunity to take part in discussion,

At the end of the course participants should have a basic understanding of all these topics to provide a minimum standard of care and equip them for further learning and professional development. The course promises to be a fulfilling educational and wonderful experience, with a dinner arranged at the famous Parisian brasserie of La Coupole on 16 May. Commercial sponsors are welcomed. You can find out more and register on the ESHRE website.

Precongress course Munich

Our precongress course this year will be on **Targeting and managing special patient groups - including**

PARAMEDICAL BOARD AGM

The Paramedical Board encourages all paramedical members to join their Annual General Meeting (AGM) in Munich. The meeting will be held on Monday 30 June during the lunch break. The agenda is as follows:

1. What is ESHRE?
2. The Paramedical Group
3. Society activities
4. ESHRE Certification for Nurses and Midwives
5. Annual Meeting Lisbon 2015 – Paramedical programme
6. Any other business
7. Date of the next AGM

In Munich Helen Kendrew, Matron at Bath Fertility Centre in the UK, will take over as Chair of the Paramedical Board from Helle Bendsten, whose term of office will come to an end. Helen, worked as a nurse member on the committee reviewing the NICE guidelines published in 2013 and was also the nurse representative on the 'One at a Time' advisory group. She is an Expert Advisor to the UK's regulatory authority (HFEA) and says she is delighted to be taking the chairmanship of the Paramedical Board.

After eight years Inge Rose Joergensen will step down from the PMG board. As a nurse member of the Board, she was responsible for many good ideas that were put in place in recent years, and her ideas, organisation skills, and enthusiasm will be much missed.

Inge will be replaced by Annick Geril, midwife at Ghent University Hospital, Belgium. Two applications for the position were received, with the selection based on review, interview and the Board's membership balance according to location and expertise. After the interviews all Board members individually ranked the candidates, with scores on 15 topics. Annick scored highest, and will present herself at the AGM in Munich.

Helen Kendrew, incoming Chair of Paramedical Board.

Midwife Annick Geril, new member of the PM Board.

hands-on workshops in trophectoderm biopsy. This is an advanced course planned to provide an update on the current theoretical background, hands-on treatment and support for patient with endometriosis, genetic disorders and recurrent miscarriages. There will be an interactive session in counselling with a emphasis on nurses, midwives and counsellors working in a fertility clinic. For those working in the lab there will be a practical demonstration with hands-on training in trophectoderm biopsy. The workshop will summarise the most important features of successful biopsy, including pretreatment of the embryo, timing of the biopsy, and co-ordinated use of laser and micromanipulator. Techniques will be demonstrated on mouse blastocysts.

Other events

Our next Campus course is jointly organised with the SIG Early Pregnancy. The theme is **Bringing evidence based early pregnancy care to your clinic**, with topics covering new studies, endometrial effects, patient wellbeing, and the role of 'embryoscopy'. For such an important symposium we have chosen a wonderful winter venue -Copenhagen - on 11-12 December 2014. We have an exciting line-up of speakers and the interaction between our two groups promises much discussion. There are more details in the SIG Early Pregnancy report below.

Helle Bendsten, Chair
Jolieneke Schoonenberg-Pomper, Past Chair
Paramedical Board

Nurse certification group meeting in Amsterdam in March. From left, Helen Kendrew, Catherine Plas, Jolieneke Schoonen berg-Pomper, Helle Bendsten, Inge Rose Jorgensen, Eline Dancet, and clinical adviser Anja Pinborg.

SIG EARLY PREGNANCY

The role of endocrine factors in early pregnancy

Precongress course Munich

Our Precongress Course this year will be held in collaboration with the SIG Reproductive Endocrinology. Its theme - **The contribution of endocrinology and early pregnancy management to the success of an ART centre** - reflects the important role of reproductive endocrine factors in recurrent pregnancy loss, both after spontaneous pregnancy or after ART. The most updated scientific information will be presented, and speakers and participants are encouraged to take part in discussion.

The course has been organised for reproductive endocrinologists, fertility specialists, psychologists, gynaecologists and reproductive nurses, and focuses on the effects of obesity on early pregnancy loss and child health, the stategies and benefits of periconceptional lifestyle interventions and clinically relevant endocrine aspects of implantation and pregnancy. There will be a challenging debate on the treatment of preconceptional subclinical hypothyroidism to foster fecundity, prevent early pregnancy loss and optimise child health.

Winter Campus meeting

As noted in the Paramedical report, our joint Campus course in December will feature evidence-based considerations in early pregnancy. Early pregnancy complications, such as miscarriage, recurrent miscarriage and ectopic pregnancy, are prevalent and can have a major impact on women's lives. It is important that all clinicians treating patients with these conditions provide high quality, evidence-based care. Interactive discussion will be encouraged. The course will provide participants with guidance for the implementation of new evidence. There will be round-table discussions where participants can raise their questions with our expert speakers. The course will held at the Tivoli Congress centre in Copenhagen shortly before Christmas (11-12 December).

Mariëtte Goddijn
Co-ordinator SIG Early Pregnancy

Fertility preservation: from promise to practice

In March a broad collaboration of ESHRE's SIGs Safety and Quality in ART, Psychology & Counselling, Ethics & Law, Task Force Fertility Preservation in Severe Diseases and Paramedical Group hosted a well attended two-day Campus course on fertility preservation. Willianne Nelen, Co-ordinator of the SIG SQART and on behalf of her fellow organisers, reports on proceedings.

Focus of attention of this very popular Campus course was how to support the bridge between promising technological techniques and their actual implementation in everyday clinical practice. Fertility preservation was presented from different perspectives, as illustrated by the course's title, **From technique to implementation in daily practice**. One interesting feature of this workshop was the very active participation of patients, who impressively shared with the audience their own experiences of fertility and cancer treatment. The direction of the workshop could not be better shaped than by their stories.

The programme on the first day began with state-of-the-art lectures on fertility preservation options for boys, girls, men and women. Clinical indications, collection and cryopreservation techniques, safety issues, success rates, implications, requirements, and current utilisation rates were mainly presented as options for sperm, stem cell, testicular tissue, embryo, oocyte and ovarian tissue cryopreservation. Of special interest were the large practice variations between different European countries - for example, with centralised care or not, or with or without transportation of cells and tissues. In addition, the large differences in reimbursement and legal restrictions were quite clear.

The programme moved on with lectures on known pregnancies after fertility preservation. It was stressed that (long-term) follow-up of these techniques is important and international registries are needed.

The importance of referral and high quality care was a recurring theme: easy access of care, multidisciplinary collaboration - locally as well as (inter)nationally, as in guideline development - dedicated team members and care according to patients' preferences and needs.

Tools such as patient websites, leaflets, communities and decision aids were presented from all over the world as illustrations of personalised their care. Of special interest was a decision aid for younger women with breast cancer from the Breast Cancer Network of Australia (http://www.bcna.org.au/fact-sheets-and-booklets) and information materials from (inter)national organisations such as the American Oncofertility Consortium (http://oncofertility.northwestern.edu/patients/fertility-preservation-options-nu), fertile HOPE and the International Society of Fertility Preservation (http://www.isfp-fertility.org/books/principles-and-practice-of-fertility-preservation/). Initiatives such as the national AYA platform (http://www.aya4net.nl/) for young cancer patients, where a community is formed together with their care givers and health care professionals, are innovative and promising.

The second day the programme concentrated on communication. First, the barriers and facilitators in raising fertility preservation questions were addressed. This was done by summarising the multidimensional problems in this kind of communication. For instance, issues such as decision making while under the threat of cancer, the problems associated with communication between doctors, parents and teenagers. Nevertheless, it was repeatedly emphasised that young adult patients and cancer survivors increasingly talk about infertility as a significant survival concern. They welcome any time allocated to fertility counselling and preservation, but also for information about contraception, sexuality, and body image. Examples of facilitators were actively introducting these topics to patients, patient education materials and patient decision aids. These services help health care providers and encourages patients.

There was also special attention paid to the long-term fertility-related communication needs of cancer survivors. The overall message was, 'fertility matters!' Fertility does have an impact on final recovery and raises a need for new information on subjects such as life planning, social identity and fertility. Long-term communication can be improved by clear, user-centred, proactive and non-judgemental healthcare professionals.

The issues of informed consent in the case of incompetent children and equity of care were discussed. In general, parents are given decision-making power for medical interventions in children judged to unable to make these decisions. The question is whether the parents should decide on the basis of a substituted judgement standard, a best interest standard, or on the argument of autonomy.

A review of sperm banking and counselling showed inequality throughout Europe - and a large gap between patient preference and need, and between recommended care within clinical guidelines and actual care.

New guidelines ready for review in Munich

Plans for Munich

We are now looking forward to your contributions and attendance at the Annual Meeting in Munich, where we are excited to collaborate with the SIG Safety and Quality in ART for our annual Precongress Course. The course is titled **On seeking evidence from different perspectives: patients and professionals' views** and centres around questions on the value of evidence, our patients' perception of evidence, their choice of treatments without evidence, the role of placebo, and the role of communication in translating evidence into patient behaviour. These fundamental questions will be discussed from the perspective of patients, doctors, basic scientists, psychologists and yoga experts.

In addition, our Past Co-ordinator Chris Verhaak has set up a collaboration with the Task Force on the Management of Fertility Units and Fertility Europe to organise course 14 on **New generation patients**. This course aims to provide medical and paramedical staff in IVF units with useful information on the emerging populations of patients and on the tools appropriate to their specific needs. We hope you will join us in Munich for these interesting presentations and discussions.

Finally, we invite our members to join us for the next SIG business meeting, which will take place after the precongress courses at 17.00 on Sunday 29 June. This meeting is an excellent opportunity to let us hear your suggestions for future courses and workshops and for us to fill you in on all our current and future activities.

The new *Psychology and Counseling Guidelines* will also be presented in Munich and made available for review from all relevant stakeholders. We invite everyone interested to read the guidelines and offer us his/her views on their usefulness and the feasibility of implementation in clinics. The aim of the guidelines is to offer best practice advice on how psychosocial care can be incorporated into daily practice to the benefit of patients and healthcare providers in the field of infertility and medically assisted reproduction.

The guidelines will focus on the types of psychosocial care which should be delivered to all patients in fertility clinics, regardless of their idiosyncrasies and treatment choices. They will also clarify when, how and who should be referred to more specialised psychosocial care. The guidelines review is a compulsory step in the implementation process. Once all reviews are submitted, the Guidelines Committee will address all feedback and make relevant changes before presenting the final document.

Uschi Van den Broeck
Co-ordinator SIG Psychology & Counselling

STEERING COMMITTEE

Uschi Van den Broeck (BE), Co-ordinator
Sofia Gameiro (GB), Deputy
Cora de Klerk (NL), Deputy
Mariana Martins (PT), Junior Deputy
Christianne Verhaak(NL), Past Co-ordinator

First project to gather data on 'social' oocyte cryopreservation

As a newly created SIG, we are busy consolidating the collection of data on oocyte freezing for self use. This started as a project to assess storage and use of the growing practice of 'social' or 'non-medical' oocyte freezing, an obvious task considering our special interest in social issues and reproduction.

However, there also seems to be little data on the storage and use of oocytes for medical indications in various European countries, and this may also warrant more scrutiny. We already have several committed collaborators from Belgium, Czech Republic, Italy and Spain, but we are also contacting all members of ESHRE's Committee of National Representatives with a few simple questions about their respective national practices. Hopefully, we can gather more interested parties to collaborate. We will have a lunchtime meeting during the Annual Meeting in Munich, where the Steering Committee will report on the first details and steps of this project.

Later on this year, we will be taking part in the EIM meeting scheduled to take place in Leuven in November, with a presentation on socio-cultural factors and legal aspects of access to ART

For 2015, the SIG Ethics & Law has proposed a Precongress Course on the subject of **Current information and communication practices in reproductive medicine: challenged by the internet?**, and we are pleased to be able to collaborate.

Françoise Shenfield
Co-ordinator SIG Socio-Cultural Aspects of (In)fertility

STEERING COMMITTEE

Françoise Shenfield (GB), Co-ordinator
Paul Devroey (BE), Deputy
Anna Pia Ferraretti (IT), Deputy
Virginie Rozée (FR), Junior Deputy

IVF without the threat of OHSS

Campus meeting on GnRH agonist triggering

Swings and roundabouts. Faculty of the POI Campus workshop held in Utrecht in December.

The SIG RE held a very successful workshop in Utrecht in December on primary ovarian insufficiency, an update and presentation of progress on the forthcoming ESHRE guideline. More than 160 participants heard a distinguished group of experts discuss all aspects of premature ovarian failure, including its association with genes and autoimmunity, the diagnostic work-up in suspected POI patients, its long and short-term health implications, our ability to forecast POI, and its management.

Future activities

This year's Precongress Course in Munich, **The contribution of endocrinology and early pregnancy management to the success of an ART centre**, is organised by the SIGs RE and Early Pregnancy. The course will provide an update of clinically important research areas of reproductive endocrinology at the intersection with routine fertility treatment with a special focus on reproductive success/failure and recurrent pregnancy loss.

In the meantime, everything is ready for our Campus meeting of 2014 on **Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering**, which will take place in Thessaloniki, Greece, on 31 October-1 November. The course will present a critical review of the use of agonist triggering for the elimination of ovarian hyperstimulation syndrome. World-renowned specialists in the field will provide a state-of-the-art update on GnRH agonist triggering and will address controversial areas regarding the safety and effectiveness of the method. Focus will be put on the problem of OHSS as assessed by its incidence, prevalence, morbidity and mortality, as well as its pathophysiology and predictability. Additional discussions will cover the extent to which the preovulatory LH peak is affected by GnRH agonist triggering, how efficiently agonist triggering leads to corpus luteum formation, and how endometrial gene expression is altered by agonist triggering. The central debate of the course will focus on GnRH agonist triggering as an optimal strategy for OHSS prevention in IVF, as well as on the difficulties and advantages of other approaches, such as a 'freeze-all' embryos approach with transfer in subsequent cycles, luteal phase rescue with small doses of hCG, and steroid supplementation.

Our ESHRE Campus event in 2015 will take place in Helsinki and will be titled **Old and new in reproductive endocrinology**. And for our Campus meeting in 2016, I would like to invite all SIG RE members to send their proposals to me at stratis.kolibianakis@gmail.com. These will be discussed by the steering committee and the best of them presented during the business meeting of our SIG in Munich.

Stratis Kolibianakis
Co-ordinator SIG Reproductive Endocrinology

STEERING COMMITTEE

Efstratios Kolibianakis (GR), Co-ordinator
Frank J. Broekmans (NL), Deputy
Daniela Romualdi (IT), Deputy
Terhi Piltonen (FI), Junior Deputy
Georg Griesinger (DE), Past Co-ordinator

Time for an update of ESHRE's guide to good laboratory practice

Six years has passed since publication of our last review of good laboratory practice in IVF. We now consider it an appropriate time for update and the addition of new information. But the aim, as before, will be to help our embryologist colleagues do their work in a consistent and excellent way.

STEERING COMMITTEE

Maria José de los Santos (ES), Co-ordinator
Sophie Debrock (BE), Deputy
Giovanni Coticchio (IT), Deputy
Susanna Apter (SE), Junior Deputy
Kersti Lundin (SE), Past Co-ordinator

It is also the responsibility of ESHRE to acknowledge the European directives on tissues and cells, to comply with the regulations and to co-operate in their implementation. We also have a responsibility to evaluate the increasing number of technical and practical features now being

What's hot and what's not in stem cell research: time to choose

Led by the success of our Precongress Course in London, our PCC this year - **Of stem cells and gametes: more similarities than differences?** - will be focused on the differentiation potential of pluripotent cells into gametes. Speakers will provide an overview of the differentiation capacity of different kinds of stem cells, both embryonic, adult and induced pluripotent, towards gametes. Recent advances in understanding the differentiation process from the embryo to primordial germ cells will be explained, and alternative and controversial sources of cells for gamete derivation described (and debated!).

This course is not only for researchers in stem cell biology, but also and especially for embryologists and physicians interested in understanding the potential and state of research on in vitro gamete production. This subject will also be debated during the Stem Cells session of the scientific programme, 'From pluripotent stem cells to gametes and back'.

Headlines from stem cell research

Stem cells research is one of the most rapidly evolving fields in science. Shinya Yamanaka, John Gurdon (who will receive honorary membership of ESHRE this year), Shoukhrat Mitalipov, Jacob Hanna and many others have all presented surprising results in recent years. However, the interest and 'hotness' of stem cells research is a two-edged sword: on the one hand many astonishing results are obtained and publicised, but on the other so many rapid changes in the field make it difficult to review and compare the different results.

One clear example is the recent paper on iPS cells from Obokata and colleagues published in *Nature* in January.[1] The authors claimed to have found an easy reprogramming method to obtain pluripotent stem cells from adult cells without the need for viral transduction, nuclear transfer or chemicals. Just by exposing cells to a low-pH solution they were able to obtain a high percentage of reprogrammed cells. The work drew much attention and many headlines, but unfortunately other attempts so far have failed to reproduce the results. The report has had a rapid 'rise and fall', and now seems to be in the process of being retracted.[2]

This is only one example of how confusing results can be in this field. But this is one reason why the SIG Stem Cells, with the contribution of several distinguished scientists from other backgrounds, has begun working towards a position paper on the subject of stem cells in reproductive medicine; our aim is to give a clear view of what has really been done, what can be done and what has to be done with stem cells in reproduction. We'll be happy to update you over the coming months.

Rita Vassena
Co-ordinator SIG Stem Cells

1. Obokata H, Wakayama T, Sasai Y, et al. Stimulus-triggered fate conversion of somatic cells into pluripotency. Nature 2014; 505: 641-647.
2. See http://www.nature.com/news/stem-cell-method-faces-fresh-questions-1.14895?WT.ec_id=NATURE-20140320.

Researcher Haruko Obokata in March admitted 'grave errors' in her paper and the possibility of retraction.

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introduced which may help us to improve the outcome of our work in IVF. These updated guidelines will be produced according to the ESHRE guideline format and with a guideline development group.

E-learning

We are also participating in the the ESHRE e-learning project, with learning objectives for both clinical and senior embryologists - as well as all other interested ESHRE members! For those unable to attend precongress courses and other workshops, the e-learning platform will be one way to pick up some of that information. The system can also be used to earn credits for upgrading the ESHRE embryologists certificate. Those following an e-learning programme will be asked to answer a multichoice questionnaire in order to gain the educational credits. We also hope that those still working to obtain certification, will find the lectures a valuable addition to the recommended readings and other sources of study.

Time-lapse in Munich

Our Precongress Course this year focuses on the use of time lapse technology in the ART laboratory, a technique which is now revolutionising the concept of embryo culture and embryo assessment.

Maria José de los Santos
Co-ordinator SIG Embryology

Diagnostic recommendations planned based on new classification of genital tract malformations

With the ESHRE Certification for Reproductive Endoscopic Surgery (ECRES) now up and running, the SIG RS is now hoping to take an active part in the new ESHRE e-learning platform initiative. The ECRES process already incorporates online e-learning with a self-evaluation tool in its programme, and the SIG is looking forward to adding online lectures, self-evaluations tools and the presentation of working guidelines to the ESHRE platform.

Finally, following the new classification of female genital tract malformations, the SIG RS has now been working systematically to produce evidence-based recommendations for the screening and diagnosis of these malformations, which has been an area of ambiguity for many years.

Recent activities

The SIG RS has been kept pleasantly busy with the completion of two successful Campus symposia held in Leuven in November and March and organised by Stephan Gordts. The courses were fully booked, with a diverse group of attendees from all over the world. Most popular were the four hands-on sessions on laparoscopic and suturing techniques, while the live surgery lectures stimulated an even livelier debate among the audience. Popular lectures included tips and tricks for laparoscopic myomectomies, and the treatment of severe endometriosis and its relation to IVF.

The Symposium in Vienna in April on **The impact of reproductive surgery on cross talk between the embryo and the endometrium** was also a great success, attracting reproductive surgeons and IVF specialists alike. The course was significantly oversubscribed to the extent that we are already planning a second symposium for next year to meet the demand.

Future events

We have a very exciting Precongress Course set for Munich this year with the most topical theme of **Fertility-sparing surgery in malignant and benign conditions**. Lectures will cover the management of women with severe endometriosis, adenomyosis, multiple fibroids and pelvic tumours wishing to preserve fertility.

Later, in December, we have the pleasure of co-hosting with the SIG Endometriosis and Endometrium a joint Campus meeting in Liege on the sibject of **Controversies in endometriosis and adenomyosis**. This will be a unique and exciting bi-disciplinary course covering themes from genetics and epigenetics to the surgical treatment of these disorders.

Finally, plans are now under way to hold a course in Lyon next year on the popular topic of **Complications in endoscopic surgery**. A diverse range of topics will be covered, from preventing and managing specific surgical complications to dealing with complaints and litigation.

Tin-Chiu Li
Co-ordinator SIG Reproductive Surgery

Faculty and students during the March Campus course on endoscopy in reproductive medicine.

Keeping up with new developments in andrology

The SIG Andrology is working hard to keep up with the enormous pace at which the field of andrology is developing its novel ideas and concepts. As the Co-ordinator of the group I am truly enjoying the many challenges and opportunities created by strong research efforts to discover diagnostic features of sperm and potential opportunities to create male gametes.

Recent events

Together with the two SIGs Reproductive Genetics and Stem Cells we have planned a Campus meeting in later April on the origins, genetics, properties and significance for fertility preservation using stem cells. Andrological highlights of this workshop reveal options for the in vitro derivation of gametes from stem cells and potential epigenetic risks associated with 'artificial' gametes.

Future activities

At the upcoming Annual Meeting in Munich andrologists will have very exciting opportunities to learn more about new developments in andrology. The Precongress Course programme was designed by Sheena Lewis and Rafael Oliva and they have invited outstanding specialists to provide insights into sperm RNA for future andrological diagnostics and how ejaculate parameters may be used as a general read-out of male well-being. The sensitivity of steroidogensis in the fetal testis represents a highlight for the basic scientist and paediatrician, while our clinical andrologist colleagues will enjoy updates on the value of anti-estrogenic treatment in men, the controversy over diet and supplements in male fertility, and the usefulness of genetic testing in the male partner of couples approaching ART treatments. The programme will be of great value to any andrologist, particularly as it relies on evidence-based therapeutic strategies.

We are also privileged that so many outstanding research sessions have been scheduled in the main programme in Munich following the submission of an impressive number of high quality abstracts. Overall 22 oral communications will be presented in four andrological sessions under the headings of sperm DNA integrity, male infertility, genetics in andrology and novel techniques in andrology. The quality of abstract submissions truly reflects the outstanding research now being performed in andrology, and I am convinced that this high standard will continue. It's for this reason that we encourage all ESHRE andrologists to send us their outstanding research abstracts, so we can maintain ESHRE's role as a reference meeting for andrologists. This year's topics will not only set the agenda for the next couple of months but it is expected that future activities of SIGA will focus particularly on novel aspects of sperm analysis and molecular analysis of the infertile man.

We will also continue our efforts to improve and publish standardised methods and hope to implement external quality schemes throughout Europe, USA and Australia in conjunction with the WHO.

IUI again in the news

An 'old' andrological topic seems to come back with great frequency and promise, with recent reports and discussion indicating that IUI appears to be a useful approach in the treatment of mild and moderate male infertility. We will follow up these discussions and provide insights and recommendations after considering the latest clinical trials. It's my view that the technique may have been too critically assessed in the past. Indeed, with regard to fertility treatment in developing countries this cost-effective treatment may well see a revival when performed with accuracy and precision, says Willem Ombelet in his dual function as SIGA Deputy and Co-ordinator of the Task Force Developing Countries and Infertility.

In addition to the promotion of research and knowledge, we will continue our critical evaluation of tests for DNA integrity and chromatin changes in sperm, and maintain our highly rated semen analysis training and external quality assurance programmes.

Stefan Schlatt
Co-ordinator
SIG Andrology

One of Us million-signature petition against research on embryos reaches EU public hearing

- ESHRE describes pro-life arguments as 'misguided'
- Many MEPs express support for ESHRE's position

A public hearing before MEPs and European Commission officials in Brussels allowed the organisers of the pro-life 'One of Us' million-signature campaign to express openly their opposition to research involving embryos and its funding by the EU. Under the terms of the Initiative, the Commission must provide petitioners whose campaigns gather a million signatures with an opportunity to explain their ideas and demands in more depth. Following the hearing, which took place on 10 April, the Commission has until 28 May to provide a communication of response (which may go so far as to consider a change of legislation).

In explaining their European Citizens Initiative, the One of Us organisers stated that the desired outcome of their petition was 'a concrete ban on life-destroying policies in the EU budget'. ESHRE, not surprisingly, formally objected to the One of Us claims, describing the arguments as misguided and ill-judged.

ESHRE's press release, issued to coincide with the public hearing, stated: 'ESHRE . . . has always based its ethical judgements on responsible science and a duty of care to infertile patients and the health and wellbeing of the future child. It is thus a matter of grave concern to ESHRE that the opinions expressed in such campaigns as One of Us will jeopardise EU funding for research in reproduction and regenerative medicine. For the One of Us campaign to describe such research solely as "embryo-destructive" misrepresents the advances already achieved in stem cell research, or indeed in the world's five million babies conceived by reproductive technologies.'

The first person to testify at the public hearing was Patrick Gregor Puppinck, president of the committee backing the Initiative. He reiterated the campaign's position that 'human dignity and the life of all human beings is important from conception'. He also called for a ban on 'the financing of abortion in development aid', an argument picked up in other indiscriminate rambling rants by his pro-life colleagues.

ESHRE was well represented by ExCo members Petra De Sutter and Roy Farquharson, and former SIG Stem Cells Co-ordinator Karen Sermon (see page opposite). Many other groups as well as ESHRE expressed their opposition to the One of Us arguments, including the Wellcome Trust which raised concern about prospects for research in genetic diseases.

That concern seemed to be echoed by the Spanish MEP Teresa Riera Madurell, European Parliament rapporteur for the Horizon 2020 programme, who told leaders of One of Us that adequate checks were already in place to ensure ethical standards were respected in

stem cell research. 'The only thing your ban would achieve would be to slow down research at the European level,' she said.

The European Commission representatives, Máire Geoghegan-Quinn, Commissioner for Research, Innovation and Science, and Robert-Jan Smits, Director General of DG Research and Innovation, explained that the Commission never publishes a specific call for research projects involving hESC, but always for projects about specific diseases. Smits also remarked that hESC research has already brought big advances in the treatment of blindness and ear disease.

ESHRE set up an e-mail facility for Society members to contact their own MEPs with a copy of ESHRE's statement, and sent its own open letter to MEPs - to which UK MEP Rebecca Taylor tweeted: 'Good letter from ESHRE expressing concern re one of us initiative.' Several MEPs also responded to the ESHRE e-mail, including Bas Eickhout from the Dutch Greens, who said his party supports embryonic stem cell research: 'The EU is not obliged to act on the One of Us arguments, and the Green Party will not do so.'

The One of Us petition gathered 1.8 million signatures, more than the 1 million required for a European Citizens Initiative. Validation of the signatures showed that Italy provided almost one-third of the total, while other countries, including Belgium, failed to meet the required minimum.

Meanwhile, European elections will take place at the end of May, with the next members of the European Commission selected by the end of 2014. That Parliament and Commission will both have major roles to play in the initiation of the next funding programme after Horizon 2020.

'A morning like this is a bone-chilling reality check.'

Former SIG Stem Cells co-ordinator Karen Sermon's view from the floor

'The public hearing for the European Citizens Initiative 'One of Us' was extremely important for all of us working in reproductive science. The aim of the initiators is no less than a ban on all funding for research on human embryonic stem cells, because these presuppose the destruction of human embryos. Those behind the Initiative are also against aid to those developing countries which might include funding for induced abortions as part of family planning or prenatal care clinics.

Petra De Sutter (from ESHRE's Executive Committee) had rallied the troops, calling on colleagues and young PhDs working locally to be present with as many as possible to form a counterweight to what we expected to be a very large and active participation from the One of Us group. As it turned out, our expectations (or fears?) proved accurate. One of Us had come with a sizeable and rowdy crowd of supporters. The room was packed, and some people had no seat.

The tone was set when the leader of One of Us, Patrick Gregor Puppinck, presented the Initiative by reiterating all the well known anti-research and anti-abortion arguments - while adding a few I hadn't heard yet. Here's just a small selection: 'Every scientist will tell you that an embryo is a person'; 'Induced abortion (in medically appropriate situations) is a frequent cause of maternal mortality'; 'Imposing our way of life and forcing family planning on people in developing countries is imperialistic and comparable to colonisation'; 'Researchers represent powerful economic lobbies, much more powerful than the average European citizen'. Puppinck got loud applause from his acolytes, which ended in a standing ovation.

During the whole session, whoever chose the side of embryo research, or pro-choice, or even dared to take a nuanced point of view, was loudly booed or whistled.

The most vehemently attacked were three female MEPs who were very critical of the One of Us claims. The three MEPs argued that the Initiative was inspired by the Roman Catholic faith, and was thus not representative of other faiths in Europe - or for that matter of agnostics and atheists. The three were clearly pro-choice, looking at the whole question from the feminist perspective and the right to family planning.

The whistling concert reached its peak when an MEP from Portugal dared to question the financial links between the One of Us campaigners and ultraconservative preachers from the USA, which brought an intervention from the chair to call the meeting to order.

However, it was also clear that One of Us had secured political help, as most of the MEPs who were listed on the programme to ask questions were actually supporters of the petition. Remarkably, these MEPs were all gentlemen of a certain age, reminding us that even in the 21st century paternalism still lurks.

We scientists are sometimes said to live in an ivory tower, far away from what really preoccupies the public. This session was very informative in that sense for my PhD students: they work with embryos and embryonic stem cells without fear for the future (some of them even came especially to Belgium in order to be allowed to do this type of research), but a morning like this is a bone-chilling reality check. Puppinck repeated at least three times that this was only the beginning. So consider yourselves warned.'

30th ANNUAL MEETING

European Society of Human Reproduction and Embryology

Munich – Germany
29 June to 2 July 2014

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