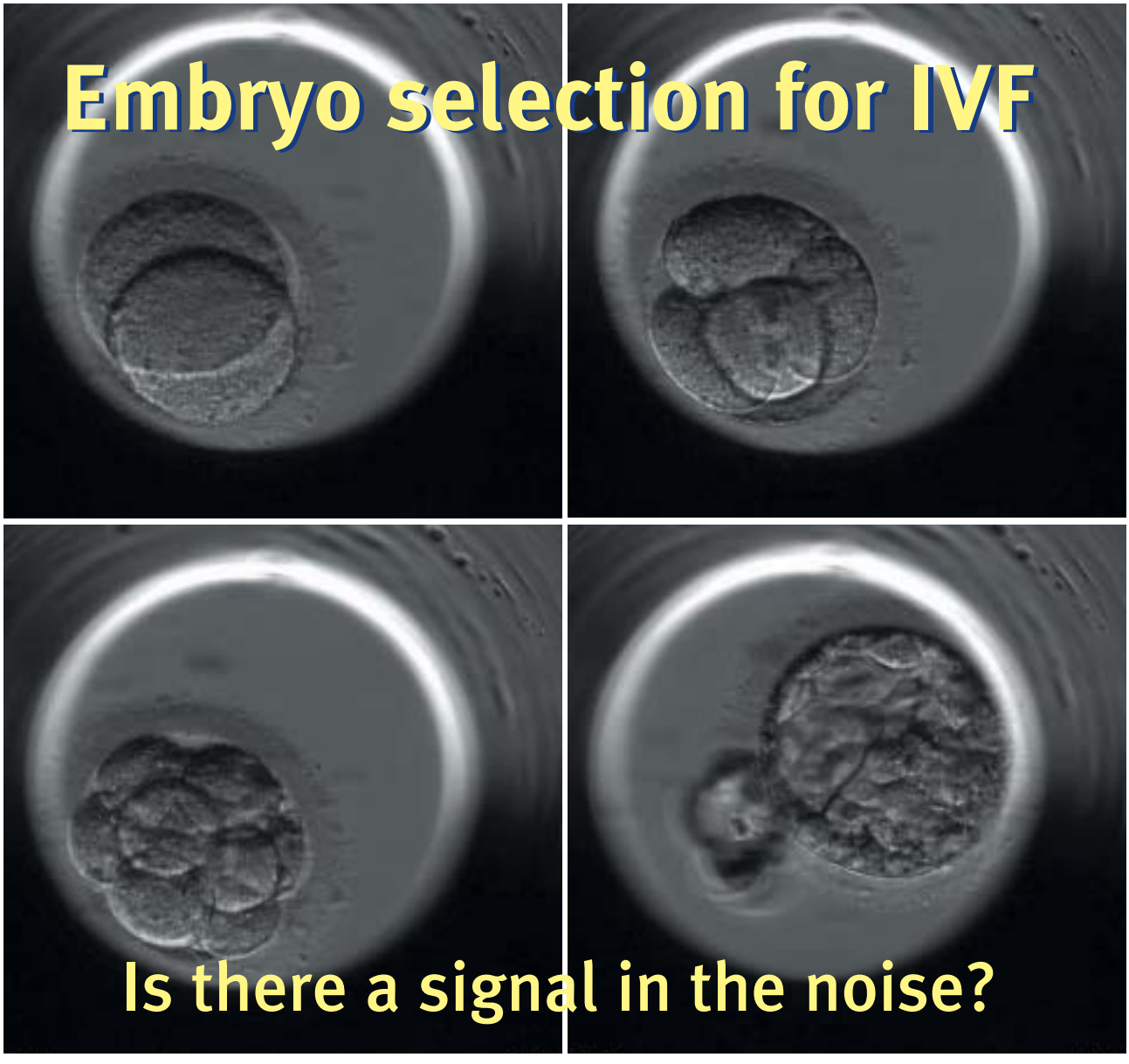
Focus on

REPRODUCTION

European Society of Human Reproduction and Embryology // SEPTEMBER 2011 //



- ESHRE news
- A record-breaking annual meeting
- The embryo as a patient

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European Society
of Human Reproduction and Embryology
28th Annual Meeting

Istanbul - Turkey
1 to 4 July 2012

The information in this announcement
is subject to change.
For updated information consult
the ESHRE web-site at **www.eshre.eu**

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CARE Fertility Group

CONTENTS

Focus on
REPRODUCTION

Chairman's introduction

We have a new picture for the chairman's introduction! The time has now come for me, your new madam chairman and the first since Lynn Fraser in 1999, to take over the chairmanship of our Society.

There's no need to say how proud I am to hold this position and responsibility. You are all aware that our system of Chairman Elect, Chairman and Past Chairman ensures continuity of direction and I have been extremely lucky to learn from Luca Gianaroli and Joep Geraedts. Luca has done an enormous amount of work for the Society and we thank him for this - and especially for being so positive and enthusiastic even in the face of difficult situations. As I have told him, he's not an easy act to follow! But I also acknowledge the work done by the Executive Committee these last two years and especially thank Jean François Guérin, Timur Gürgan, Carlos Plancha, Veljko Vlaisavljevic and Søren Ziebe, who are stepping down. We will miss them but I am sure they will continue to serve ESHRE from their respective positions and countries.

A new Executive Committee is in now place after ratification at the AGM in Stockholm and I am looking forward to working with the new members. There are plenty of ongoing tasks and new challenges ahead. As always, ESHRE's Central Office, with Bruno and his very efficient team, will be of paramount importance.

After a very successful annual meeting in Stockholm - the best ever in terms of scientific quality, venue and services - we now look to new locations in Istanbul, London and Munich. We must continue the trend of scientific excellence in all our meetings and Campuses, and this represents a real challenge. Attracting young scientists, especially the ones involved in basic science, is one of our immediate goals, both for the meetings and the ESHRE journals. Special Interest Groups and Task Forces, the core of our Society, can play an active role here.

Another important challenge is to continue the development of ESHRE's role as a reference society in reproduction among the European institutions. We have already made big efforts in this direction and expect to achieve more results which positively affect our day-to-day work - and our patients.

As I said at the beginning of this introduction, being Chairman of the world's most important society in reproductive science and medicine is a real challenge for me and I will do my best to serve the Society and its members. I count on you all!

Anna Veiga
ESHRE Chairman 2011-2013

NEWS

FEATURES

Where East meets West

Timur Gürgan, local chairman of next year's annual meeting, previews the scientific - and social - programmes in Istanbul

With the success of ESHRE's 2011 annual meeting now behind us, it's the time to begin again in search of further success in Istanbul in 2012. So, on behalf of the local organising committee, it gives me a great pleasure to invite you to the 28th annual meeting of ESHRE to be held in Istanbul, Turkey, from 1-4th July 2012. Please mark the date in your diaries!

TIMUR GURGAN: 'SOMETHING FOR EVERYONE IN ISTANBUL.'

The invited scientific programme is already in place and the first printed announcement distributed in Stockholm. As ever, the meeting will bring together a distinguished international faculty of clinicians and basic scientists, experts from all over the world with different cultural, historical, ethnic and religious backgrounds, and in fitting reflection of a venue which bridges the border between West and East. For this for ESHRE is as far East as an annual meeting has ever been and we hope it will help attract more participants from the Middle and Far East, India and Russia.

It will also enable us to share with you the joy of Turkey's history and culture, but with it the rapid change of everyday life as we prepare our candidacy for the European

Abstract submission policy

Full details of ESHRE's abstract submission policy are on the ESHRE website (www.eshre.eu), but please note:

- All abstracts must arrive at ESHRE's Central Office no later than 1st February 2012.
- Abstracts should be submitted in English only.
- Any person submitting an abstract can only be the first author for one abstract.
- The material presented should be unpublished and original material, which has not yet been presented in any other meeting.
- All abstracts will be refereed 'blind'.
- Authors are requested to indicate their preference for oral and/or poster presentation on the abstract submission form. The decisions of the selection committee are final.

Union. And hand in hand with this development Turkey is also increasing its strength in science and medicine. No longer is it a dream for Turkey to be a centre of high quality medicine; indeed, we now have 120 IVF centres providing some 40,000 treatment cycles each year, with significant success rates. It's fair to say that ESHRE itself has contributed much to the training which made this kind of progress possible. Indeed, for the first time next year's precongress programme will feature an exchange course with the Middle East Fertility Society on improving outcome in IVF.

The 2012 annual meeting will take place at the brand new congress centre located in the heart of the city. It was built to host the International Monetary Fund summit of 2009 and can accommodate more than 12,000 participants (and houses an exhibition area of more than 9000 square meters). The congress centre is only a short walk from most of the city centre hotels.

Istanbul has two international airports, Atatürk International on the west side of the city and served by the metro, and Sabiha Gökçen on the east side in Asia. Residents of some countries (but not all) will require a visa, and these are conveniently available on entry into Turkey at the airport; details of all visa requirements can be found on the website www.mfagov.tr.

Istanbul is a unique city - built on two continents and having served as the capital of three empires: Roman, Byzantium and Ottoman. Today the city is home to legendary treasures in the Hagia Sophia museum and Topkapı Palace, but everywhere its history can be felt and appreciated. And Istanbul's restaurants are similarly legendary, with kebabs, fish, and so many different dishes prepared with olive oil - and of course the sweet desserts of fruits, nuts and pastry in a tempting combination.

Everyone coming to ESHRE 2012 can enjoy the famous night life of Istanbul, especially at the congress party which will be held on the famous Suada island on the Bosporus, with panormaic views over Asia and Europe. And of course we should not forget the shopping, from modern malls to the 600-year-old Grand Bazaar covered market with more than 4000 shops.

There will be something for everyone in Istanbul, from a superb programme organised by the Scientific Committee to the colourful social activities in the exotic surroundings of the city. We hope ESHRE 2012 will be a rewarding educational, social and cultural experience for you all.

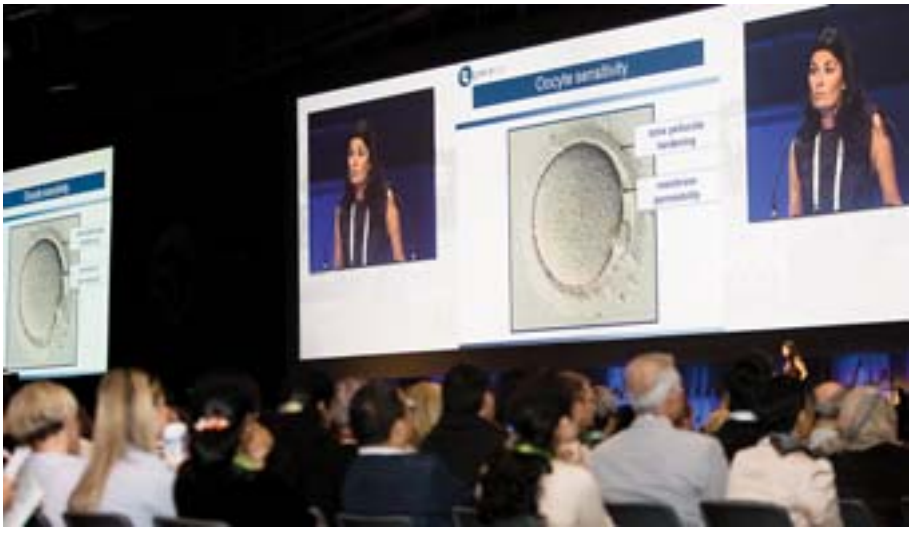
Timur Gürgan
Chairman Local Organising Committee

Istanbul is a city steeped in history but now making rapid change as it prepares its candidacy for the European Union.

More than 8000 through the doors in Stockholm

Another record-breaking congress for ESHRE

Rarely - if ever - can so many have attended an invited session at an ESHRE annual meeting, especially at 8.30 on a Monday morning. But the fact is that more than 3000 found seats for the opening two keynote lectures of this year's meeting in Stockholm, the first from Terry Hassold of Washington State University on our current understanding (or lack of) of aneuploidy, and the second from Laura Rienzi from the GENERA centre for reproductive medicine in Rome with results from several recent studies of oocyte vitrification. The latter was the second Human Reproduction lecture, following inauguration of the event in Rome last year, but, as Bill Ledger noted the following day, 'vitrification was all over this congress'.



Laura Rienzi from Rome delivers the second Human Reproduction keynote lecture before an audience of at least 3000.

Packed lecture rooms were a hallmark - yet again - of this year's meeting. The bare statistics show that 8361 people registered - not quite an attendance record - but enough to ensure standing room only in some lecture halls and a commercial exhibition area like Las Vegas on a Friday night.

Developments in the IVF lab once again provided many of the talking points of the meeting. Indeed, Hassold's opening keynote lecture underlined the magnitude of the challenge of aneuploidy in the human, and how far we are still away from explaining or dealing with it. 'We've been staggered at the frequency of abnormalities we see,' said

Hassold, adding that the human female appears to have an 'exceptionally high level' among the animal species. There are, he explained, multiple sites and stages at which these chromosomal non-disjunctions can occur, but are especially so at the first maternal meiotic division.

This was also a pattern similarly (but not exclusively) seen in a spin-off from ESHRE's own polar body screening study started in 2009 and now completed as a pilot for a stronger randomised trial. Array CGH analysis of all 23 chromosome pairs (in 105 zygotes generated from 34 cycles in women all over the age of 35) indicated multiple chromosome errors in both meiotic divisions. This pattern of meiotic aneuploidy, however, was judged to be different from that observed in naturally conceived zygotes (where the pattern of error predominates in the first meiotic division); in attempting a biological explanation for the discrepancy, the investigators proposed 'a role for ovarian stimulation in perturbing meiosis in ageing oocytes'. 'So we need to look further into the incidence and pattern of meiotic errors following different stimulation regimes,' said investigator Alan Handyside, 'including mild stimulation and natural cycle IVF. The results should enable us to identify better clinical strategies to reduce the incidence of chromosome errors in older women undergoing IVF.'

There have been similar safety concerns - expressed for several years - over the effect of culture media on embryo development, and this too was the subject of a whole session in Stockholm. A study from the Academic Hospital of Maastricht in the Netherlands compared the effects of two commercially available sequential media on fetal growth after IVF (in a total of 294 singleton pregnancies), with ultrasound measurements at eight, 12 and 20 weeks' gestation. However, only free-beta hCG levels differed significantly between the two media groups at 12 weeks, but a 'larger than expected' fetal weight was evident at 20 weeks in one of the two media groups.

Dr Nelissen, presenting the data from Maastricht, was not yet able to apply any positive or negative clinical implications to the results, which is the same conclusion reached by a meta-analysis from Amsterdam. Trawling the literature to unearth 37 applicable studies, the investigators found 'little evidence' to indicate which culture medium seems 'best' for preimplantation embryos in terms of ART outcome. Well designed randomised trials are now urgently needed, they reported.

The concerns over culture media underlying this session are to be taken up by a new working group ratified by ESHRE's Executive Committee in Stockholm with a brief to examine changes in methylation patterns associated with culture media and make recommendations for the improved regulatory control of commercial formulations.

In the opening keynote lecture Terry Hassold described the level of aneuploidy in women as 'exceptionally high'.

Oocyte vitrification

Laura Rienzi's Human Reproduction lecture was based on a study from her group in Rome whose publication attracted the most full-text downloads during the first six months of publication between January 2009 and June 2010. That original study, a randomised non-inferiority outcome trial of fresh versus vitrified MII oocytes, was also an indication of how much the whole concept of oocyte cryopreservation has been driven by Italy, where 2004 legislation banning embryo freezing made some alternative option a clinical necessity.

Lap of honour: In Stockholm the Swedish gynaecologist Lars Hamberger and Australian IVF pioneer Alan Trounson were awarded honorary membership of ESHRE. They are seen here receiving their awards from outgoing Chairman Luca Gianaroli.

Indeed, it was striking to see in the first oocyte cryopreservation data collected by ESHRE's IVF monitoring group and presented by Jacques De Mouzon two days later that - in 2008 at least - Italy was responsible for 79% of all cycles reported (and 70% of all deliveries derived from cryopreserved oocytes.) And Rienzi herself reported in her lecture that almost all patients now offered oocyte storage in the routine Rome IVF programme accepted the offer. Vitrification, she said, has proved 'the breakthrough', her data from the three studies described showing that vitrified oocytes perform just as well as fresh in terms of fertilisation, pregnancy and delivery. A prospective follow-up study found that overall ongoing pregnancy rates from the fresh, and first and second warming cycles were 37.4, 25.0 and 27.3%, respectively. The cumulative ongoing pregnancy rate per stimulation cycle was 53.3%, with maternal age the only variable found to influence outcome. A third study noted in the lecture was a three-centre trial with the University of Milan and IVI Valencia, where more than 2700 oocytes have been warmed for fertilisation and 147 deliveries already recorded. So far, said Rienzi, results reflect a 5.4% live birth rate per 'woman-oocyte', suggesting that each patient requires nine oocytes to maximise results. It was notable that the results were always presented within the context of either medical or social fertility preservation, and this, insisted Rienzi, was reason strong enough to justify the cryopreservation.

However, the further potential of vitrification as a development in oocyte banking for egg donation was highlighted in a presentation from one of Rome's collaborating groups, IVI Valencia. Reported results from four years of oocyte banking (with oocytes vitrified for at least six months) showed that more than 22,000 stored oocytes were donated to 1602 recipients (with an average age of 41 years). Treatments totalled 1856 donation cycles, with an implantation rate of almost 42% per cycle. Total ongoing pregnancy rate (from 'fresh' cryopreserved and revitrified oocytes) was 50% when a total of 13 oocytes were available, and 59% with 15. Vitrification, said Ana Cobo Cabal presenting the data, 'offers excellent clinical outcomes, achieving the advantages of gamete storage without jeopardising success rates'.

Oocyte donation is one of several techniques whose use is now increasing throughout the world. The same pattern is apparent in the use of ICSI, whose worldwide use is now twice that of traditional IVF, and in frozen embryo transfer, whose use in Europe now represents almost 25% of all ART cycles. Karl Nygren, presenting the world data on behlf of ICMART, also noted a rapid decline in the number of triplet pregnancies in the decade 1998-2007, with rates under 1% now apparent in Europe, Australia, Asia (from limited cycles reported) and the Middle East. However, twin pregnancy rates have remained relatively stable throughout the decade, and in Europe have remained static (at around 20%) for the past two

The live surgery session held on Tuesday morning attracted its usual high attendance. The session, chaired by Stephan Gordts and Vasilios Tanos, relayed live pictures from an operating theatre of Tübingen University Hospital, Tübingen, Germany.

A new Chairman and a new Executive Committee

After two years, Luca Gianaroli's term as Chairman of ESHRE came to an end in Stockholm, where he was succeeded by Anna Veiga. The new Executive Committee, with a two-year term ahead of them and pictured above, comprises (back row, left to right) Niels Lambalk, Luca Gianaroli (Past Chairman), Anis Feki, Bruno Van Den Eede (Managing Director), Milan Macek Jr., Carlos Calhaz-Jorge, Anne-Maria Suikkari, Roy Farquarson; (front, left to right) Juha Tapanainen (Chairman Elect), Françoise Shenfield, Jacques De Mouzon, Anna Veiga (Chairman), Cristina Magli, and Ursula Eichenlaub-Ritter. Not pictured are Etienne Van den Abbeel, Antonis Makriagiannakis and Moidrag Stojkovic.

years of data collection.

The world's lowest rate of multiple pregnancy is now in Sweden, where 70% of embryo transfers in 2007 were single. In a presentation in Stockholm, Jan Holte from Uppsala described the development of a mathematical model based on four variables (embryo quality, patient age, IVF history, and response to stimulation) designed to predict the chances of pregnancy after the transfer of one or two embryos and the risk of twins.

Over a four-year period between 2004-2007, they applied the model to 3410 embryo transfers. During this period the proportion of single embryo transfers increased to 76.2% (compared to 11.1% in the previous period), and the rate of twin deliveries reduced from 26.1% to 1.9%. Live birth rates per fresh embryo transfer fell from 29.1% to 24.6%, but were similar when transfers of frozen-thawed embryos were included. Holte found that the model correctly predicted pregnancy rates in all women, regardless of their chances of becoming pregnant.

As ever, many of the presentations selected for the press programme were widely covered throughout the world, with popular stories featuring miscarriage (prediction, specialist care), reducing multiple pregnancy rates (with single embryo transfer), and the award-winning presentation of Elpida Fragouli on the chromosomal assessment of oocytes by cumulus cell analysis.❑

ESHRE 2011: award-winning presentations

Clinical Science Award for Oral Presentation

O-121 A pilot, double blind randomised controlled trial of prednisolone for women with recurrent miscarriage and raised uterine natural killer cell density

AW Tang, Z Alfirevic, MA Turner, J Drury, J Topping, F Dawood, R Farquharson, S Quenby; Liverpool and Warwick, UK

Ai-Wei Tan presents details of her group's study of prednisolone in recurrent miscarriage, which won the Clinical Science Award for Oral Presentation.

Clinical Science Award for Poster Presentation

P-539 An association of IL-18 gene polymorphisms with impaired glucose regulation in Korean patients with polycystic ovary syndrome

JW Kim, TK Yoon, WS Lee, JE Han, SW Lyu, SH Shim; Seoul, South Korea

Dr Kim receives the Clinical Science Award for Poster Presentation from Chairman Elect Juha Tapanainen and EIM Chairman Anna Pia Ferrarettti

Basic Science Award for Oral Presentation

O-217 Follicle-specific predisposition to aneuploidy as revealed by transcriptomic analysis of cumulus cells

E Fragouli, Z Huang, V Bianchi, A Borini, U Kayisli, P Patrizio, D Wells; Oxford, UK, Bologna, Italy, New Haven, USA

Elpida Fragouli with her Basic Science award for Oral Presentation.

Basic Science Award for Poster Presentation

P-240 Human embryo-endometrium interactions at the time of implantation

M Peters, S Altmäe, J Reimand, T Laisk, M Saare, O Hovatta, R Kolde, J Vilo, A Stavreus-Evers, A Salumets; Tartu, Estonia, Stockholm, Sweden, Uppsala, Sweden

Fertility Society of Australia Exchange Award (pictured left)

O-180 Influence of 5-HTTLPR variants in the SLC6A4 gene over pregnancy outcomes among recipients of donated eggs

AR Palomares, AM Lendinez Ramirez, B Pérez-Nevot, F Martinez, A Jimenez, M Ruiz Galdón, A Reyes-Engel; Malaga, Spain

Armando Reyes Palomares presents details of his Fertility Society of Australia exchange award.

Nurses Award

O-146 'Patient-centred infertility care' is a European concept: results from an international multi-lingual qualitative study

E Dancet, TM D'Hooghe, WLD Nelen, W Sermeus, JA Garcia-Velasco, LG Nardo, H Strohmer, C Wyns, JAM Kremer; Leuven, Belgium, Nijmegen, The Netherlands, Madrid, Spain, Manchester, UK, Vienna, Austria, Brussels, Belgium

Elizabeth Dancet (right) receives the Nurses Award from Juha Tapananinen and Jolieneke Schoonenberg-Pomper, chairman of the Paramedical Board.

ART Laboratory Award

O-097 Improved embryo development in a time-lapse incubator system evaluated by randomized comparison of surplus embryo development to the blastocyst stage

J Speksnijder, C van de Werken, SM de Jong, AJAM Dons, JSE Laven, EB Baart; Rotterdam, The Netherlands

Stockholm gets highest ever satisfaction rating

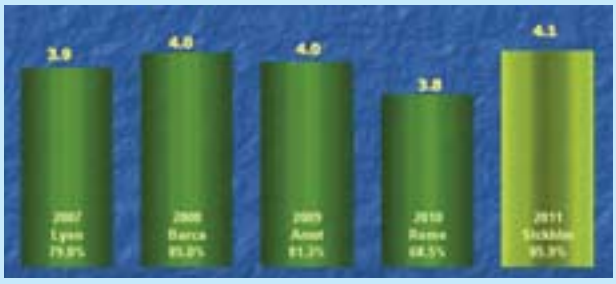
Results from the annual meeting satisfaction survey conducted each year by ESHRE show that the 2011 event in Stockholm achieved the highest rating ever. On a scale of 1-5 this year's event scored a record average of 4.1, just higher than previous ratings in Barcelona in 2008 and Amsterdam in 2009. The survey was conducted among 500 participants who each answered questions from a 10-minute questionnaire. The interviews were conducted face-to-on site on Wednesday 6th July, with comparisons made to the previous four annual meetings.

Also rising sharply were ratings for the scientific quality of the invited lectures, while the quality of the oral communications and debates remained high and similar to previous years.

There was also a perceived improvement in the poster discussion sessions, which in previous events had attracted only a moderate response. Almost half the participants questioned took time to view the posters, with many viewing both the paper and electronic versions. However, interest in the paper posters remained strong, with delegate preference still apparently tending towards the traditional poster boards. However, the e-poster system was highly rated for ease of use (a score of 4.1).

The congress centre in Stockholm scored highly for its efficiency and provision of venue-related services, although satisfaction with the catering was only moderate (3.2). Similarly, the city-related services - notably transportation and hotel booking - were rated very highly, and higher than at previous events.

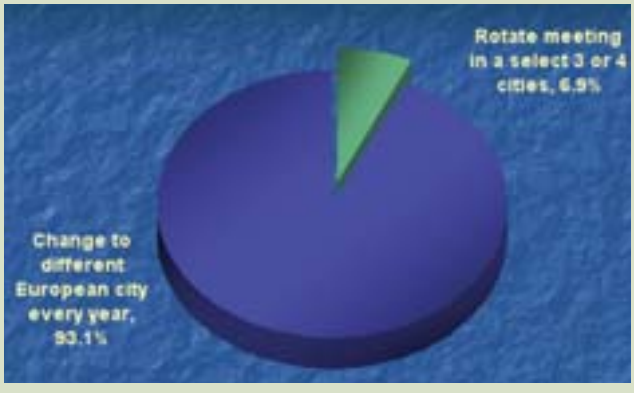
This year's meeting continued the trend of fewer delegates now supported to attend by industry, and more by their own employers. Registrations were funded in roughly equal measure by industry, employers and the delegates themselves.



Overall satisfaction scores in Stockholm were higher than at the previous four annual meetings.

Interest in the paper posters remained strong, with delegates still apparently preferring the traditional poster boards.

Congress venue: rotating locations or a different city each year?



With the challenge of finding a European congress venue able to accommodate 10,000 delegates becoming more and more difficult each year, the prospect of rotating the location through three or four suitable cities with a successful track record seems an attractive option. Huge congresses with 20,000 or more delegates have to do this anyway of necessity, but it seems that ESHRE's attendees still overwhelmingly favour the idea of a different location each year. Only 7% preferred a limited location roster.

ESHRE's polar body array CGH trial now good to go

ESHRE's polar body array CGH study, a randomised trial of 23 chromosome analysis for preimplantation genetic screening, is ready to begin, with funding in place and most of the study centres contractually engaged. A pilot study completed last year showed that analysis of both polar bodies can be completed within a time period consistent with fresh transfer, with reliable chromosome identification in about 90% of attempts.

Joep Geraedts (pictured above), chairman of the PGS Task Force directing the trial, reported in Stockholm that the protocol is now agreed and that the total study would require a population of 600 couples. Randomisation will take place with the administration of hCG, and the analysis when at least four normally fertilised oocytes (2PN) are available. The target population, said Geraedts, is women planning IVF or ICSI who are at high risk of having aneuploid embryos because of their age. Inclusion criteria are infertility as an indication for ART, age between 36 and 41, BMI 20-30 kg/m^2, and a willingness to accept the transfer of two embryos. The trial has two primary aims, said Geraedts: to estimate the likelihood of having no euploid embryos in future ART cycles, and to improve live birth rates.

The study is being undertaken with the support of BlueGnome of Cambridge, who will supply the technology (and some training) sufficient to run 5000 samples. Other training will be undertaken by the trial's two lead training centres in Bologna and Bonn/Heidelberg. The five other centres chosen to take part are the Centre for Medical Genetics, Brussels, the University Women' s Hospital, Kiel, Department of Medical Genetics, Athens, Shaare Zedek Medical Center, Jerusalem, and the Institut Universitari Dexeus, Barcelona.

EU guidance on reporting adverse events in ART now at draft stage

The EU's SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) project in ART, in which ESHRE has collaborated with a committee of competent authorities, has now reached the stage of draft guidance for a system of reporting (and investigating) serious adverse reactions and events.

Edgar Mocanu, chairman of ESHRE's EUTCD Task Force, reported that the draft guidance covers:

- suspected adverse events linked to culture media and equipment
- mix-ups in the identification of gametes and embryos
- lost traceability (because of lost information or misrecording)
- adverse events in the context of cross-border care
- adverse reactions and events related to procurement
- the diagnosis of genetic disease in the context of non-partner donation

Once fully developed, the guidance document will be be proposed to the European Commission for application across the EU.

Hysteroscopy study on schedule for completion next year

As of June this year 268 patients had been randomised in the Trophy (Trial of Outpatient Hysteroscopy) study, a multicentre trial conducted at eight European centres with the support of ESHRE's SIG Reproductive Surgery. The study, reported investigator Stephan Gordts from the University of Leuven, Belgium, aims to assess the effects of outpatient hysteroscopy on subsequent IVF outcome after repeated IVF failure in a total population of 800 subjects. The primary endpoint of the trial is live birth rate per IVF cycle, with secondary endpoints of embryo implantation rate, pregnancy rate per IVF cycle, and miscarriage rate per pregnancy achieved. The study hopes to confirm earlier single-centre studies (with live birth data) that hysteroscopy (with immediate correction or operative hysteroscopy) can improve the prospects of pregnancy in poor prognosis patients (with two to four failed cycles). With 268 patients already randomised, Gordts said that completion on schedule next year looked likely.

TROPHY study investigator Stephan Gordts: on schedule.

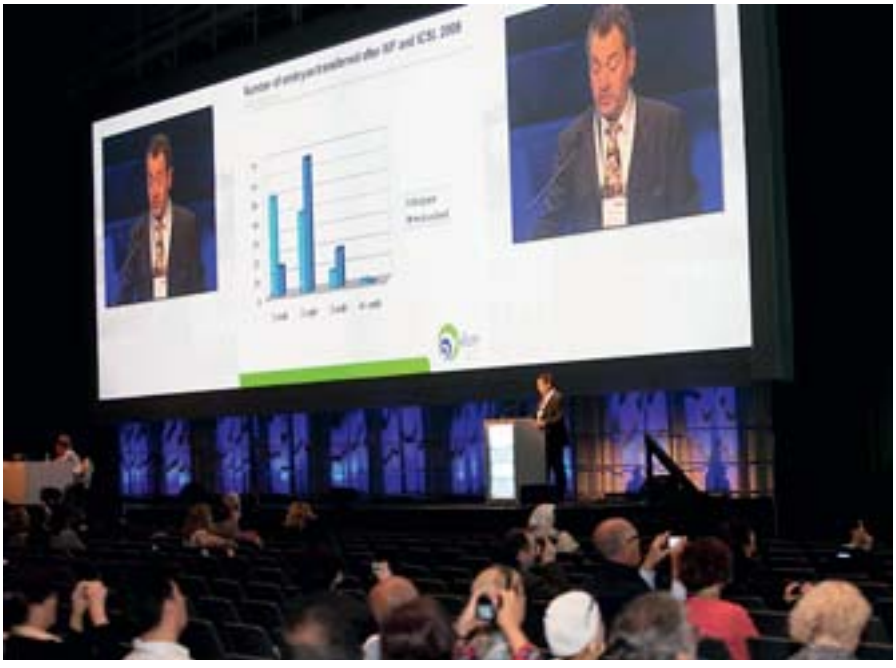
ART success rates have 'reached a plateau'

EIM monitoring data show that both pregnancy - and multiple pregnancy - rates have not changed from the previous year

Both the pregnancy and multiple pregnancy rate recorded in the preliminary results of ESHRE's European IVF monitoring for 2008 appear to have levelled off. Overall pregnancy rate per transfer following IVF was put at 32.5%, and following ICSI at 31.9%; both these rates were slightly lower than those recorded for 2007.

Similarly, pregnancy rates achieved after egg donation and in frozen embryo cycles - after showing substantial gains from 1997 - appear also to have peaked, with no gains shown on the previous year. 'It seems evident that we've reached a plateau,' said EIM Chairman Jacques De Mouzon.

And Europe's twin rate, in 2007 rising once again to 21.3% after IVF and ICSI, remained stubbornly level at 20.6% in 2008.



The EIM Consortium's chairman Jacques De Mouzon presents the latest data in Stockholm. 'It seems evident that we've reached a plateau,' he said.

Yet, as De Mouzon warned in his presentation, 'Europe' is not a homogeneous region, and such generalised results as those of the EIM mask huge national disparities. Nowhere is this now more starkly seen than in the pattern of single embryo transfer and multiple pregnancy rate. Among the major IVF countries, for example, only 13% of IVF/ICSI cycles in the UK were SET in 2008; the majority (almost 80%) were double embryo transfers. This contrasts vividly with patterns in the Nordic countries where the SET rate in Sweden and Finland - even in 2008 - was approaching 70%.

As a result of this disparity of policy, as reflected in an EIM calculation described by De Mouzon as the 'optimal end-points' of IVF, Finland and Sweden achieved cumulative delivery rates of 30.5 and 29.4% in 2008, with 29.7% similarly recorded in the UK. But the counter-balance to these excellent results was a multiple delivery rate of 9.7% in Finland and 6.6% in Sweden, but of 23.5% in the UK.

Such results from the UK made another presentation in the Stockholm programme - from the UK regulator, the HFEA - on UK 'policy' to reduce multiple pregnancies appear little more than smoke and mirrors. While talk of 'strategy' and 'stakeholders' seemed worthy enough, there was little hard evidence from the HFEA that 'we're slowly getting there', especially when one slide from the presentation showed a current UK twin rate of 44% following the transfer of two blastocysts. 'We'll be writing to the clinics in October,' said the representative of the beleaguered HFEA.

Yet despite such glaring disparities with Finland and Sweden (which now has the world's lowest multiple pregnancy rate) the UK is not alone. Around 50% of cycles in Hungary, Russia and Ukraine were double transfers in 2008, and around 30% triple. More than 5% of deliveries in Turkey and Lithuania were triplet, and more than 4% in Macedonia and Albania. And more than 50% of transfers in Greece, Turkey, Bulgaria and Romania were of three embryos or more.

The result of these excesses is that the proportion of singleton deliveries in the EIM dataset was less in 2008 (78.3%) than in 2003 (79.2%), and the proportion of twin deliveries higher than in 2006 (20.6% vs 19.9%). ⇨

The 'optimal endpoints' of ART. Cumulative delivery rates after fresh and frozen embryo transfer. Deliveries per initiated cycle 2008.

	Initiated cycles IVF/ICSI	Deliveries ex fresh IVF/ICSI cycles	Mulitple deliveries ex fresh cycles	FER cycles (thawings)	Deliveries FER	Multiple deliveries FER	**Deliveries fresh (%)**	**Cumulative delivery rate - fresh + FER (%)**	**All multiples**
Finland	4952	980	111	(3790)	528	55	**19.8%**	**30.5%**	**9.7%**
Sweden	11,010	2386	169	4733	854	45	**21.7%**	**29.4%**	**6.6%**
UK	39,476	10,078	2511	8957	1630	245	**25.5%**	**29.7%**	**23.5%**

However, De Mouzon did note that in women under 40 having IUI the twin pregnancy rates (8.3%) were less than half those following IVF or ICSI.

And De Mouzon added that, over the 11 years of IVF data monitoring in Europe, overall multiple delivery rates had indeed declined, from 29.5% in 1997 to 21.7% in 2007, with a four-fold reduction in triplet deliveries from 3.7% to 1.1%.

On other safety issues, De Mouzon noted 2947 cases of OHSS among the 535,000 cycles reported, an incidence rate of 0.8%, derived from the data of 30 contributing countries (from a total of 36).

Nine of those 36 countries also reported for the first time data on 3359 transfer cycles from cryopreserved oocytes, with 358 deliveries (8.6% per cycle and 10.7% per transfer).

Also new were data from 12 countries on IVM cycles, which produced 172 pregnancies at a rate of 18.3 per cycle and 22.4% per transfer. In both treatments more than 50% of cycles reported were performed in Italy.

With Europe now representing 52% of world ART activity, it was no surprise to see many of the trends of the EIM data also evident in ICMART's world report (for 2007).

ART activity in Europe is now well over 500,000 cycles a year and continues to rise - although the world's two biggest centres of action remain Japan (159,761 cycles) and the USA (130,287). France performs the most IVF in Europe (73,085 cycles), followed by Germany (63,787) and Spain (52,905).

EIM data also show that Spain is now responsible for 30% of all Europe's egg donation treatment (followed by the Czech Republic (15%) and Russia (12%).

Karl Nygren presents preliminary ICMART data for 2007. Estimates put current global activity at 1.5 million cycles per year.

Karl Nygren, presenting the ICMART report, said its submitted data are thought to cover up to 70% of global activity, with many cycles missing from Africa, Middle East and Asia. Nevertheless, almost 1 million cycles were reported for 2007, prompting an estimate that around 1.5 million cycles will take place in the world this year, with at least 340,000 babies born.

Cumulatively, the total of IVF babies since Louise Brown is now put at 4.6 million, with a landmark 5 million expected to be reached next year. The mean number of embryos transferred globally was 2.14 and the aggregate delivery rate per aspiration 21.7%. The USA - as ever - had the highest cumulative delivery rate of 40.7% per started cycle, albeit with a twin delivery rate of around 30%.

Simon Brown
Focus on Reproduction

ICMART's global snapshot of ART

- An estimated 1.5 million cycles worldwide per year
- An estimated minimum of 340,000 ART babies born per year
- An estimated 4.6 million babies since 1978
- 66.6% of all cycles are ICSI
- 19.9% in women over 40 years
- Mean number of transferred embryos = 2.14
- Delivery rate per aspiration = 21.7%
- Cumulative delivery rate = 27%

A further step in ESHRE's collaboration with the ASRM

Programme for joint winter meeting now finalised, with emphasis on controversies in reproductive medicine

The Italian ski resort of Cortina d'Ampezzo, chosen as the venue for the first ESHRE-ASRM best practice meeting for its off-piste and off-programme opportunities.

The first 'best practice' meeting to be organised jointly by ESHRE and ASRM in Italy next March is, according to ASRM chairman Rogerio Lobo, 'an experiment', but one which both societies have grasped with enthusiasm as a further way of working more closely together. 'Of course,' says Lobo, 'we've each got our respective roles in the USA and Europe, but we still have shared interest in many areas, and this is one way where we can encourage those shared interests.'

The meeting will take place from 1-3rd March 2012 in the ski resort of Cortina d'Ampezzo in the Italian Dolomites, a well established winter sports centre. Both ESHRE and ASRM have stressed the importance of the location for off-programme and off-piste exchanges between society members. 'It's not a ski meeting,' insists Lobo, 'but we do want to make time for an informal as well as formal programme.'

The three-day scientific programme - which will leave mornings free for leisure activities - has been built around established and emerging controversies in reproductive medicine, with presentations on each topic reflecting a US and European perspective. Oocyte cryopreservation, for example, now moving into the mainstream of European treatment for both medical and social indications (as well as for oocyte banking for egg donation), remains an 'experimental' technique in the US. There are also well rehearsed differences in the diagnosis of PCOS (and the relative role of hyperandrogenism), the application of single embryo transfer policies, and day 3 or day 5 embryo transfers, all of which will be explored in Cortina.

Lobo additionally sees ESHRE and ASRM taking a stand against the many small meetings now popping up like mushrooms which he describes as 'self-promoting and purely commercial'. 'So we're not planning a fly-by-night meeting or running a travel club,' he says. 'The idea is to put our best foot forward in a programme which reviews the best of science but without any self-interest.'

The 'best practice' initiative also represents a continuation of the ever strong and cordial relationship between ESHRE and the ASRM, which for the past 20 or more years has been most evident in reciprocal exchange sessions at the respective annual meetings - in both the scientific programme and precongress courses. ESHRE has traditionally been wary of close relationships with other societies, forging its collaborative links most usually at the SIG level for training and logistical reasons. ASRM, however, has always had a more conceptual overlap with ESHRE, despite the enormous differences between the two societies.

ASRM CHAIRMAN ROGERIO LOBO: 'A PROGRAMME WHICH REVIEWS THE BEST OF SCIENCE BUT WITHOUT ANY SELF-INTEREST.'

Both describe themselves as 'international' societies, which their membership readily reflects, and it's noteworthy - as if further proof were needed - the ASRM has recently appointed a European, Antonio Pellicer, to the co-editor's chair of *Fertility and Sterility*. The ASRM, inasmuch as it is nominally an American society, also represents an homogenous professional group, with a strong core of practice guidelines at his heart, often applied at the clinical level in the absence of regulation.

'So there are big differences between ESHRE and ASRM,' says Lobo, 'but I don't think they drive us further apart or bring us any closer together. The US is more homogeneous than ESHRE's representation of Europe, and ASRM has a broader range of clinical interests. But there's still a lot we have in common, especially at the scientific and clinical levels. And this is what we're looking to develop in Cortina.'

● More information and registration details on the ESHRE website, under 'Annual meeting'.

PGD for aneuploidy screening still dominates world activity in preliminary results for 2009

Around 3000 cycles of array CGH reported to new working group

Despite the negative results of clinical trials and a less than enthusiastic response by the Practice Committee of the ASRM in 2008, preliminary results from the ESHRE PGD Consortium for 2009 - its 12th round of data collection - show that PGD for aneuploidy screening still accounted for more than all other PGD procedures combined (which included sexing for x-linked disease, chromosomal abnormalities, social sexing and monogenic diseases). Data were collected on more than 6000 cycles in 2009, with PGS representing well over 3000 cycles. 'PGS is still dominating,' said Gary Harton, chairman of the Consortium, 'but screening for monogenic disease continues to grow each year.'

PGD Consortium chairman Gary Harton presents preliminary resuts from the Consortium's data collection for 2009: PGS is still dominating, he said.

The cumulative picture of the Consortium's activity - accounting for 12 rounds of data collection beginning in 1997 - reflected the same pattern. Over the 14 years, 30,250 embryos were transferred following aneuploidy screening, with 10,888 embryos transferred following PGD for monogenic disease, and 6458 for chromosomal screening. This was derived from a total of 46,522 embryos biopsied for monogenic disease, 36,787 biopsied for chromosomal abnormality, and 131,539 for PGS. Cumulatively, there have now been more than 6000 babies born following PGD, 74.5% of them as singletons and 48% by Cesarean section.

The most common monogenic disorders diagnosed over the 13-year period were beta-thalassaemia, sickle cell disease, cystic fibrosis and spinal muscular dystrophy among the recessive disorders, Huntington's disease among the dominant, and fragile-X, Duchenne muscular dystrophy and haemophilia among the sex-linked.

Harton also reported that 164 centres are now supplying data, with three of these centres performing more than 500 cycles a year; 60 centres supplied full data for 2009. Spain (14 centres), Germany (11 centres), and the USA (nine centres) had the greatest national memberships.

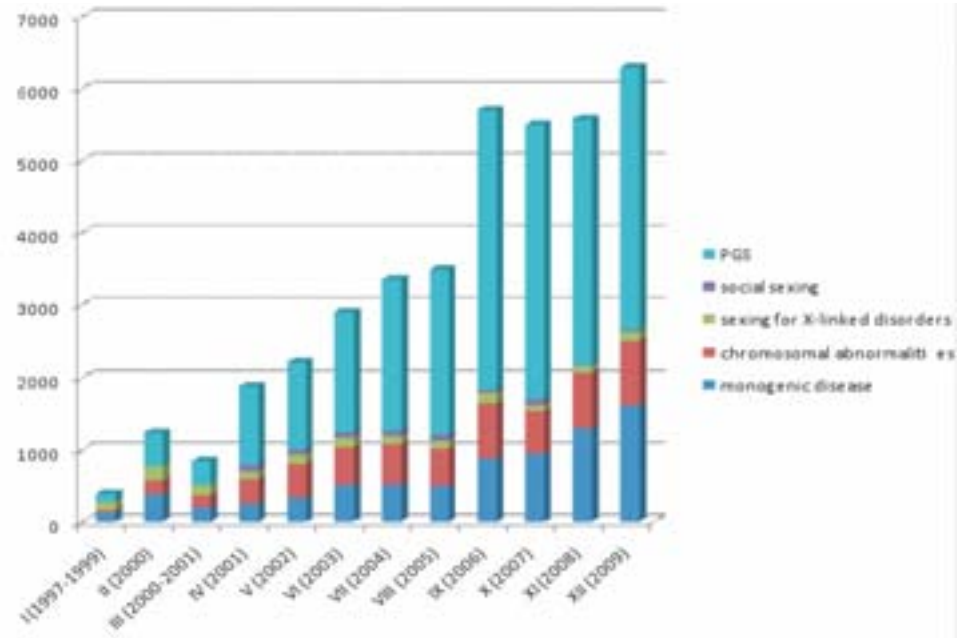
Membership, Harton explained, is of three types, to reflect the way in which PGD is now performed: full members are those centres supplying complete data from oocyte collection through to pregnancy; transport members are those who perform the genetic testing but without access to full IVF data; and associate members are those new labs just embarking on PGD.

The Consortium now has five active working groups:

- Misdiagnosis monitoring and audit (chair Jan Traeger-Synodinos)

Highlights from data collections I-XII

- 39,507 total cycles
- 23,853 PGS (60.4%)
- 14,960 PGD (37.9%)
- 694 social sexing (1.7%)
- 227,823 embryos biopsied
- Monogenics increasing each year
- PGS still dominates PGD worldwide
- 7550 clinical pregnancies reviewed (74.5% singletons)
- Miscarriage rate 'unremarkable'
- Birth weights comparable to other datasets



Evolution of PGD Consortium data over time, showing the continuing dominance of PGS for aneuploidy

- Accreditation (chair Katerina Vesela)
- Database (chair Celine Moutou)
- Molecular methods (chair Francesco Fiorentino)
- Arrays (chairs Leeanda Wilton and Dagan Wells).

Presently, the misdiagnosis monitoring group is completing two re-analysis studies on PCR and FISH cycles using untransferred supernumerary embryos. The aim, said Harton, is to determine how accurate the PGD analysis is, and if there is any discordancy between the initial PGD results and the re-analysis. Accuracy, he added, may be affected by the analysis method used, the number of cells biopsied, mode of disease inheritance, embryo quality, and whether the analysis was performed on day 3 or day 5 of embryo development. Presently, the full data on the PCR cycles have been submitted within the deadline from eight centres, have been analysed, and are now ready for review; data from the FISH cycles have been cleaned, but not yet analysed. 'The FISH-based study is looking difficult,' said Harton, 'because of mosaicism, so we're having to discuss its viability.'

A report from the array working group suggests that most clinical cases are currently being performed with the BlueGnome array technology (as used in ESHRE's array CGH trial); however, there are some clinical cases also being performed with SNP array. Around 3000 cycles have already been performed by the members of the working group, but the moment of biopsy varies throughout the world. For example, most US centres analyse at the cleavage stage (although analysis at the blastocyst stage is growing quickly, with around 15% of cases in one laboratory), most cycles in the UK are polar body analysis (with some blastocysts), while all cases in Germany are performed at the polar body stage (no doubt because of embryo protection laws - but see below).

Among the Consortium's future projects outlined by Harton are continued yearly data collection with new web-based data entry and deeper analysis of data, new learning tools for labs, guidelines and an external quality assessment (EQA) scheme for array-based PGD, and completion of the misdiagnosis monitoring working group's follow-up studies on amplification-based and (possibly) FISH-based analysis. In addition, the accreditation working group will continue to assess and help PGD labs towards accreditation, and has two new workshops on accreditation planned for 2011 (Athens) and 2012 (Istanbul) in conjunction with EuroGentest.

After heated debate, German parliament votes to lift ban on PGD

In July Germany's parliament voted by a majority of 326 to 260 to overturn the country's ban on PGD. The controversial move followed a heated national debate (in which Chancellor Angela Merkel voiced her opposition to PGD) and a Federal Court ruling last year that PGD was not in violation of the country's embryo protection laws.

The Bundestag move will now allow PGD, but only on condition that there is a strong likelihood of passing on a genetic defect, or when the chances of miscarriage or stillbirth are (genetically) high. All applications for PGD must be approved by an ethics committee and couples are required to undergo counselling. According to news reports, the bill thus provides an exception to the current Embryo Protection Act of 1990, which originally outlawed PGD but otherwise now remains intact.

After a tense three-hour debate, the results of the free vote in the lower house of the Bundestag showed a clear support for the highly controversial bill.

Onwards and upwards

Impact factors of all ESHRE journals make record gains

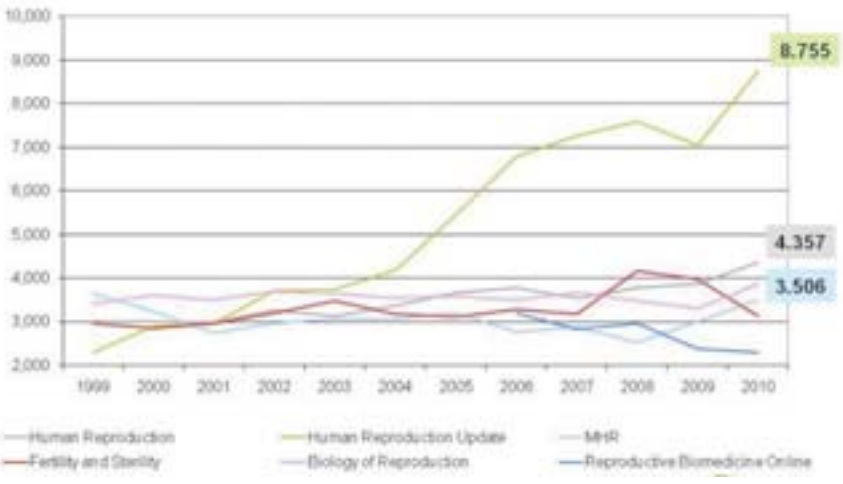
While impact factors may still be controversial in some corners of science and clinical research, in academic publishing they remain the clearest statement yet of journal quality. Which is why ESHRE - and its journal publishers Oxford University Press - had such huge cause for celebration in June when the ISI Web of Knowledge announced its impact factors for 2010.

All three ESHRE journals - *Human Reproduction*, *Human Reproduction Update* and *Molecular Human Reproduction* - made record gains in their impact factors and now dominate the two categories of 'Obstetrics and Gynaecology' and 'Reproductive Biology'.

- *HRU* increased its impact factor to 8.755 and now leads - by a very wide margin - both categories of O&G and Reproductive Biology.
- *HR*, which is now second in the category of Reproductive Biology and third in O&G, increased its impact factor to 4.357.
- And *MHR*, whose future was less than secure as recently as five years ago, has made enormous strides to now sit fourth in the category of Reproductive Biology with an impact factor of 3.506. This is a remarkable gain on last year's figure of 3.005.

Notable among the results is the decline of *Fertility and Sterility*, which fell from a 2009 impact factor of 3.970 to 3.122 in 2010. Outgoing editor Alan DeCherney blamed the slump on a backlog of accepted manuscripts in need of publication and on the inclusion of short reports (case studies, correspondence) in the calculations. *Reproductive Biomedicine Online* also fell back from last year - from 2.380 in 2009 to 2.285 in 2010.

'We had an idea from the publishers that our impact factor would increase,' says *Update* editor John Collins, 'but the final figure was considerably higher than the "slightly over 8" prediction.' Collins explains the record impact factor as 'almost entirely due to the quality of the manuscripts', which in turn reflects the confidence of authors in the journal itself. 'This is somewhat self-fulfilling -



The three ESHRE journals now occupy three of the top four impact factor positions in the category of 'Reproductive Biology', and two of the first three positions in 'Obstetrics and Gynaecology'. The impact factors of both Fertility and Sterility and Reproductive Biomedicine Online fell from the previous year.

Reproductive biology

Title	Total cites	5-yr Imp Factor	Impact Factor
Human Reproduction Update	4791	9.599	8.755
Human Reproduction	25468	4.258	4.357
Biol Reprod	21683	3.979	3.870
Molecular Hum Reprod	4525	3.170	3.506
Semin Reprod Med	1156	3.399	3.369
Reprod Toxicol	3243	3.317	3.137
Fertil Steril	25664	3.475	3.122
Reproduction	5703	3.409	3.049
Placenta	4958	3.060	2.985
Sex Plant Reprod	1001	2.231	2.680

Obstetrics and gynaecology

Title	Total cites	5-yr Imp Factor	Impact Factor
Human Reproduction Update	4791	9.599	8.755
Obstet Gynecol	24030	4.665	4.392
Human Reproduction	25468	4.258	4.357
Gynecol Oncol	15387	3.068	3.760
Semin Reprod Med	1156	3.399	3.369
BJOG - Int J Obstet Gyn	11097	3.343	3.349
Menopause	3161	3.474	3.318
Am J Obstet Gynecol	31640	3.460	3.313
Ultrasound Obst Gyn	6829	3.093	3.163
Fertil Steril	25664	3.475	3.122

because the higher impact factors bring in more articles from good authors, which in turn gives the editors more choice. It's also true, of course, that review journals generally tend to have higher impact factors. But it's also fair to say that the ESHRE journals excel on other indicators of a successful medical journal, such as a rising number of submitted manuscripts, profitability, short time-lag to publication, reader involvement, readability, the adoption of technological advances, integrity of the literature, editorial independence and fairness to authors and reviewers.' Outgoing ESHRE Chairman Luca Gianaroli, in his comments on the journals at the Annual General Assembly, noted a mean time of 4.9 weeks between acceptance and online publication for *Human Reproduction*, a mean time of 5.1 weeks for *Update*, and a mean time of just 1.1 weeks for *MHR*.

André Van Steirteghem, editor of *Human Reproduction*, agrees that manuscript quality is the essence of a high impact factor. 'I've never believed in manipulating the impact factor with self-citations or other artefacts,' says Van Steirteghem. 'In fact, I am now more convinced than ever that the best thing you can do is accept only those manuscripts which meet the quality standards of the reviewers and of my own opinion as editor. So over the years I have tried to make *HR* more professional, have had more contact with the associate editors and have developed a closer editorial team of managing and deputy editors. Regular meetings and teleconferences have all been very useful - and for sure an added value.'

For Steve Hillier, editor-in-chief of *MHR*, the key to the impact factor hike lies in several factors, but notably in the introduction of the 'New Research Horizons' section, which, he says, has attracted some interesting and well cited submissions. But this, adds Hillier, 'is only one step on the way to establishing *MHR* as the journal of choice in its domain'. Future plans include even tighter editorial control and 'a drive to ensure that *MHR* leaves the rest of the pack in its wake'.

ESHRE journal editors, from the top, Steve Hillier (MHR), André Van Steirteghem (HR) and John Collins (HRU).

No change in subscription fees to ESHRE journals for members

The Annual General Assembly of ESHRE in Stockholm (see following page) agreed to Executive Committee proposals to freeze members' subscription fees to the ESHRE journals for 2012. This means that subscription prices for both the online and print editions of *Human Reproduction*, *Human Reproduction Update* and *MHR* will remain as in 2011 for all ESHRE members. However, subscriptions for non-members will rise by 5% in 2012. Non-members include academic and corporate institutions, as well as personal subscribers.

New chairman for Committee of National Representatives

Following the resignation last year of Peter Braude from the chairmanship of ESHRE's Committee of National Representatives (CNR), and in a bid to strengthen the working relationship between the CNR and Executive Committee, the ExCo and CNR have agreed that the chairman of the CNR should be the Past Chairman of the Society - and thus Luca Gianaroli was duly appointed to the chairmanship until the end of his term in 2013.

It is hoped that a permanent ExCo member will facilitate communication and exchange between the two committees. With members of the CNR elected by their national colleagues, the CNR provides all ESHRE members with sounding-board access to the ExCo and the opportunity for involvement in congress planning, abstract refereeing, and - most importantly - local representation.

Elections to the CNR were completed last year, and membership of the present committee remains in place until next year.

GENERAL ASSEMBLY OF MEMBERS

// ANNUAL MEETING 2011 //

ESHRE's General Assembly of Members took place at the Stockholmsmässan, Stockholm, on 5th July 2011 at 18.00. The minutes of the meeting are recorded below. Matters arising and their approval will take place at next year's Assembly in Istanbul.

1. Minutes of the last meeting held in Rome

- The minutes of the 2010 Annual Assembly of Members (AGM), having been circulated to all members in Focus on Reproduction (September 2010), were approved. There were no matters arising.

2. Membership of the Society

- Membership of the Society now stands at 5477, a slight decrease on last year's number, with almost 71% of members now coming from Europe. The top membership countries are USA (355 members), UK (340), Italy (306), Netherlands (290), Germany (290), and Spain (270). Growth in membership continues from India (159 members), Japan (100) and China (51).
- Disciplines most prominently represented are embryology (1670 members) and reproductive endocrinology (1516), but there is strong membership growth in andrology and reproductive genetics. 'ESHRE is not a society of clinicians,' said the Chairman, noting that around 50% of the membership is now drawn from basic science, laboratory disciplines and nursing. 'This is what ESHRE has always aimed for,' added the Chairman.

3. Society activities

Training

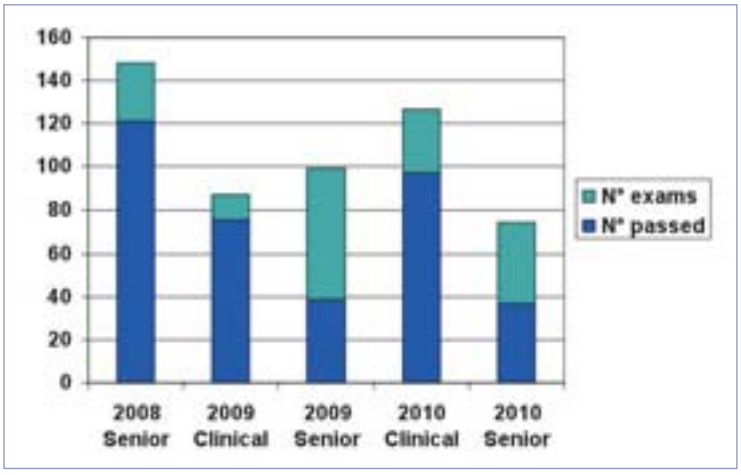
Campus events and precongress courses continue to dominate the training programme, with a 2011 level of activity slightly reduced from 2010's peak (of almost 40 total events). The Chairman explained that the 2011 Campus programme had been slightly scaled back to 2009 levels, but, he said, 'there is still much going on', with already more than 20 planned for 2012 (including precongress courses). Sixteen precongress courses were run in Stockholm, with seven of them fully booked; 13 precongress courses have been scheduled for 2012 in Istanbul.

Future annual meetings

The Society's 28th annual meeting will take place in Istanbul from 1-4th July 2012 at the Istanbul Congress Center; the 29th annual meeting in 2013 will be held in London and the 30th in 2014 in Munich.

Embryology certification

- While the number of applications for senior certification continues to fall (following introduction of the scheme for seniors in 2008), applications received and accepted for certification in clinical embryology remains buoyant, with more than 140 accepted in 2011. Almost 100 passed their exams and received clinical certification in 2010.
- Two innovations in the certification programme were introduced in Stockholm:



Embryology certification results achieved since the scheme was launched in 2008.

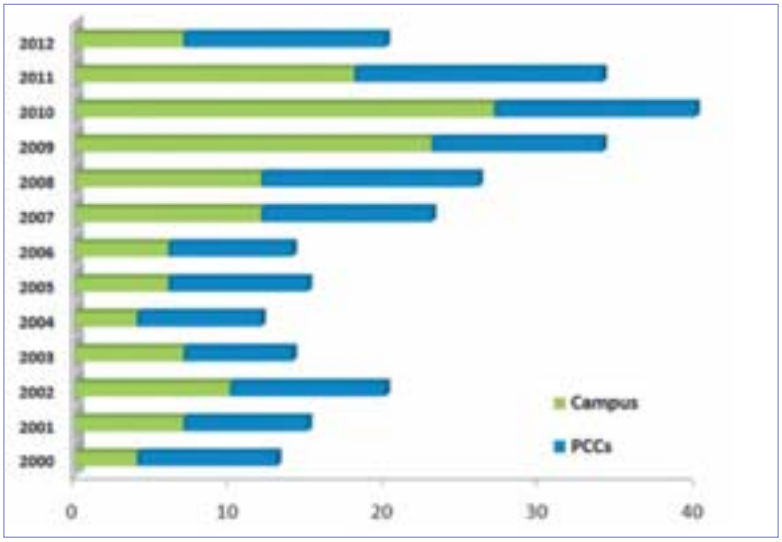
* The Continuous Embryology Education Credit System by which embryologists can collect education credits, and thereby renew their certificate. Senior clinical embryologists will need ten credits and clinical embryologists six credits, obtained over a three-year period, in order to apply for renewal. Attendance at scientific meetings, publications, contributions to meetings and courses will all be taken into consideration for the award of credits.
* The ESHRE certification scheme will also be extended to outside the borders of Europe. Appropriately, this will begin with the 2012 examination to be held before the annual meeting in Istanbul.

Collaborations

- In 2011 ESHRE became a member of the Alliance for Biomedical Research in Europe, an organisation of various associations which aims to promote research across all medical disciplines.

4. ESHRE journals

- 2010 impact factors for all three ESHRE journals were released in June and show remarkable increases: *Human Reproduction Update* from 7.042 in 2009 to 8.755 in 2010; *Human Reproduction* from 3.859 to 4.357, and *MHR* from 3.005 to 3.506. The results, said the Chairman, were 'astonishingly high', and 'a great achievement'. *Human Reproduction Update* now leads the category of obstetrics and gynaecology, with *Human Reproduction* in third place, while all three ESHRE journals occupy the first four positions in the category of reproductive biology. The Chairman singled



Campus events 2005-2011, with those already planned for 2012. With Campus and precongress courses a reaffirmed priority, SIG and Task Force expenditure is expected to reach almost 1 million euro in 2011.

out the achievement of *MHR* in raising its impact factor so much in just 12 months - 'an incredible jump, and we are very proud of this,' he said. The Chairman congratulated the editors and the editorial office.
- Circulation of all three journals continues to rise, particularly among academic consortia, which suggests an even wider readership than indicated by circulation alone (which for *Human Reproduction* now stands at 7000). Circulation of *MHR* reached almost 5000 in 2010, a fine achievement, said the Chairman, given the journal's predicament only five years ago.
- Time from acceptance to online publication has been cut dramatically by all three journals, *Human Reproduction* to a mean of 4.9 weeks, *Update* to a mean of 5.1 weeks, and *MHR* to a median of just 1.1 weeks.
- 2012 subscription prices for the journals (online and print) will remain as in 2011 for all ESHRE members, but for non-members (including academic and corporate institutions, as well as personal subscribers) the price will rise by 5%.

5. Paramedical group

- Jolieneke Schoonenberg-Pomper, chairman of the Paramedical Board, reported that 11% of the total ESHRE memberships (604) were from the Paramedical Group; this represented an increase of 0.6% from 2010. Paramedical members comprise nurses, midwives, lab technicians, counsellors and psychologists, and ESHRE-certified clinical embryologists.
- Among the training events previewed was a first workshop for paramedics, junior doctors and embryologists to be held in eastern Europe (in St Petersburg in September). In March 2012 the Paramedical Group will host a training course for those new to the theory and practice of medical research in Amsterdam.

6. Financial report

- The Chairman presented the report of the Finance Sub-committee showing the balance sheet (income and expenditure) for 2010 and the budget for 2011. Both income in 2010 (5,909,026 euro) and expenditure (5,759,414 euro) were slightly less than budget, and showed a small favourable balance of 149,611 euro. The budget for 2011 sets a higher negative balance of -190,038 euro, much accounted for by continuing investment in the SIGs and Task Forces; SIG expenditure has been budgeted at 699,000 euro for 2011 (12% of total expenditure), with Task Forces accounting for a further 4%. The annual meeting continues to provide the Society's greatest source of income (66%) and expenditure (57%).
- The financial state of the Society was described as 'good', and the report was approved by the members.

7. New Executive Committee

- Five members of the Executive Committee stood down having served two two-year terms: Jean François Guérin (FR), Timur Gürgan (TR), Carlos Plancha (PT), Veljko Vlaisavljevic (SL), and Françoise Shenfield (GB), who will remain an ex officio member of the ExCo as Co-ordinator of the Special Interest Group & Task Force Sub-committee following the completion of Søren Ziebe's two-year term of office.
- The nomination of five current ExCo members to continue their membership for a second two-year term was approved by the membership: Ursula Eichenlaub-Ritter (DE), Antonios Makrigiannakis (GR), Miodrag Stojkovic (RS), Anne-Maria Suikkari (FI), and Etienne Van den Abbeel (BE) were re-appointed for a second term of two years.
- The nomination of seven new members of the ExCo was approved by the membership, and Carlos Calhaz-Jorge (PT), Jacques De Mouzon (FR), Roy Farquharson (GB), Anis Feki (CH), Niels Lambalk (NL), Milan Macek Jr. (CZ), and Cristina Magli (IT) were appointed as new members of the ExCo.
- The nomination of the Finnish gynaecologist Juha Tapanainen as Chairman Elect was approved by the membership. Juha will take over as ESHRE Chairman at the 2013 General Assembly in London, after Anna Veiga completes her two-year term as Chairman.
- Luca Gianaroli stood down as ESHRE Chairman, to be formally replaced by Anna Veiga. Luca received warm appreciation from the membership for his tireless and inspiring work.

8. Election of honorary members for 2011

- The two nominees proposed by the Executive Committee for honorary membership in 2012 were Sir Ian Wilmut (international) and Victor Gomel (national). Both nominations were ratified by the AGM.

7. Any other business

- There was no other business.

● The next Annual Assembly will be on 3rd July 2012 in Istanbul at 18.00 pm.

Special Families campaign builds Wall of Hope for infertile couples in Europe

Fertility Europe in Stockholm

Twenty-nine patient representatives from 17 European patient organisations/countries from across Europe attended our Annual Members Meeting in Stockholm. We had a full agenda and one of the liveliest sessions was on our policy work and taking forward the work of our policy sub-group, which was formed the previous year in Rome. The group, led by Isabelle Chandler, had met on several occasions during the year via Skype in order to draft our first policy paper on *Equity of access to Medically Assisted Reproduction*, which had been discussed at our previous members meeting in Prague in March 2011. The many useful comments and suggestions from that meeting were then incorporated into the draft presented in Stockholm. An excellent discussion with further suggestions for amendments and refinements were made - which the sub-group will work on over the next few months with the aim of circulating a final draft soon. The plan is to use this policy paper as a briefing document to give to policymakers and the press, and as a platform to share ideas with ESHRE. Our members come from all over Europe with different laws and different cultures - so it is important that the policy is something that all patient organisations can support. We agreed that our next policy paper should be about prevention.

Our members had expressed a desire to know more about the work of ESHRE and how it functions. We were therefore delighted to once again welcome Anna Veiga, the incoming Chairman of ESHRE, to the meeting to speak to explain the Society's history and its work in advocacy, education and data collection.

Finally, our Executive Committee member and Vice-Chair Denisa Priadkova from Bocian/Slovakia, brought us all up to date with our Special Families project. The Wall of Hope, with postcards from patients from all over Europe, came from an idea 18 months before and had now become a reality in the main entrance hall of the congress centre in Stockholm. The project will run until the end of 2011 and is aimed at raising awareness right across Europe.

Finally, but very importantly, can we thank ESHRE once again for their generosity in allowing our delegates entry to the congress, providing the room for our meeting and of course our booth in the exhibition. We are truly grateful.

Clare Lewis-Jones MBE
Chair Fertility Europe

Our Special Families campaign

Couples with fertility problems need hope and reliable information. In June 2011, in order to provide them with both, Fertility Europe introduced in 19 European countries its first Special Families Campaign on www.fertilityeurope.eu.

The campaign sends a multiplied message of hope for fertility in the form of postcards with stories, messages and notes on prevention and treatment. Thousands of postcards with moving stories are expected to cross Europe before October 2011.

The goals of the Special Families campaign are to raise awareness of fertility and give a voice and a face to those concerned. Those who successfully travelled the bumpy road to a family life are a source of hope for millions. Sharing their dramatic and emotional stories with others is a great way to share hope.

The Special Families campaign is a collection of postcards made from pictures and stories of special families and sent from Fertility Europe member countries. The postcards will be created at www.fertilityeurope.eu/specialfamiliescards and sent by e-mail to family planning couples facing difficulties in conceiving and collected in the National Galleries on the internet.

● For more information on the Special Families Campaign please contact Denisa Priadková, Vice Chair of Fertility Europe at info@fertilityeurope.eu

SPECIAL INTEREST GROUPS

// STEM CELLS //

A dapper little SIG, but more hands are welcome

Steering committee
Karen Sermon (BE), Co-ordinator
Rita Vassena (ES), Deputy
Anis Fekis (CH), Deputy
Carlos Simon (ES), Past Co-ordinator

The year has been a good one for the SIG Stem Cells: two successful hands-on workshops in Valencia and Barcelona were followed by a well attended and scientifically stimulating precongress course. Indeed, the hands-on workshops were such a success, also attracting participants from outside ESHRE, that we have now decided to make this a recurrent activity, with the next workshop probably taking place in early 2012 in Stockholm.

Precongress courses

The precongress course organised jointly with the SIG Embryology covered everything - or at least those parts of everything that we know of - between the embryonic stem cell and the blastocyst. It was interesting to see how questions such as what really determines toti- and pluripotency can be answered when looked at from the viewpoint of the embryo, or from that of the stem cell. Very often, the answers are the same, which strengthens our conviction that embryonic stem cells can act as a model for embryos, and as such have a place in the scientific community of ESHRE.

We plan to have our next PCC in Istanbul on pluripotent stem cells, cancer disease and fertility preservation, a field in full ebullition that will interest many ESHRE members, both clinicians and scientists. Along with an interest in stem cells as models in developmental biology, and their use for fertility specialists as potential sources of gametes after differentiation, this is a further aspect of stem cells where reproductive scientists (in the broadest sense of the word) and stem cell biologists meet.

Membership

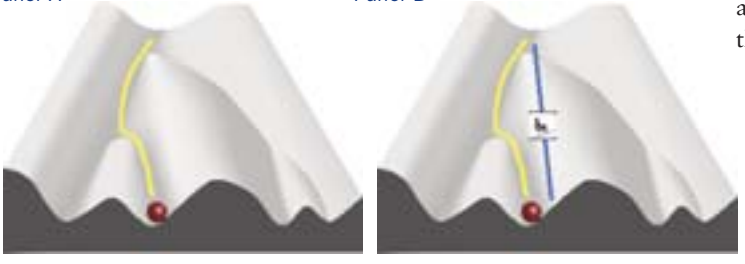
Our past success is in no small way thanks to our Past Co-ordinator Anna Veiga (now chairman of ESHRE) and Co-ordinator Carlos Simon, helped and assisted by deputies Anis Feki (now a member of the Executive Committee of ESHRE) and myself, with Rita Vassena as Junior Deputy (who is certainly a future coordinator in the making!). However, because of his increasing duties elsewhere, Carlos Simon has delegated his role as Co-ordinator to myself one year earlier than planned. This means that Rita Vassena has been promoted to Deputy, and that there is now a seat available as Junior Deputy. So I take this opportunity to call upon interested members of the SIG Stem Cells to come forward and participate in the running and organisation of the SIG. Once elections for (junior) deputies are scheduled, we will then have valuable candidates to ensure the continuation and expansion of the SIG.

Indeed, the SIG Stem Cells is a relatively small SIG, nominated by many ESHRE members as their second field of interest. We in the steering committee, however, believe that there is a tremendous potential for many members who could join - so please, the next time you fill in your ESHRE membership renewal form, consider the SIG Stem Cells as your first choice special interst. Moreover, as a relatively young SIG working in a constantly moving and scientifically challenging field, we would specifically wish to encourage all those young PhDs and post-docs working in IVF and research labs to join the SIG Stem Cells, and to ultimately become a significant factor in its future success.

I hope to prove a worthy successor to Carlos Simon, and, with the help of an enthusiastic membership, to make the SIG stem cells an ever-expanding success.

Karen Sermon
Co-ordinator SIG Stem Cells

Panel A *Panel B*



Panel C

Illustration of a novel concept presented during a long day's work at this year's precongress course: Waddington's epigenetic landscape described in 1940 holds the dogma that, once cells have rolled down from their undifferentiated peak into a differentiated valley, they cannot go back (panel A). Current experiments with induced pluripotent stem cells challenge that dogma (panel B). In the future, it is probable that we will be able to manipulate cells from one level of pluripotency to another, and from one differentiated state to another, as illustrated by the 'new epigenetic landscape' in panel C.

RCOG meeting a highlight of the year so far

Steering committee
Vasilios Tanos (CY), Co-ordinator
TC Li (GB), Deputy
Gregoris Grimbizis (GR), Deputy
Natasa Kenda Suster (SI), Junior Deputy
Marco Gergolet (IT), Past Co-ordinator

One of the highlights of the year for the SIG Reproductive Surgery was a two-day meeting in London jointly organised by the Royal College of Obstetricians and Gynaecologists, ESHRE and European Society for Gynaecological Endoscopy. It was a very successful and well attended event, with very positive feedback. Course organisers Luciano Nardo (GB), Stephan Gordts (BE) and Marco Gergolet (IT) aimed to provide those with an interest in reproductive surgery with reviews of current evidence-based care and up-to-date recommendations for good clinical practice. A strong scientific programme and international panel of speakers guaranteed some excellent lectures with lively discussion and debate over the two days.

The opening day began with a session on basics, covering set-up and safety measures for laparoscopy and the implementation of training and accreditation in reproductive surgery. The session moved on to tubal surgery - with discussion on why the fallopian tube fails - salpingectomy versus salpingostomy, reversal of sterilisation and peri-adnexal adhesions. A session on endometriosis followed, which covered the rationale of treating early stage endometriosis, endometriosis and IVF, and rectovaginal endometriosis. Ovarian surgery concluded the first day's programme, with discussion on management of endometrioma, adnexal torsions and borderline ovarian tumours.

Day two concentrated on uterine surgery and fertility preservation. Beginning with indications and the classification of myoma, the programme covered the pros and cons of hysteroscopic and laparoscopic myomectomy, the risks and benefits of surgical treatment for adenomyosis, the treatment and prevention of intrauterine adhesions and treatment of congenital uterine anomalies. The final session of the event was on fertility preservation, beginning with techniques and efficacy before cancer treatment. Ovarian stem cells and orthotopic versus heterotopic ovarian transplantation were discussed before the final thought-provoking lecture on 'Uterine transplantation: reality or fiction?'.

Feedback from the meeting indicated that it was an enjoyable and educationally worthwhile event, with widespread appreciation of the expertise shared and the opportunity for interactive discussion on some interesting and sometimes controversial topics.

In May we organised a Campus course in Grado, Italy, on how surgery can increase the success rate of ART. The event was well attended, with stimulating discussion after each presentation - a sign of the good quality of the lectures and preparation of the participants. The goal of the organisers was not *ex cathedra* lectures but a peer-to-peer exchange of experience. The first day was focused on diagnostic tools, followed by congenital and acquired uterine anomalies. The second morning considered ovarian and fallopian tube pathology. The final lectures addressed a need for the standardised training of young surgeons and for an integrated reproductive medicine and surgery service across Europe.

Speakers at this year's precongress course: left to right, Marco Gergolet, Maria Mercedes Binda, Vasilios Tanos, Stephan Gordts, Rudi Campo and Antoine Watrelot.

Events in Stockholm

Once again, our precongress course this year proved of high quality. The course addressed the problem of gynaecological adhesions and their reproductive implications. The lectures covered the theoretical explanation of adhesion formation and the clinical implications of leaving or treating them. The first part of the course covered intra-abdominal and particularly tubal adhesions, and the second uterine synechiae.

The business meeting reviewed plans for the coming year, and welcomed the re-formed steering committee.

Marco Gergolet
Past Co-ordinator
SIG Reproductive Surgery

A working group to investigate culture media

Steering committee
Kersti Lundin (SE), Co-ordinator
Maria José de los Santos (ES), Deputy
Josephine Lemmen (DK), Deputy
Cristina Magli (IT), Past Co-orindator
Ana Sousa Lopes (BE), Junior Deputy

The SIG Embryology has had another active year in which we tried to develop a fruitful mix of basic, clinical and practical interest.

We are happy to announce that our membership has increased since last year, now, with 1670 members, the largest of ESHRE's SIGs (closely followed by the SIG Reproductive Endocrinology).

This year also sees a change in the steering committee, with myself, Kersti Lundin, taking over as Co-ordinator from Cristina Magli, who will now be the Past Co-ordinator. Etienne van den Abbeel who has been a very active and appreciated committee member has stepped down from his position as Past Co-ordinator. Deputy board members are Maria José de los Santos and Josephine Lemmen. We also have a new Junior Deputy member this year, Ana Sousa Lopes from Belgium. Carlos Plancha will help our close collaboration with the Task Force Basic Science in Reproduction.

Courses and workshops

Our courses and workshops are always very well attended, usually with a number of participants ranging between 100 and 200. In the spring we ran a very successful update workshop in a beautiful and sunny Salzburg, organised in collaboration with the Austrian Reproductive Medicine Society. The course - **Practical aspects of non invasive selection of gametes, embryos and blastocysts in a modern IVF laboratory** - was covered by a number of excellent lectures, working our way from sperm DNA fragmentation and IMSI/ICSI through oocyte and embryo quality assessment to the newest proposals of embryo selection. We were also invited to a fantastic party at the old castle. Looking at it from below, it was amazing that we could walk there at all, but we did, and were rewarded with food, drinks and games.

Because embryology is such a core issue in assisted reproduction, we often collaborate with other SIGs and Task Forces. Thus, at the annual meeting in Stockholm this year, our precongress course was jointly organised with the SIG Stem Cells, and was again very well attended with just over 300 registered participants. The course focused on **The blastocyst: perpetuating life**, and covered both basics, such as mitochondria and microRNAs during embryo development, as well as more practical aspects such as cryopreservation. Webcasts from the course can be followed on the ESHRE website.

Forthcoming events

Next year, on 19-21st April, we are organising a workshop in Stresa, Italy, in collaboration with the SIG Reproductive Genetics and Task Force Basic Science in Reproduction, the seventh workshop on **Mammalian folliculogenesis and oogenesis; oocyte legacy for embryology development**. These courses have a basic and research orientation, aiming for highly interactive sessions and have been very successful. Please read more on the ESHRE website.

Our other great news, of which many of you will be aware, is that we have now published a consensus document on embryo assessment in collaboration with Alpha Scientists. The paper is published in both *Human Reproduction* and *RBM Online*, with free access. We see this first document as a great step towards a worldwide common assessment system for oocytes and embryos.

The consensus on embryo assessment developed by the Alpha Scientists in Reproductive Medicine and the SIG Embryology is now published.

We will also now be focusing on the launch of the planned *Atlas of Embryology*, which will build upon the assessment system of the consensus paper. A lot of images have already been collected from many contributors, but, as with most projects, things take longer and involve more work and more problems than originally expected. The IT section at ESHRE's Central Office have been working very hard to put a media platform in place, where all pictures can be downloaded and stored in a way that provides easy access for the users. Hopefully, this will be completed by early autumn. As soon as we have a trial version, it will be announced on our website.

Finally, we are pleased to announce that ESHRE's Executive Committee has agreed to the formation of a new working group within SIG Embryology to look into the many issues related to culture media, such as composition, requirements, research models, child and placental correlates. We all realise that these are extremely important subjects, and it will also be the topic for our precongress course in Istanbul 2012.

Kersti Lundin
Co-ordinator SIG Embryology

More published data on endometriosis

Topics of interest to the SIGEE were again well represented at this year's annual meeting in Stockholm - there was something for everyone in the programme.

Our precongress course, on the **The impact of the reproductive tract environment on implantation success**, was well supported with over 100 members at all sessions. Huge thanks go to our contributors and the eager discussants, which ensured a very successful, inspiring and informative start to the meeting.

Our SIG business meeting also had a healthy attendance, with the following key points discussed:

- Lone Hummelshoj updated us on three important WERF studies. Data from the Global Study of Women's Health (GSWH) are now published (http://www.ncbi.nlm.nih.gov/pubmed/21718982). Krina Zondervan will deliver a keynote lecture at this year's World Congress on Endometriosis based on data from the GSWH and Women's Health Symptoms Study (WHSS). The EndoCost study protocol was published last year (http://www.ncbi.nlm.nih.gov/pubmed/21160141) and extracts of data were presented in Stockholm, with more being presented at WCE2011.
- A major achievement this past year has been the development of an informational five-minute film about endometriosis, which to date has had more than 15,600 plays. It aims to help women recognise the symptoms of endometriosis and explain the treatment options. It will be made available in French, German, Italian and Spanish. WES president Hans Evers and the vice-president of the European Parliament, Diana Wallis MEP, produced filmed statements at the time of the film's launch urging women with symptoms to seek early help. All three films may be viewed at http://endometriosis.org/news/general/first-ever-awareness-film-on-endometriosis-launched-by-world-endometriosis-society/ .

Those members who wish to be kept up to date with news in endometriosis may follow Lone on Twitter at www.twitter.com/endometriosis.

Future activities

We now look forward to our SIG agenda for the next 12 months and beyond.

By the time you read this many SIG members will have attended the 11th World Congress on Endometriosis meeting in Montpellier - I am sure this will be an outstanding success and further strengthen the global endometriosis network.

The day after the congress WES has arranged a consensus workshop on the management of endometriosis, where 32 international professional and patient organisations will participate; Gerard Dunselman and Thomas D'Hooghe will be representing ESHRE.

Next on our SIG calendar is the ESHRE Campus meeting on **Endometriosis and IVF** in Rome on 28-29th October (http://www.eshre.eu/page.aspx/1224). The meeting promises to be comprehensive and features sessions on the impact of endometriosis on the IVF procedure and the impact of IVF on endometriosis, treatments pre- and post-IVF from the surgeon's perspective and the effect of endometriosis on IVF-derived pregnancies

Looking further ahead we have an exciting precongress course prepared for Istanbul on 1st July 2012: this will be a joint course with the ASRM on the theme of **Pain and endometriosis**. Please put this event in your diaries now. The course will consider clinical issues as well as mechanistic insights and the best available evidence for clinical management. It should appeal to all those with an interest in endometriosis and pain mechanisms.

And please come forward now with your suggestions for our SIG's precongress course in London in 2013. We need your suggestions. We hope to see many of you again soon in Montpellier and Rome - and please let us know what you would like to see your SIG deliver for you

Hilary Critchley
Co-ordinator SIG Endometriosis & Endometrium

Long-term prognosis after recurrent miscarriage

Steering committee
Ole B Christiansen (DK), Co-ordinator
Mariette Goddijn (NL), Deputy Co-ordinator
Siobhan Quenby (GB), Deputy Co-ordinator
Marcin Rajewski (PL), Junior Deputy
Roy Farquharson (GB), Past Co-ordinator

The annual meeting in Stockholm must be deemed a big success in our efforts to enhance interest in early pregnancy complications within ESHRE. The lectures in the precongress course organised in collaboration with the SIG Reproductive Genetics were of high scientific standard and most of them were very useful for both geneticists and clinicians.

Firsts in Stockholm

For the first time there were four early pregnancy sessions at the main meeting. The sessions on Monday and Tuesday morning were especially well attended and discussions were good. Two presentations from one of the selected oral communication sessions were chosen for discussion at the press conference, and received widespread press coverage. These two studies looked at the long-term prognosis for pregnancy and live birth in patients with recurrent miscarriage, and the data presented will be very useful in counselling patients in clinical practice. The study by Lund et al showed that 67% of patients with recurrent miscarriage referred to a Danish miscarriage clinic would experience a live birth within five years, whereas a study by Kaandorp et al showed that 86% of Dutch patients would achieve a pregnancy after 24 months, with a median time to subsequent pregnancy and live birth of 41 weeks.

Also for the first time ever, the Clinical Science Award winner at an ESHRE annual meeting came from the SIG Early Pregnancy. Dr Ai-Wei Tang from the Liverpool Women's Hospital won the prize for her presentation of a randomised trial of prednisolone for women with recurrent miscarriage and high uterine natural killer cells.

At the business meeting, which was also attended by Professor Mary Stephenson from Chicago, who is organising an early pregnancy special interest group in the USA, it was agreed to write a SIG Early Pregnancy report for *Human Reproduction* with guidelines for the evaluation of biochemical pregnancies and their treatment among patients with recurrent miscarriage. Repeated biochemical pregnancies are an increasing problem and attitudes on how to deal with them vary considerably.

During the latter part of this year we will be asking all our SIG members to nominate candidates for the election of a new Junior Deputy and Deputy Co-ordinator to take over from the summer 2012.

Early pregnancy reports featured in two of the ESHRE press conferences, with Ole B Christiansen (left), and Kaltum Adam (below) with a model for predicting the risk of miscarriage

Ai-Wei Tang with her Clinical Science Award for Oral Presentation, flanked (left) by ESHRE's Chairman Elect Juha Tapanainen and the SIG EP Past Co-ordinator Roy Farquharson.

Future activities

Our future activities are running as scheduled: the joint ESHRE SIG Early Pregnancy and European Society of Reproductive Immunology meeting about early pregnancy complications in Copenhagen in August looks set to have been a success, with more than 130 registered in advance.

Preparations for the postgraduate ESHRE exchange course on early pregnancy at the ASRM meeting in Orlando in October are almost completed. And although our planned precongress course in Istanbul 2012 **Gamete quality and ovarian reserve as markers for early pregnancy loss** was omitted by error in the printed announcement distributed in Stockholm, the course is indeed in preparation and will be announced later.

Our winter symposium in November/December 2012 will be held in Amsterdam and organised by our next Co-ordinator Mariette Goddijn.

Ole B. Christiansen
Co-ordinator SIG Early Pregnancy
olbc@rn.dk

SPECIAL INTEREST GROUPS

// REPRODUCTIVE ENDOCRINOLOGY //

A new guideline for premature ovarian insufficiency

Steering committee changes

A new committee took over the SIG RE in Stockholm and gave warm thanks to Past Co-ordinator Adam Balen and his committee for their hard work and for setting the scene with so many fine workshops and precongress symposia. The new committee consists of Frank Broekmans (NL), Efstratios Kolibianakis (GR), and a new junior representative Daniela Romualdi (IT). The committee is now looking forward to serving the SIG and representing reproductive endocrinology within ESHRE for the next two years.

Steering committee
Georg Griesinger (DE), Co-ordinator
Frank Broekmans (NL), Deputy
Efstratios Kolibianakis (GR), Deputy
Adam Balen (GB), Past Co-ordinator
Daniela Romualdi (IT), Junior Deputy

Precongress course on ovarian ageing

This year's precongress course attracted more than 200 participants who followed an impressive array of speakers covering all the important scientific and clinical detail of the life cycle of the ovary. Claus Yding Andersen set the scene on the question of whether or not ovarian stem cells still exist in postnatal life. Richard Anderson reviewed the determinants of ovarian ageing, and Helen Picton and Ursula Eichenlaub-Ritter went deeply into the basic science of oocyte metabolism and genetics and how these interact with the developmental potential of the female germ cell. Next were two more clinically orientated presentations: Scott Nelson with a comprehensive update on the value of AMH in ovarian reserve assessment and ART outcome prediction, and Melanie Davies with a summary of evidence on hormone replacement therapy in premature ovarian insufficiency patients. The last session was devoted to fertility preservation (Dror Meirow) and how delayed pregnancy affects society as a whole with respect to population size and the demand for fertility treatments (Siladitya Bhattacharya).

The course once again showed how much can be achieved in a single day on a single topic. It is expected that next year's precongress course in Istanbul - **Optimising the IVF protocol and the use of adjunctive therapies** - with its strong focus on the clinical side of IVF will continue in this tradition and will excite substantial interest, so please register early if you are interested.

The embryo as a patient

Former SIG coordinator Nick Macklon hosted a workshop in beautiful Winchester in southern England. The theme was an examination of how the 'Barker hypothesis', now known as the Developmental Origins of Health and Disease (DoHAD) concept, applies to the periconceptional phase of development. Professor Barker, originator of the eponymous hypothesis, gave an inspiring introductory lecture outlining how evidence grew to support his hypothesis. A number of international speakers - ranging from developmental biologists (Tom Fleming and Mark Hanson), to reproductive epidemiologists (Regine Steegers-Thuinissen) and to clinicians (Rob Norman and Scott Nelson) - showed how nutrition, the early endocrine environment, and toxins may all affect early and later development. Nick provides a full report on page 40.

Upcoming events

- **What you always wanted to know about polycystic ovary syndrome**, Sofia, Bulgaria, 8-9th December 2011. This comprehensive meeting on PCOS, hosted by Stanimir Kyurkchiev, will cover the full spectrum of the syndrome, from definitions to pathogenesis, treatments for hyperandrogenism and infertility to long-term health risks and quality of life.
- **Anti-Mullerian hormone: An update**, Lille, 10-12th May 2012. Didier Dewailly will be hosting this workshop which




The SIG RE's new steering committee, from left to right, Co-ordinator Georg Griesinger, Deputies Frank Broekmans, Efstratios Kolibianakis, and new Junior Deputy Daniela Romualdi

Collaboration with the Cochrane group

Steering committee
Petra De Sutter (BE), Co-ordinator
Arianna D'Angelo (GB), Deputy
Willianne Nelen (NL), Deputy
Jan Kremer (NL), Past Co-ordinator
Kelly Tilleman (BE), Junior Deputy

Following the recent committee elections, we welcomed two new members to the SIG steering committee, Arianna D'Angelo and Kelly Tilleman. Both Karl Nygren and Christina Bergh were thanked for their much valued contribution to our activities, and we hope they continue to participate in the SIG SQART.

Our precongress course in Stockholm (on the subject of patient centredness) was evaluated positively. About 80 people attended and the presentations were judged as good. Unfortunately, only three patient representatives attended, but there was some stimulating discussion.

Future events

The programme of the 2012 precongress course is now finalised. The course will be organised jointly with the SIG Reproductive Genetics and will be titled **Getting the measure of congenital, genetic and epigenetic risks for children born following ART: basic and clinical data**. The programme hopes to be of interest to reproductive physicians, embryologists and basic scientists and will deal with topics such as imprinting, retrotransposons, miRNA. Also featured will be the clinical aspects of epigenetic deregulation in IVF, karyotype abnormalities or other congenital anomalies in children born after ART, low-birth weight and other long-term health implications of children born after IVF and ICSI.

We also expect high interest in a Campus course scheduled for 2012 in Dublin (Edgar Mocanu will be our host) in collaboration with the EUTD Task Force. This will deal with implementation of the European Tissue and Cells directives, risk management, and quality and safety in the ART laboratory, and will include several workshops on applying the directive and dealing with inspections.

Our precongress course in 2013 in London will be based on the ethical aspects of safety issues and developed jointly with the SIG Ethics and Law. The programme is still under construction, but will deal with the ethical aspects of introducing new technologies.

Cochrane collaboration

The SIG SQART been asked by the Cochrane group to collaborate in a project which aims to develop a tool to facilitate implementation of the evidence from Cochrane reviews at all the stages of an ART cycle into daily care. Cindy Farquhar and Willianne Nelen will work together on this. This represents a high level of interest in the SIG SQART and we hope many ESHRE members will follow suit and join us!

Petra De Sutter
Co-ordinator SIG SQART

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will explore all aspects of AMH - its function within the ovary, relationship with follicle number throughout life, and its potential use for assessing ovarian reserve and predicting the menopause.

Business meeting

Only 30 people found their way to the SIG business meeting in Stockholm and accordingly one point of discussion was how interaction with the SIG members could be developed. All agreed on the importance of identifying the needs of SIG members in terms of workshop type (a science emphasis or a more training/educational emphasis) and frequency.

Overall, the feeling in the group was that workshop numbers have reached a maximum in the last two years, and that accessibility, costs and expected participant numbers will need to play a stronger role in deciding the future schedule. However, it was agreed that 2012 would be timely for an update workshop on GnRH antagonists in ART, following a similar event in 2003 in Brussels. Some proposals for the precongress course in London were discussed, but no final decision has been reached as yet.

Guideline development

Under the auspices of the SIG RE and with the support of Nathalie Vermeulen, ESHRE's full-time researcher on the guideline programme, a clinical guideline on premature ovarian insufficiency (POI) will be developed. POI has been identified as a key subject for guideline development. Patients commonly receive inconsistent advice, and disparate approaches to the management of this disorder exist between subspecialities.

A group of experts has now been formed with representatives from gynaecology, pediatrics, genetics, osteology, cardiology, immunology and embryology. A patient representative will also participate in the guideline development group in order to ensure that the patient view will be included. In Stockholm a scoping checklist was finalised, and hopefully by 2013 the guideline should be ready for publication.

Georg Griesinger
Co-ordinator SIG Reproductive Endocrinology

SPECIAL INTEREST GROUPS

// ANDROLOGY //

A new check-list on semen quality available soon

Our precongress course in Stockholm was on the theme of **Lifestyle and male fertility**. Our speakers presented recent data and opinion from the latest studies on a range of topics from those well publicised risks such as obesity, STIs, cancer and recreational drugs through to such less discussed topics as the relationship between exercise (and even intellect!) with semen quality. The meeting was very well attended and each lecture generated vigorous discussion.

We followed the PCC with our annual business meeting where our retiring co-ordinator Roelof Menkveld gave his final annual report and then welcomed the new steering committee. We thank Roelof for his unstinting work and wisdom during his term of office and are very glad he will remain as Past-coordinator to keep us on track! Following the elections the steering committee is now composed of those listed above. We are delighted that all those elected have agreed to serve and we look forward to a vibrant SIG under their leadership.

Steering committee
Sheena Lewis (UK), Coordinator
Willem Ombelet (BE), Deputy
Stefan Schlatt (DE), Deputy
David Mortimer (CA), International Advisor
Charlotte Heavisides (UK), Junior Deputy
Roelof Menkveld (ZA) Past Coordinator

Forthcoming activities

Our first event is an upcoming Campus workshop in association with the SIG Psychology and Counselling on the theme of **The whole man** to be held in Seville on 22-23rd September. This joint workshop will ensure multidisciplinary connections and an opportunity for quite different sectors of the ESHRE membership, from clinicians, psychologists, infertility counsellors and paramedical staff to embryologists and andrologists; all with an interest in male fertility can share their knowledge.

The workshop has been designed to provide a unique opportunity to update social, psychological and medical knowledge in the area of male infertility. It will discuss the impact of infertility on men's well-being and provide an update on male infertility, reaching from an overview on male reproduction to diagnostic procedures and the impact of diagnosis and treatment on men's psychological well-being to current laboratory test procedures and the long-term health of children conceived by ART. The venue is beautiful Seville where we also have a terrific social programme planned. We are looking forward to the development of new networks and collaborations that will lead to greater understanding of the needs and care of our male patients.

The SIG Andrology also has an Education and (laboratory) Semen Quality Control sub-committee and Clinical Andrology Training sub-committee. In the coming year we aim to promote both these committees actively and develop links with other European societies to strengthen our programmes.

Goals and future projects

When in Stockholm we began our terms of office with a brain-storming session on specific goals for the next two years. From this meeting and much e-mailing between committee members, we have agreed several priorities:

- To encourage clinical andrologists (both clinicians and scientists) to make a commitment to active participation in the SIGA. To this end, we will endeavour to design Campus workshops of interest to each. Already we have planned two Campus workshops for the forthcoming year: one on a clinical theme to interest clinical andrologists and urologists (to be co-ordinated by Stefan Schlatt and held in Münster, Germany) and a further one on a scientific/laboratory theme in Thessaloniki, Greece, to be co-ordinated by Ulrik Kvist and Sia Zeginiadan. Further details will be available soon.
- To finalise and publish a specific ESHRE guide on seminal quality and improving the accuracy, transparency and completeness of studies by means of a specific check-list and a flow diagram. The final check-list produced will have various areas of application: designing and constructing a seminal quality study, reviewing a paper on the question, educational purposes, or as an instrument for quality appraisal of research articles in this field. This will be available soon.
- To provide practical training and accreditation in semen analysis performance to ESHRE standards through continuing ESHRE semen analysis courses. The next will be the first in the UK- to be held in Birmingham and run by Jackson Kirkman- Brown and Lars Björndahl in association with the British Andrology Society on 16-17th September 2011.

Sheena Lewis
Co-ordinator SIG Andrology

// PSYCHOLOGY AND COUNSELLING //

A first step into Eastern Europe

Steering committee
Chris Verhaak (NL), Co-ordinator
Jan Norré (BE), Deputy
Uschi Van den Broeck (NL), Deputy
Petra Thorn (DE) ,Past Co-ordinator
Sofia Gameiro (PT), Junior Deputy

The new board was introduced during the SIG business meeting in Stockholm. Chris Verhaak succeeded Petra Thorn as Co-ordinator and will from now on represent our SIG. Jan Norré and Uschi Van den Broeck continue as Deputies and our new Junior Deputy is Sofia Gameiro. We would like to thank Petra for her input over the past three years and wish the new board the best of luck!

The main programme in Stockholm provided an update on the practices of infertility counselling with excellent presentations by Chris Verhaak and Eric Blyth. Participants in our precongress course enjoyed excellent presentations on theory and practice 'in third party reproduction'. Discussions were plenty and in depth, and gave both researchers and clinicians a chance to interact and exchange experiences. This is after all what a conference like ESHRE is all about! We now look forward to the new precongress course in Istanbul in 2012 which will focus on 'the burden of treatment'.

Our first joint Campus workshop with the SIG Andrology will take place in Seville in September on the theme of **The whole man**. The course is targeted at both medical and psychosocial professionals and will introduce participants to issues they may not yet have addressed in their daily practice. It will provide information and an opportunity for discussion on the needs and ways of providing for the latest psychological and medical care of the infertile man in our clinics.

In March 2012 we will move into Eastern European regions with a Campus course in Budapest. The course will focus on developing competence in psychosocial care and counselling and is devised for medical and administration staff to improve their understanding of the psychosocial needs of patients in difficult situations - breaking bad news, third party reproduction or loss and bereavement. Special attention will be paid to issues relevant to Eastern Europe and to cross-border reproductive care.

Uschi Van den Broeck
Deputy Co-ordinator SIG Psychology & Counselling

// REPRODUCTIVE GENETICS //

A new steering committee, and events planned for 2012

Steering committee
Joyce Harper (GB), Co-ordinator
Claudia Spits (BE), Deputy
Ursula Eichenlaub-Ritter (DE), Deputy
Stéphan Viville (FR), Past Co-ordinator
Tania Milachich (BG), Junior Deputy

At our business meeting in Stockholm the former steering committee (chaired by Stéphane Viville with Deputies Sjoerd Repping and Filipa Carvalho, Junior Deputy Claudia Spits and Past Co-ordinator Karen Sermon) handed over to the new team of Joyce Harper, Deputies Claudia Spits and Ursula Eichenlaub-Ritter, Junior Deputy Tania Milachich and Past Co-ordinator Stéphane Viville), as seen in the photo.

A huge thanks to the outgoing co-ordinators, who have organised many fantastic courses and workshops. These included the precongress course 'From genes to gestation' (with the SIG Early Pregnancy), 'Basic genetics for ART practitioners' in Bucharest, 'Accreditation of a PGD laboratory' (with the PGD Consortium and EuroGentest) in Athens, and 'Comprehensive preimplantation screening: dynamics and ethics' (with the SIG Ethics and Law) in Maastricht.

Our precongress course in 2012 is on **Known and unknown congenital, genetic and epigenetic risks for children born following ART**. We are also organising a **Basic genetics for ART** course in Rome and a quality management meeting in Istanbul. We will also be involved in the 7th Campus course on mammalian folliculogenesis and oogenesis organised in Stresa, Italy, in April with the SIG Embryology, SIG Reproductive Endocrinology, and Task Force Basic Science.

Joyce Harper
Co-ordinator SIG RG

TASK FORCES

// CROSS-BORDER REPRODUCTIVE CARE //

New research project about to start, but it's not too late to join

ESHRE's annual meeting is always a time for strengthening collaboration among members and this year was no exception. It is also a time for organisational changes, and so Guido Pennings is now the Co-ordinator of the Cross-border Reproductive Care Task Force, whose membership now comprises Anna Pia Ferraretti (the new chairman of the European IVF Monitoring Consortium), Jacques de Mouzon (a new member of ESHRE's Executive Committee), Tonko Mardesic, Amparo Ruiz, Veerle Goossens (from ESHRE's Central Office) and Françoise Shenfield as Past Co-ordinator (who will co-ordinate ESHRE's SIG sub-committee for the next two years).

Data collection on egg donation in Europe

With our *Good Practice Guide* for practitioners involved in cross-border reproductive care now published,[1] our plans to collect data on egg donors in Europe were finalised in Stockholm, with the confirmed participation of 10 European countries and a study start date in September.

Thus, a meeting in Stockholm of Task Force members and agreed country co-ordinators - whose role is to enrol national centres performing a large number of egg donation cycles - found that several members had already translated the egg donors anonymous questionnaire and were finalising their list of collaborating centres. These centres have agreed to give the questionnaire to consecutive egg donors over a 1-4 month period, depending on the number of donation cycles they perform, so that a minimum of 10 questionnaires per clinic is obtained. Another questionnaire, on the clinic's own egg donation activity, is also required and will be sent to ESHRE's Central Office for collation. As an encouragement, any clinic returning more than 10 egg donor questionnaires will receive a free annual ESHRE membership to a member of its team. So, if your clinic is not yet included, please contact one of the mentioned country coordinators

- Belgium, Petra De Sutter (petra.desutter@ugent.be)
- Czech Republic, Tonko Mardesic (mardesic@iol.cz)
- Finland, Viveca Soderstrom-Anttilla (viveca.soderstrom-anttilla@vaestoliitto.fi)
- France, Jacques de Mouzon (jacques.demouzon@inserm.fr)
- Greece, Dimitri Loutradis (loutradi@otenet.gr)
- Poland, Rafal Kurzawa (Kurzawa@ams.edu.pl)
- Portugal, Carlos Calhaz-Jorge (calhazjorgec@gmail.com)
- Spain, Juana Hernandez and Amparo Ruiz (JHERNANDEZH@telefonica.net, amparao.ruiz@ivi.es)
- UK, Siladitya Bhattacharya and Françoise Shenfield (s.bhattacharya@abdn.ac.uk) (mfi@easynet.co.uk) respectively for academic and private centres
- Ukraine, Valery Zukin (v.zukin@ivf.com.ua).

We hope that this project will provide reliable data about oocyte donation in Europe. Transparency about practice is the best way to counter any rumours about misconduct that are frequently found in the media.

Françoise Shenfield Past Co-ordinator
Guido Pennings Co-ordinator

1. Shenfield F, Pennings G, de Mouzon J, et al. ESHRE Good practice guide for cross-border reproductive care for centres and practitioners. Hum Reprod 2011; 26: 1625-1627.

// PREIMPLANTATION GENETIC SCREENING //

Mission accomplished

Following completion of its pilot study of polar body array CGH for preimplantation genetic screening, the Task Force will be disbanded and its responsibilities passed on to the PGS trial study group. This is in line with ESHRE policy that Task Forces should be temporary groups dealing with specific questions.

The PGS Task Force was set up after the annual meeting in Lyon in 2007, where it became clear that cleavage stage biopsy and FISH were not reasonable approaches to PGS. It was then that the idea of a proof-of-principle study developed. The positive outcome of that study is now behind the design of a randomised clinical trial in women with advanced maternal age. The trial has two aims: first, to assess the impact of 24-chromosome polar body PGS on live birth rates; and second to estimate whether consistent oocyte aneuploidy in one cycle is predictive of consistent aneuploidy in future cycles.

All the prerequisites for a successful trial are now in place - a sponsor (the Cambridge-based company BlueGnome, a specialist developer of microarray-based screening technologies), the study and training centres, and ESHRE's data management. Following the move of Markus Montag, one of the pilot study co-ordinators, from Bonn to the University of Heidelberg, both sites will now operate as a joint training and trial centre.

Joep Geraedts
Trial co-ordinator

The recurring example of Mahmoud Fathalla

In May this year Egypt's Professor Mahmoud Fathalla received the degree of Doctor Honoris Causa from the University of Hasselt in Belgium in recognition of his tremendous research on the origin and advantages of diversity in reproductive health. Fathalla is recognised thrughout the world as an exceptional champion of the health and rights of women in poor countries.

We chose this occasion to organise a steering committee meeting of the Task Force to discuss future activities. We have now selected ten pilot countries where accessible fertility centres will be introduced. With the support of WHO, we hope to persuade the politicians and healthcare providers of these countries to get involved in the project and recognise the severity of involuntary childlessness.

In the meantime we finalised the protocol of our first trial to examine the value and effectiveness of a new method of low-cost IVF; the study will take place at the Genk Institute for Fertility Technology. If the results are reassuring, many other studies will be organised in different centres in resource-poor countries.

'Women's health and diversity'

A May symposium on **Women's health and diversity** saw Sheryl Vanderpoel of WHO stress the essential importance of infertility care in reproductive health, especially in developing countries. She cited the World Population Plan of Action 1974 in which the following statement was made: 'All couples and individuals have the basic right to decide freely and responsibly the number and spacing of their children and to have the information, education and means to do so.' She also drew inspiratin from M Fathalla: 'Family planning services are not demographic posts. Women are not targets for contraception, from which policy makers and administrators set quotas for services to accomplish. Family planning programmes work best when they are part of, or linked to, broader reproductive health programmes that address closely related health needs.'

Guido Pennings also commented on the ethical issues of infertility treatment in developing countries. He drew the following conclusions:

- Efforts should be made to reduce excessive social reactions to infertility inspired by pronatalism.
- Infertility treatment should be part of an integrated reproductive care programme which includes family planning, mother care, and reproductive health.
- Education, empowerment of women and economic prosperity are the most effective solutions to most problems related to both population growth and infertility.
- Access can be improved by strongly reducing the direct costs of treatment.

And Mahmoud Fathalla himself gave a memorable lecture on women's right to health. He suggested seven propositions, which included the right to safe motherhood and the right to the benefits of scientific progress

Research - Infertility in resource-poor countries

Nathalie Dhont, one of the active members of our Task Force, has successfully defended her PhD at the University of Ghent on the *Clinical, epidemiological and socio-cultural aspects of Infertility in resource-poor settings - Evidence from Rwanda*. The most important conclusions of this very interesting thesis were the following:

- A history of sexual violence, HSV-2 infection and HIV infection are important predictors of infertility in Rwanda
- Obstetric events, HIV and other STIs contribute approximately equally to secondary infertility
- The risk of acquiring HIV is increased in infertile couples
- Infertile couples should be targeted for HIV prevention programmes and their infertility problems addressed; this calls for accessible and affordable infertility services
- There is an urgent need for political willingness to put infertility care on the public health agenda in resource-poor countries.

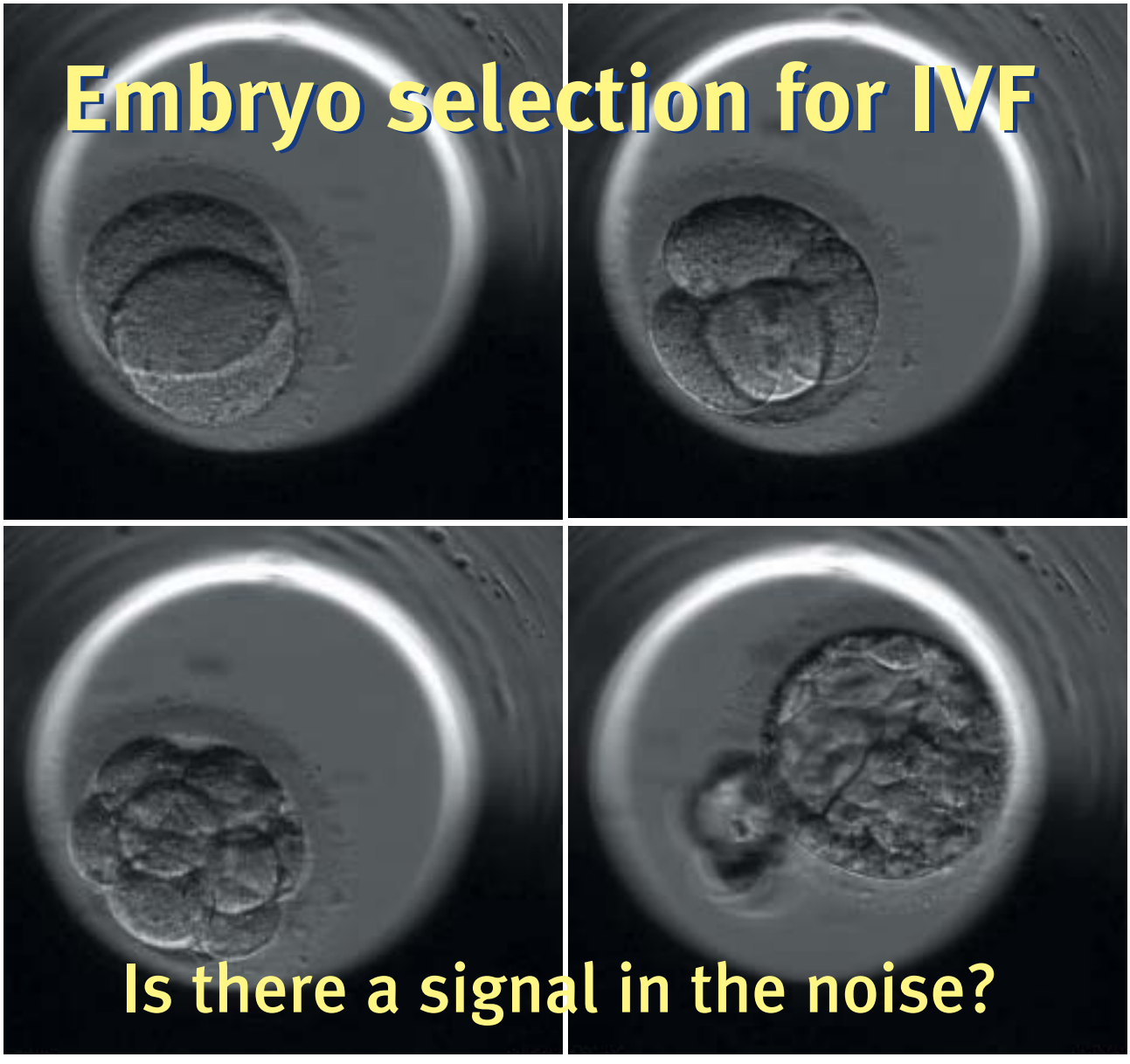
Willem Ombelet
Co-ordinator TF Developing Countries and Infertility

Study group meeting on social aspects of fertility care in developing countries

The social study group of our Task Force will organise an expert meeting in Genk, Belgium, on 21-22nd November 2011, in co-operation with WHO and Walking Egg npo. The meeting will study

- Barriers to infertility care and how to overcome them
- Infertility care in times of HIV/AIDS
- Quality of care in counselling, patient-staff interaction, privacy
- Ethical concerns and clinical practice
- Male involvement in infertility care and masculinity

The meeting will also make an inventory of the current state of infertility care in developing countries.



Embryo selection for IVF

Is there a signal in the noise?

It has been claimed that vitrification will render embryo selection redundant. Simon Fishel and embryologist Alison Campbell disagree, saying that embryo selection is in the best interests of the patient. They here describe the latest - and foreseeable - techniques of embryo selection and propose where their value is likely to lie.

There are few, if any, serious IVF practitioners who would not support research to improve the efficacy of the technique. Stimulation drugs and protocols, optimisation of endometrial and humoural factors, and assessment of embryo viability are some of the areas of investigation, albeit of high complexity.

Why is embryo selection considered to be vital? There are two reasons. First is the axiom that embryos are not equal in their capacity to make a viable pregnancy and baby - because fewer than two in ten implant.[1,2] And second, the current system of 'grading' embryos according to a range of microscopic morphological criteria - which are either highly subjective or semi-quantitative and all with varying degrees of apparent correlation to viability - is unsatisfactory.[3]

The embryo, once *in vitro*, is an independent entity; it is separated from the complexity of female physiology and develops on a predetermined metabolic pathway. Its parentally derived genetic make-up and its maternal cytoplasmic composition have predetermining features. And it is the examination of several aspects of these elements within defined culture media which may provide us with meaningful, quantitative information.

'Meaningful quantitative information' is perhaps at the heart of the concept of embryo selection. And essentially, we have two options for realising that concept: a binary option - that is, the embryo is viable or non-viable, normal or abnormal; or a probability option - that is, a ranking of one embryo over another, often based on putative data thought to be indicative of a propensity to implantation or delivery. An example of the former is whether the embryo has monosomy at chromosome 1, or trisomy at chromosome 18. The ranking approach, however, relies on sophisticated algorithms which may or may not have any biological fidelity and are based on observations post-embryo transfer, when the embryos are at the mercy of complex female physiology.

Time and tide wait for no (wo)man

A recent journal commentary has, by spurious argument and statistical sophistry, suggested that, because all embryos can be frozen, there is no need for embryo selection as this could 'never lead to improved live birth rates'.[4] The argument, as presented by the authors, was actually predicated on selection being essential because 'embryos that are cryopreserved have a reduced chance of implanting', but, they said, as long as we can freeze and serially transfer all embryos - now that cryopreservation is efficient and endometrial receptivity better understood - 'the live birth rate per cycle can never be improved'.

Yet efficient IVF is about maximising the chance of a live birth per single attempt - be that per cycle started, per egg collection or per embryo transfer. Hence, the proposition misses the mark, because most patients wish to avoid multiple visits to an IVF clinic - either for reasons of cost, social and emotional stress, or both.

Mastenbroek et al do concede that 'the only parameter that could possibly be improved by embryo selection would be time to pregnancy'. Time in reproductive medicine is a valuable commodity, and is inversely related to reproductive efficiency - indeed, time should be reduced at all cost. So a 35-year-old patient with eight frozen embryos will not be too impressed if on the transfer of the last embryo her 'success' results in a singleton pregnancy from an egg collection performed several months or years earlier - when, by a method of selection, her success might have been gained much sooner.

This same patient may well have achieved the 100% success per cycle started which the commentary implied (provided the successful egg collection was the only cycle started), but the result might also have been perceived as one live birth per seven attempts (one egg collection and six embryo transfers). And not to mention that in a country such as the UK the government regulator (HFEA) must be paid for every attempt, equating to £731.50 for the seven attempts, as well as the clinic's fees per treatment. A further point in this stark example is that, should the couple wish for a second child, a much longer gap than ideal has been created. Patient age and time to completion of their family is critical for optimum success.

Selecting viable embryos at each attempt, therefore, should be beneficial to the patient for many reasons. This is why for several decades there has been so much determined work by scientists to find ways of doing this effectively. Necessity should be the mother of robust scientific innovation!

ALISON CAMPBELL, SIMON FISHEL: 'FOR EMBRYO SELECTION TO BE RELIABLE, WE REQUIRE BOTH THE ROBUST TECHNOLOGY AND ITS DIRECT RELEVANCE TO BIOLOGICAL OUTCOME.'

Sadly, however, we are all too well aware of the flawed technologies, the flawed analysis and erroneous conclusions, which have deleteriously entered the IVF psyche - the story of fluorescence in situ hybridisation (FISH) for aneuploidy assessment, for example. And unless and until a robust technology emerges - such that the computed data have high fidelity - any significant biological relevance must always be treated with utmost caution. Thus, if the ploidy of the inner cells mass could be assessed accurately, the next step should be to ascertain with certainty that the data have biological relevance. Does an aneuploid inner cell mass indeed beget an aneuploid fetus or result in a miscarriage? Or would an euploid inner cell mass guarantee only euploid babies once the embryo reaches delivery? Or does some astonishing form of biological correction out-manoeuvre all our attempts at selection, even with highly accurate information at a precise moment in time? Thus, for embryo selection to be reliable and enduring we require both the robust technology and its direct relevance to biological outcome.

Speaking of aneuploidy

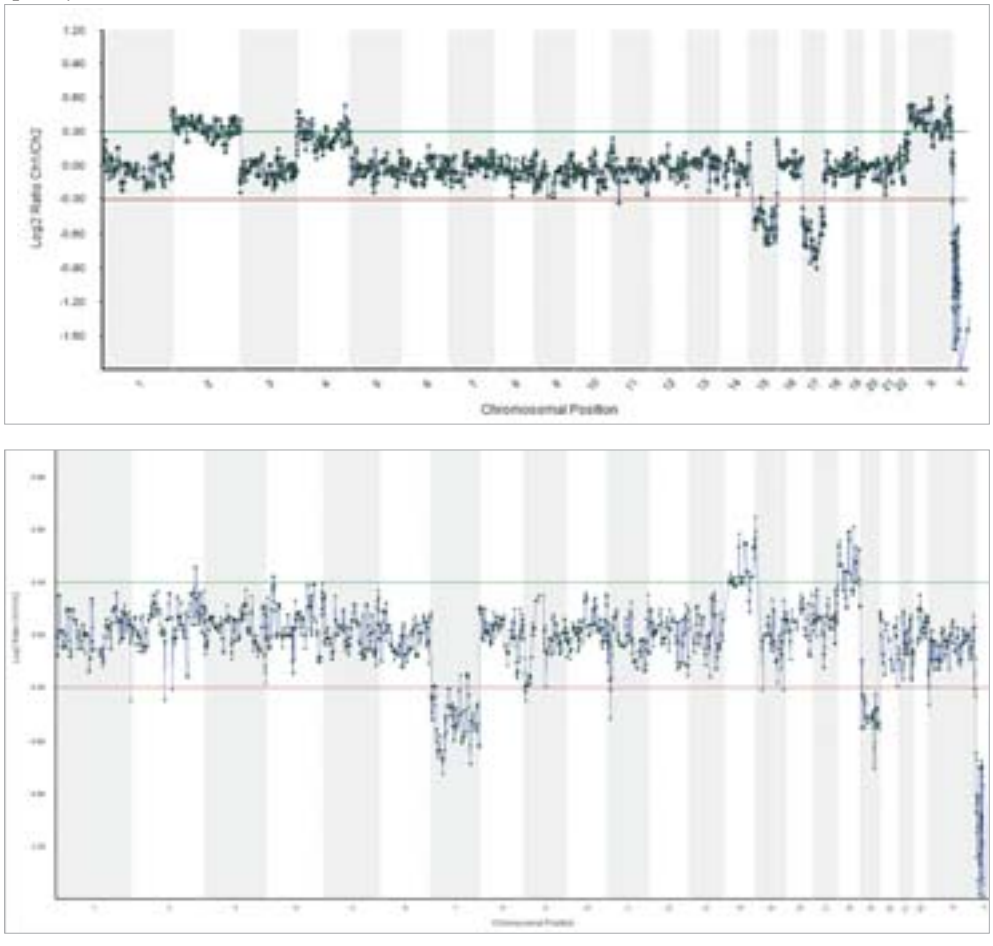
Because human oocytes and embryos carry a significant amount of aneuploidy, and because aneuploidy is believed to be the single largest cause of embryo implantation failure and miscarriage, chromosomal status has become a prime candidate for analysis during IVF.[5] Unlike most other embryo assessment approaches, aneuploidy has clear clinical relevance, is binary in its relationship to biological significance, and is of high enough prevalence to make it a priority for screening.

Just like the 'polywater story' in the 1960s and 70s, early approaches using FISH became a fashion which, unlike polywater, took decades to unravel before its flaws were appreciably understood.[6,7] IVF history will record the use of FISH only in this failed context, and in the future we must avoid similar traps by recognising the weakness of any new technology, selective publishing, meaningless studies, and biased messengers.

However, despite the failure of FISH as it was used and interpreted, the biological relevance and clinical imperative of aneuploidy *per se* to human IVF remains. Logic still determines that by eliminating such embryos each attempt at IVF will be more efficient; and, in some cases, patients will learn important information about their gametes and embryos, thereby helping them make progress.

In 2008 our group and BlueGnome (Cambridge, UK) pioneered the development of array CGH for clinical use, first in polar bodies and then in blastomeres and trophectoderm tissue for assessment of the cell's full chromosome complement.[8,9] It soon became apparent that aneuploidy assessment could be undertaken within 48 then 24 hours, making fresh embryo transfer feasible.

We considered polar body analysis initially in the belief that, if the oocyte is aneuploid, the embryo will also be (and early studies confirmed this) - though we recognised that paternally-contributed and post-fertilisation mitotic aneuploidy would not be detected. But until there is appreciable data on the incidence of mosaicism in the blastomeres of day 3 embryos and the relative risk of false positive and negative results, we need to remain circumspect in the use of blastomere analysis. Similarly, until we fully understand concordance between the trophoblast, both mural and polar, and the inner cell mass, caution is also needed in the assessment of blastocyst aneuploidy. Significantly, the ESHRE PGS Task Force has



Above, array CGH analysis of polar body 1, correlating to an euploid pattern in the corresponding oocyte; below, polar body 1 correlating to an aneuploid pattern (-7, +14, +18, -19) in the corresponding oocyte.

also backed polar body assessment for its studies on aneuploidy for IVF;[10] the highly important data from the randomised trial is much anticipated.

Other platforms such as microarray molecular karyotyping, SNPs, and (q)PCR are emerging as dependable technologies. However, it is essential for commentators to appreciate the variations and limits of each when making comparisons between them; for example, comparing array CGH with metaphase CGH may lead to differences in chromosome gains because of the inherently greater signal noise in the latter technology - thus distorting what might be envisaged as biological fact.

However, these concerns about the fidelity of the data will soon be in the past; what is essential to the future of these technologies is the certainty that the data are of biological relevance. For example, recent studies demonstrate that single chromatid errors are probably of much greater incidence than meiotic non-disjunction in human aneuploidy;[11] and that the effect of advancing maternal age on aneuploidy is more pronounced in M2 than previously considered at M1.[12]

The future of clinical treatment could thus change significantly should the reliable assessment of aneuploidy become routine. For example, now that blastocyst vitrification is efficient and successful, by assessing the trophoblast and by freezing and subsequently transferring a single euploid embryo, we could maximise singleton pregnancies, reduce multiple pregnancies and potentially eliminate OHSS. For those patients with fewer eggs or ethical concerns, assessment of the first and second polar body may remain an option.

Finding correlates - the ranking approach

Currently, embryo selection methods rely primarily on a morphological evaluation of the embryo derived from five or six single conveniently scheduled observations during its *in vitro* development. In many centres, selection of the embryo(s) for transfer tends to be weighted towards its morphology just prior to transfer - a single time point which focuses on cell number and the degree of fragmentation represented by various grading schemes. Apart from the subjective nature of the assessments themselves, inter-laboratory comparison makes reliability very difficult.

The Istanbul consensus workshop on embryo assessment was convened by the Alpha Scientists and ESHRE to define common terminology and the minimum criteria for oocyte and embryo morphology measurement.[13] It was hoped that effective comparisons and standardised reporting would provide an evidence-based grading scheme claimed to be associated with embryo viability (as summarised in the table above), and covering all stages of development from the oocyte to the blastocyst. Whilst standardisation is essential, how the adoption of the scoring system will relate to outcome is yet to be determined.

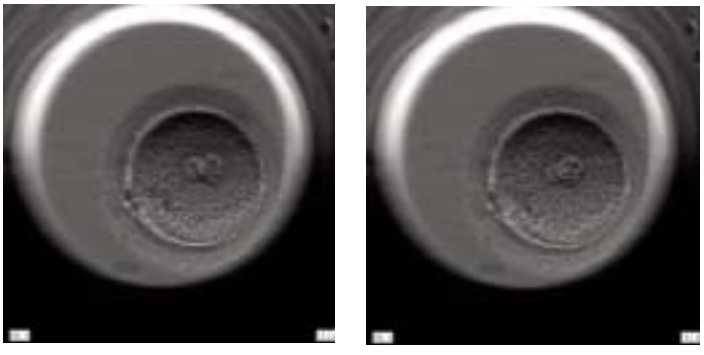
There is growing evidence to support the selection of embryos which display 'optimal' morphokinetic characteristics. But these can be difficult to determine when using standard incubation and embryo visualisation methods when only limited observations are made (both to minimise stress to the embryos and ensure working convenience). Furthermore, there is always inter-patient variability in the timing of these observations, even though many of the developing embryo's morphological features must be accurately assessed at specific time points; some of these, for example, will be directly related to the moment of sperm entry and egg activation.[14,15,16] Hence, although the assessment needs to be performed at strict time intervals - for example, 'post-insemination' - we do not yet know if these assessments are accurate enough for comparison between embryos.

Recent advances in time-lapse microscopy have resulted in several reports of improved embryo selection based on the analysis of images of embryo development. The EmbryoScope, for example, provides time-lapse images taken at several planes, allowing the undisturbed assessment of embryos at multiple time points per hour throughout the entire culture period. Our own (unpublished) assessment of time-lapse microscopy suggests that for some quality indicators, such as

Istanbul consensus on oocyte and embryo morphology

Assessment - topics covered

Oocyte, zygote and cleavage-stage embryo scoring defined by Spain's ASEBIR
UK ACE grading scheme for cleavage-stage embryos and blastocysts
USA SART scheme for cleavage-stage embryos and blastocysts
Molecular and cellular anatomy of the oocyte
Fertilisation and zygotes
Cleavage-stage embryos
Multinucleation
Morulae and blastocysts
Embryology morphology - cell number, fragmentation, cell size
Cumulus-complex scoring
Zona pellucida, polar body, pervitelline space, ooplasmic and vaculorisation scoring
Pronuclei scoring



Time-lapse microscopy images of the same zygote, demonstrating the differing appearance of pronuclei just one hour apart.

Examples of current methods for studying embryo viability

Measurement	Comment	Suggested references
Oxygen consumption	Embryo culture media	Tejera et al 2011; Wiener-Megnazi et al 2011
Quantitative amino acid profiling	Embryo culture media	Sturmey et al 2008
Ca(2+)-induced ooplasmic flows	Particle image velocimetry	Ajduk et al 2011
Birefringence imaging	Oocyte assessment	Montag, Van der Ven 2008
Gene expression	Discarded oocytes	Steuerwald et al 2007
Gene expression	Cumulus cells	Hamamah, Fallet 2010
Soluble HLA-G	Embryo culture media	Warner et al 2008
Protein profiling	The secretome	Katz-Jaffe, Gardner 2008
Metabolomics using RAMAN and NR spectroscopy	Embryo culture media	Nagy et al 2008
Metabolomics using HPLC-MS	Embryo culture media	Marhuenda-Egea et al 2010
Light-induced dielectrophoresis	Direct embryo measurement	Valley et al 2010

pronuclear scoring, even strict time-point scoring may not be enough to support traditional grading because of the dynamic nature of the pronuclei. The two images on page 37 illustrate the very different appearance (and grade) of the same zygote's pronuclei only one hour apart.

The time of the first cleavage related to insemination has also been shown to be predictive of both embryo quality and implantation potential.[17] 'Early' cleavage on day 1 has been correlated with poor prognosis when more than two cells result,[18] and even such 'simple' measurements require strict timing, generally considered to be 25-27 hours post insemination.

Insemination method, culture media and incubation conditions may also have an influence on timing of early developmental events.[19] Transient characteristics, such as multinucleation, have also been reported to have a detrimental effect on embryo implantation, pregnancy and birth rates, and these can be missed when embryos are limited to a single daily observation.[20]

Time-lapse imaging and analysis are thus powerful tools; they not only ensure that such phenomena are observed and recorded without disruption to culture, but confirm that the timing and duration of an event could also be predictive of outcome. Wong et al recently demonstrated that the duration of the first cytokinesis and the second cell cycle can be used to predict development to the blastocyst stage in human embryos.[21] In a retrospective analysis of EmbryoScope-acquired time-lapse human embryo data, a significant association was also demonstrated between the timing of pronuclear fading, the first three cleavage events and successful implantation, with an inverse relationship also demonstrated between the ability of embryos to develop to the blastocyst stage and the length of time for zygote division.[22]

There also now exists a range of metabolomic, proteomic and genomic techniques purporting to assess embryo viability and enhance embryo selection; a slightly dated but useful overview has been provided by Brison et al.[23] The table above highlights some of the areas being investigated. Given the rise and fall of some previously acclaimed metabolomic tests and their associated algorithms, it seems that the aforementioned pitfalls will unfortunately continue for sometime to come - at the expense of the patient!

Summary thoughts

The best means of embryo selection is non-invasive, either by harmless observation of the embryo *per se*, or analysis of its environs. The information obtained should be precise, and preferably binary; ranking is always likely to create dilemmas and, by definition, reduced efficiency. However, most biological data will inevitably be graduated, and therefore any ranking would need to generate highly correlative data for specific parameters. Ideally, data should be obtained independently of the influential reproductive tract - never an easy task.

Thus, we are currently faced with few genuinely useful technologies to help practitioners make choices and patients achieve maximum success at each attempt. The only genuine binary data, coupled with known prognostic effects independent of the reproductive tract, is ploidy. Hi-fidelity ploidy data provide independent biological information which is clinically well understood. Unfortunately, the methodology is invasive and the data are expensive to obtain. However, this same information is relied upon prenatally throughout the world, and with our increasing knowledge of primary embryo ploidy (that is, post-conception, as distinct from post-implantation) it should become an increasingly essential predictor of clinical outcome following IVF.

Aneuploidy screening remains a clinical imperative; but the technological imperative is making it more efficient, available and cheaper. In the meantime, we wait with anticipation developments in other non-invasive methods for potentially reliable candidates for embryo selection. In any event, nothing will replace good practice and attention to the finest detail in all departments of an IVF programme.

Simon Fishel is Professor of Human Reproduction and Managing and Scientific Director of CARE Fertility Group, Nottingham, UK. Alison Campbell is Head of Embryology, CARE Fertility Group, CARE Manchester, UK.

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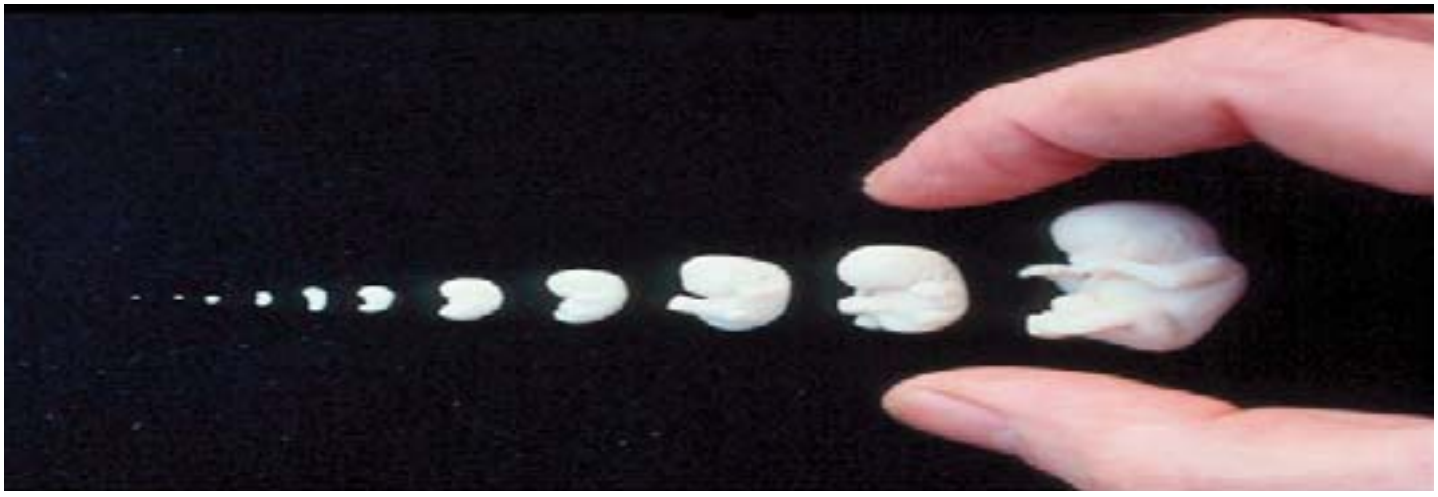


The embryo as a patient

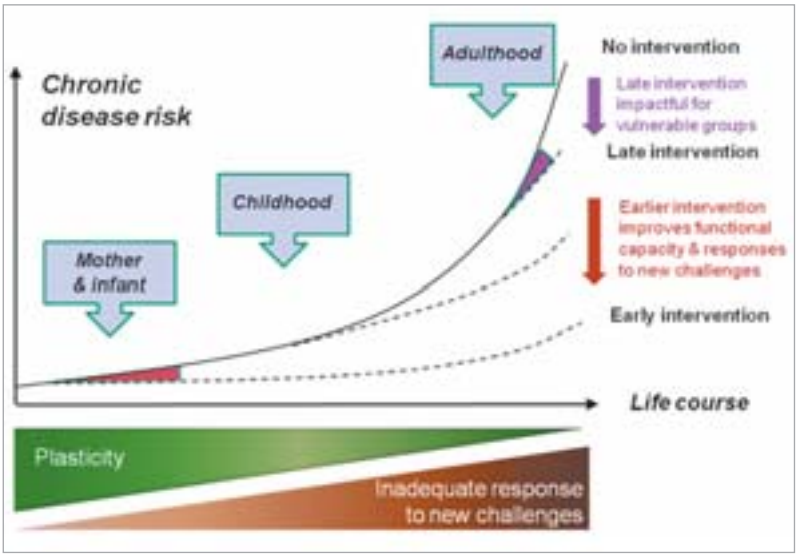
Today, success in IVF is defined not just as a positive pregnancy test, but one with low complication and multiple pregnancy rates. However, there is now growing evidence that responsibility in IVF goes much further than that. In May this year ESHRE's Special Interest Group in Reproductive Endocrinology held a Campus meeting to explore where these limits may lie. A number of renowned speakers posed the question: How does the developmental environment of our patient, the embryo, impact on its long-term health? The meeting's organiser, Nick Macklon, reports.

More than 20 years ago David Barker, an epidemiologist working in Southampton, showed convincingly in a cohort of men born in southern England (for whom both maternity and long-term health records had been kept) that markers of prenatal development predicted the risk of later cardiovascular disease and diabetes.[1] Developing his hypothesis, he proposed that malnutrition and other adverse environmental exposures during development alter gene expression and programme the body's structures and functions for life. This seminal work formed the basis of the Developmental Origins of Health and Disease (DoHAD) and of the concept of fetal programming, which claimed that diseases of later life - such as coronary heart disease, stroke, type 2 diabetes and hypertension, and even certain cancers such as breast cancer - originate through developmental plasticity in response to malnutrition during fetal life and infancy.

These concepts were supported by observations that people who had been small at birth differed biologically in terms of muscle and kidney functional capacity, metabolism and insulin resistance, and hormonal stress responses. Indeed, even parameters of intellectual performance were shown to be linked to birthweight.

An important development in this work was the recognition that compensatory growth above the normal rate after a period of slow growth, as is frequently observed in small babies, may have detrimental physiological and metabolic consequences in later life. It was shown that males who were taller at age seven than their birthweight and length had predicted were at greater risk of premature death than those who had not demonstrated such compensatory growth.[2]

The diseases linked to early developmental programming are among the most important causes of mortality worldwide, accounting for 60% of all deaths globally. The key implications of the DoHAD concept are that these diseases are preventable, and that the earlier the intervention, the more substantial the risk reduction



Interventions can modify risk, but early interventions during the periconceptional period may provide the most return in terms of risk reduction. (With thanks to M.Hanson and K.Godfrey.)

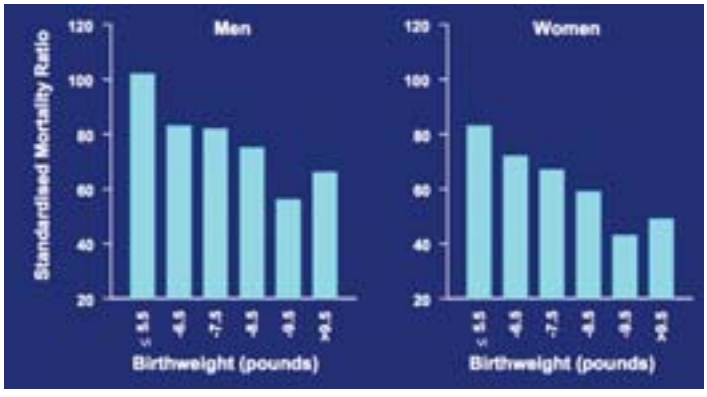
Periconceptional nutrition and the embryo

The increasing evidence that programming may begin in the periconceptional period has profound implications for those of us caring for couples trying to conceive. And as with the fetus, the story starts with nutrition.

Work by Tom Fleming's group in Southampton has demonstrated that even very short-term changes in maternal diet in the periconceptional period can have a significant impact on birthweight. In a mouse model, they showed that when blastocysts originating from a mother who had been fed a low protein diet at conception and blastocysts from a normally fed mother were transferred into a foster mother fed a normal diet, those which had been exposed to the low protein maternal diet for just a few days around conception were significantly lighter at late gestation.[3] They also showed that the embryos can 'sense the nutritional environment by upregulating protein synthesis rate and by increasing the rate of endocytosis in the visceral yolk sac'.

Maternal nutritional status has also been shown to influence the periconceptional establishment and maintenance of epigenetic marks. A key regulator of this process is the one carbon pathway. Disruption of this pathway can be caused by inadequate availability of folate resulting in hyperhomocysteinemia. This in turn can lead to failure of appropriate DNA methylation. Recent studies have shown that periconceptional folate levels can also impact on follicular fluid homocysteine levels, and may reduce oocyte number and embryo quality after IVF.[4]

Translating these findings into dietary interventions, Steegers Thuinissen from Rotterdam working with our group in Southampton has shown that a Mediterranean diet richer in folate and vitamin B12 is associated with an increased chance of pregnancy after IVF (OR 1.4; 95% CI 1.0-1.9).[5] The Rotterdam group has also demonstrated clear beneficial effects of a periconceptional Mediterranean diet on the risk of congenital heart disease and cleft lip.



The relationship between standardised mortality ratio from cardiovascular disease and birthweight.[1]

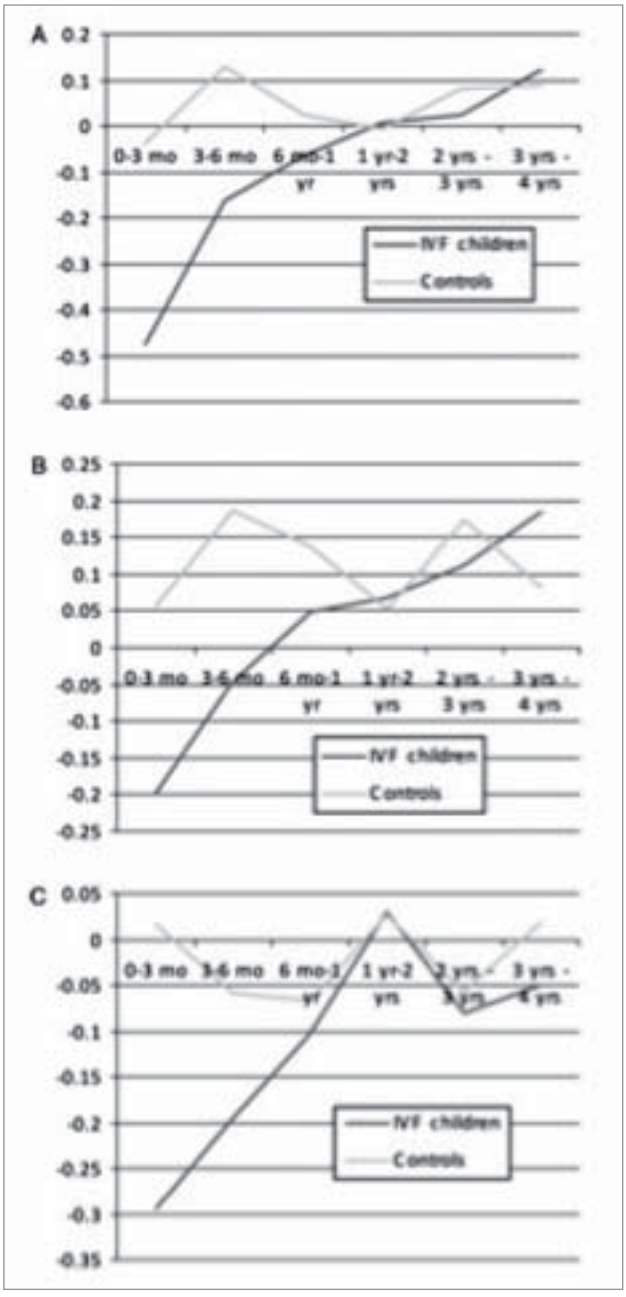
IVF and the embryo

The DoHAD principles may also be helpful in understanding how IVF itself may affect the health of the children born after. The crucial periconceptional establishment of epigenetic marks occurs during the phase of *in vitro* embryo culture. While contemporary culture media are designed to mimic the *in vivo* environment in which these key developmental processes occur, the extent to which they achieve this is unknown. The precise constitutions of commercial culture media remain closely guarded commercial secrets, but analytic studies have demonstrated large variations in basic components such as folic acid concentrations.

Given our increasing understanding of the sensitivity of the period of *in vitro* culture for future development and health, the commercial imperatives which currently limit our knowledge of the early developmental environments of IVF embryos must be balanced with the need to understand and optimise this environment for long-term health and not just pregnancy rates.

The impact of IVF on early growth has been shown to be small in absolute terms, but, since Barker and others have shown that the associations between early growth and later disease are not limited to extremes but extend across the range of birth weight, small absolute effects may have measurable long-term consequences.

Recently, a Dutch study looked at cardiovascular risk in children born after IVF.[6] After correction for confounders, IVF children were found to have a significantly higher systolic blood pressure than spontaneously conceived controls. In a subsequent analysis of the same cohort, IVF children were observed to have lower mean birthweight, as



IVF babies have a lower birthweight, length and BMI than controls, but demonstrate remarkable catch up growth in the first year or two of life.[6]

has been previously reported, but also demonstrated a remarkable degree of catch-up growth - which meant that by one to two years of age the initial differences in weight, length and BMI at birth had disappeared (see figure above).

On the face of it, this would appear reassuring, but, as predicted by Barker, rapid weight gain during early childhood in IVF children appeared to be related to higher blood pressure levels at follow-up, independent of birthweight, gestational age and height. This study provides an elegant but salutary example of how subsequent catch-up growth may worsen rather than ameliorate outcomes.

However, the periconceptional and perinatal environment influence development in other ways.

The subfertile fetus

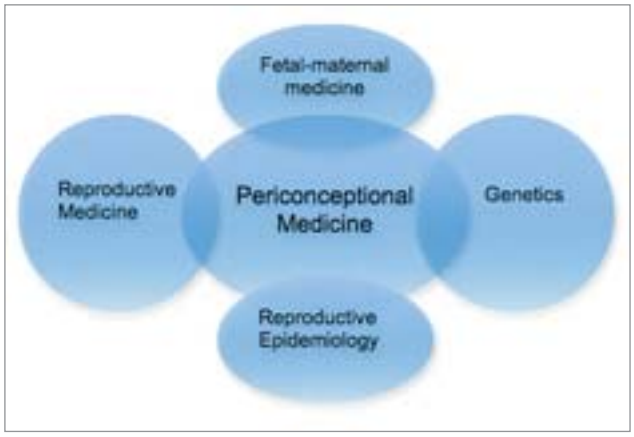
The implications of the DoHAD concept for future fertility are beginning to emerge. Interest in this area has been particularly strong in male infertility, whose incidence with other disorders of male reproductive health has been rising in recent years. It is now estimated that one in six European males demonstrate abnormal sperm counts. Together with other common male reproductive disorders in the male, such as testicular germ cell cancer and low testosterone levels, low sperm concentrations are now considered to be part of a 'testicular dysgenesis syndrome', which has its origins in fetal life as a result of insufficient androgen exposure.

A simple clinical marker for fetal androgen exposure is the anogenital distance (AGD) between the anus to the route of the penis or clitoris. This is around 1.5 times longer in boys than in girls. Animal studies have demonstrated that the AGD correlates with the risk of cryptorchidism, hypospadias, penis length and testis size in adulthood. Recently, a correlation was found between AGD and sperm count in the human.[7] Together, these findings point to a 'masculination programming window' during early fetal life, by which the level of exposure to androgens at 8-12 weeks determines later reproductive function.

This window may be disrupted by a number of environmental or lifestyle exposures. Evidence for this includes the increased risk of cryptorchidism in boys born to obese mothers and to mothers who had used high doses of painkillers such as paracetamol in early pregnancy. This latter effect may be explained by rat studies showing that paracetamol reduces fetal testicular testosterone levels.

Morever, maternal smoking during pregnancy has been shown to reduce sperm counts and testes size. In a recent study male fetuses of smokers undergoing termination of pregnancy were shown to have significantly fewer Sertoli cells than those unexposed to periconceptional maternal smoking. Since each Sertoli cell can support a fixed number of germ cells, their numbers are key determinants of sperm count. The same group has shown a similar effect on granulosa cell numbers in female fetuses exposed to periconceptional maternal smoking.[8]

The impact of smoking on ovarian volume, weight and indeed follicle numbers has been demonstrated in a number of animal models. This effect appears to be greater than that of periconceptional maternal nutritional status. Studies looking at the effect of periconceptional malnutrition, such as occurred during the Dutch famine, showed no significant impact on markers of ovarian function in the offspring. However, recent animal studies from our group



Periconceptional medicine is developing at the interface of related specialities.

indicate that the high fat western diet may have detrimental effects on ovarian morphology and follicle numbers.

Treating the embryo as a patient

It is now clear that the most crucial phase of development determining long-term health takes place in the phase cared for by reproductive endocrinologists, fertility nurses and embryologists. In other words, us.

This realisation greatly increases our responsibility beyond achieving a positive pregnancy test in our sub-fertile patients. A focus on optimising the conditions in which we produce and culture embryos is crucial, but, in order to truly optimise outcomes, we should also adopt preconceptional care into our fertility programmes. A number of groups, particularly in Adelaide, Rotterdam and our own in Utrecht and Southampton, are now doing this, and beginning to report encouraging results from simple periconceptional nutritional and lifestyle interventions.

As we enter the second generation of IVF, the goal of what we define as success is changing. And as the average age of women presenting for IVF increases, and the indications for IVF extend beyond fertility treatment to include fertility preservation, preimplantation diagnosis and 'saviour sibling' treatments, the impact of our field on other specialities is increasing. At the same time fertility specialists are working more closely with obstetricians, geneticists and reproductive epidemiologists to ensure optimal care for our increasingly complex patients.

At the interface of these specialities, a new area of expertise is developing. 'Periconceptional medicine' is that new field in which we meet to ensure the long-term health of our patients: the sub-fertile couple, and the embryo.

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