

Focus on **REPRODUCTION**

European Society of Human Reproduction and Embryology

// JANUARY 2012 //



- ESHRE news
- Conception in HIV-infected couples
- The whole man - and not just his sperm



**European Society
of Human Reproduction and Embryology**
28th Annual Meeting

Istanbul - Turkey
1 to 4 July 2012

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CONTENTS



Focus on

REPRODUCTION

● Chairman's introduction



The scientific heart of our society is driven by the Special Interest Groups, Task Forces and Working Groups, and a new Working Group on culture media within the SIGs Embryology and Safety and Quality in ART has recently been put in place. Its goals are to establish contacts with the culture media manufacturers to provide clearer information to professionals, to develop guidelines on culture media requirements, and to promote basic research in this field. Experts have been invited to join the Working Group and to develop an ESHRE consensus position paper

for *Human Reproduction*. As an embryologist, I believe that the contribution of ESHRE on this matter will be of paramount importance and I applaud the initiative of, among others, Arne Sunde, the Working Group co-ordinator.

Another important project in progress is our collaboration with the European Association of Tissue Banks (EATB) and the European Eye Banks Association. We recently organised a very well attended session on ART at the EATB meeting in Barcelona in November and are now working on a joint project for the training of inspectors for ART centres and for the European coding system.

I am also pleased to say that our 'star' project, the ESHRE Study into the Evaluation of oocyte Euploidy by Microarray analysis - 'ESTEEM' - co-ordinated by our past chairman Joep Geraedts, will start in February. This randomised trial will include 600 PGS cycles performed in seven different European centres and aims to estimate the likelihood of euploid embryos in future ART cycles and to improve birth rates in older patients. Our partner in the project, the biotech company BlueGnome, will provide arrays and technical training. This is ESHRE's first randomised trial for many years, and we expect the results to be of great importance.

Our relationship with the ASRM continues to progress, with exchange sessions at our annual meetings and preconference courses representing a fruitful collaboration. Joint plans are already advanced for this year's annual meetings in Istanbul and San Diego. So it gives me great pleasure to invite you to our first joint meeting of 'The Best of ASRM and ESHRE', to be held in Cortina d'Ampezzo, Italy, at the beginning of March. Along with our American colleagues, we have produced an attractive scientific and social programme in an exceptional location. Good science and nice skiing will be provided!

Anna Veiga

ESHRE Chairman 2011-2013

NEWS

- 4 Annual meeting 2012 Istanbul
- 6 ESHRE news
- 7 Paul Devroey bows out from the VUB
- 8 Regulatory news
- 10 Thirty years since the first hMG birth
- 13 The best of ESHRE and ASRM
- 14 The Whole Man Campus workshop
- 16 From the PGD Consortium
- 17 From the Special Interest Groups
- 24 From the Task Forces

FEATURES

- 27 The urgent need for new sperm biomarkers
Sheena Lewis asks if sperm DNA damage is a more reliable diagnostic tool than semen analysis
- 31 Conception in HIV-infected couples
Augusto Semprini reviews the risks of transmission and the appropriate fertility techniques





Istanbul abstract deadline is 1st February

City of rich cultures will be reflected in opening ceremony and congress party

A summer in Istanbul is the enticing backdrop to this year's annual meeting of ESHRE. For those travelling from the East, Istanbul has been dubbed 'the last eastern city' - and last western city when travelling from the West. But

whatever the direction, Istanbul, located on two continents, has a rich social and cultural heritage, which is certain to complement the very latest from a packed scientific programme.

The invited programme and preconference courses for this year's meeting are already in place, and deadline for the submission of abstracts is 1st February. All abstracts will be scored (blind and weighted) by ESHRE's International Scientific Committee. Last year's event in Stockholm prompted more than 1400 abstract submissions, and a similar response is expected this year.

Our congress centre, the Istanbul Convention & Exhibition Center, is in easy reach of the airports and in walking distance of many of the major hotels. The congress centre is located near Taksim square, Istanbul's central shopping, tourist and leisure district considered the heart of the modern city.

We are preparing a number of events to reflect the inimitable nature of Istanbul, from the opening ceremony itself in the congress centre to the congress party, which will be held in Suada (roughly translated as 'water island')



The Istanbul Congress & Exhibition Center, venue for ESHRE's 27th annual meeting.

a small island located on the Bosphorus and accessible by a short boat ride. A modern glass covered building on the island will be our main location for dining and dancing with friends, amid the beauty of the Bosphorus on a wonderful summer night.

Timur Gürkan
Chairman Local Organising Committee

The congress party on Tuesday night will be held on Suada, a floating resort located on the Bosphorus with a panoramic view of Istanbul.



Abstracts must be submitted online and according to designated topics

All abstracts must arrive via the ESHRE website no later than 1st February. Abstracts should be submitted in English only.

Investigators should note the following:

- Anyone submitting an abstract can only be the first author for one abstract.
- The material presented should be unpublished and original, and not yet have been presented at any other meeting.
- All abstracts will be refereed 'blind', ie, without the names and addresses of the authors.
- Authors are requested to indicate their preference for oral and/or poster presentation on the abstract submission form. Abstracts submitted but not selected for oral presentation can be referred to the poster sessions. The decisions of the selection committee are final.
- All accepted abstracts and the index of authors will be published in the abstract book, a monograph to the *Human Reproduction* journals.

There are four topic categories: basic science, clinical science, mixed (basic/clinical), and paramedical.

When basic science, clinical science or mixed are selected, one of the following topics should be selected:

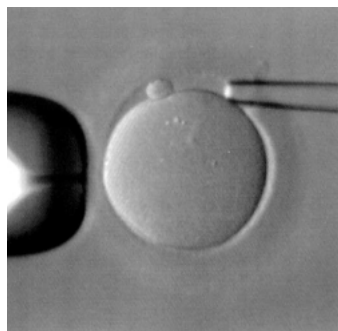
- Cross border reproductive care
- Developing countries and infertility
- Early pregnancy (including miscarriage, recurrent miscarriages, abortion, termination of pregnancy, ectopic pregnancy, molar pregnancy)
- Embryology (including IVF/ICSI, gamete and embryo selection, culture, cryopreservation, vitrification, developmental biology)
- Endometriosis, endometrium, implantation and fallopian tube
- Ethics and law

- Female (in)fertility (including oogenesis, diagnostic tests, prognostic models, intrauterine insemination, oocyte donation, body weight effects, smoking, ageing, immunology, sexually transmitted diseases)
- Andrology (including male (in)fertility, spermatogenesis, diagnostic tests, treatment, MESA, TESA, TESE, sperm donation, environmental factors related to male fertility, immunology)
- Male and female contraception
- Male and female fertility preservation (including oncofertility, medical indications, social freezing, laboratory techniques)
- Psychology and counselling
- Quality and safety of ART therapies (including guidelines, accreditation, EUTCD, certification, complications: premature labour, malformations, neonatal risks, multiple pregnancy, long-term follow-up of children)
- Reproductive (epi)genetics (including (epi)genetic causes of infertility, PGD, PGS, prenatal diagnosis)
- Reproductive endocrinology (including ovarian reserve testing, ovarian stimulation, IVM, POF, PCOS, infancy, disorders of sexual development, puberty, adolescence, menopause)
- Reproductive epidemiology and health economics
- Reproductive surgery (female and male)
- Stem cells
- Translational research (including new ideas, hypotheses, new thinking, immediate applicability in practice).

Paramedical categories are either 'laboratory' or 'nursing'.

More information on abstracts - with details of word counts, key words, title and for online submission - can be found on the ESHRE website under 'Annual Meeting'.

ESHRE's array CGH trial ready for randomisation



ESTEEM will be the first randomised trial of 23 chromosome testing of polar bodies using array CGH. The pilot study showed that reliable identification of the chromosomal status of an oocyte is possible in about 90% of polar body biopsy attempts.

Randomisation in ESHRE's trial to evaluate oocyte euploidy by array CGH is expected to begin in February. The study, which will be performed in women aged between 36 and 41 years, has two primary aims: to estimate the likelihood of having no euploid embryos in future ART cycles and to improve live birth rates in women of advanced maternal age.

The study, now known as ESTEEM (the ESHRE Study into The Evaluation of oocyte Euploidy by Microarray analysis), aims to recruit around 600 couples (at least 266 per study arm) at seven PGS centres.

Project arrangements with collaborating partner BlueGnome are already in place, and all centres have had microarray training for two days. Polar body biopsy training has been provided by the two reference centres in Bonn and Bologna.

It has now been agreed that the steering committee will comprise Joep Geraedts (who led the PGS Task Force behind the pilot study), Veerle Goossens (from ESHRE's

Central Office), and John Collins (who wrote the trial protocol). Data management, monitoring and training will be in the hands of Clinical Trial Center Maastricht, an academic research organisation able to provide online randomisation (which will allow stratification according to age and centre).

The study is expected to last around two years.

Three ESHRE guidelines now in development

Three ESHRE guidelines are currently in development, according to ESHRE's research specialist Nathalie Vermeulen. The first, an update of the endometriosis guideline, has completed its initial stages (topic selection, development group and scope) and preliminary searches for evidence, and is now in the process of summarising/grading evidence and formulating recommendations. Hopes are that the finished text will be ready for publication later this year.

A psychology and counselling guideline completed its scoping in Stockholm last year and will begin evidence searches early this year. Publication is expected in early 2013. And a guideline on premature ovarian insufficiency, proposed by the SIG Reproductive Endocrinology, has also completed scoping and hopes to finish its evidence searches and grading before the end of this year, with a view to publication in 2013.

Nathalie reported to ESHRE's Executive Committee that standard guidelines are likely to take around two years to develop and complete.

Other proposals under consideration include the diagnosis and treatment of female genital tract malformations, and guidelines for the provision and management of sperm cryopreservation in cancer patients.

Embryo certification goes international



The Portuguese embryologist Carlos Plancha has taken over as co-ordinator of the Embryologist Certification Steering Committee. The scheme, which continues to exceed all expectations, saw almost 90 clinical embryologists gain certification in 2011, and 20 seniors.

This year will be the first in which the scheme becomes open to embryologists from outside Europe, with certification exams taking place in Istanbul. In this first year (for which applications were open until November 2011) only the senior certification is available.

It will also be possible in the near future that all ESHRE-certified embryologists can if they wish renew their certificate through a new continuing embryology education credit (CEEC) scheme. 'We consider the scheme a stimulus for the continuous update of knowledge,' explains Kersti Lundin, co-ordinator of the SIG Embryology. 'It will provide a practical framework for continuous education through attending meetings and workshops, and a recognition of publications and other activities by clinical embryologists. However, this is a voluntary activity, and, as with all academic certificates, there is no loss of validity implied from a previously obtained ESHRE clinical embryology certification.' Credits may be earned in three-year blocks according to the type of activity undertaken.

Paul Devroey bows out from the VUB



Paul Devroey, Chairman of ESHRE from 2005 to 2007, will retire as Professor of Reproductive Medicine at the Dutch-speaking Free University of Brussels (VUB) in September this year, and will become Emeritus Professor the following month. He was succeeded (in October 2011) as Clinical Director of the Centre for Reproductive Medicine by Herman Tournaye, whose history at the VUB stretches back to student days.

A valedictory symposium in honour of Devroey, held at the VUB in September, attracted more than 500 participants, and with them of course came a generous recognition of the part he and Brussels have played in the recent history of reproductive medicine.

Bart Fauser, reviewing Devroey's influence as an investigator, said he was now the world's most cited author in reproductive medicine, and repeated the advice of Hans Evers to those aspiring to write a citation classic: 'They should concoct a new clinical treatment,

preferably in ART, think up a fancy acronym, publish it in English, in a journal with a high impact factor, and ask Devroey and/or Van Steirteghem as a co-author.'

Filippo Ubaldi, a former VUB trainee himself, reported that 194 publications in peer review journals have had an ex-Brusseliensis as first author - among them Kolibianakis, Papanikolaou, Nagy, Liu, Platteau and Palermo.

Devroey's own history with ESHRE dates back to the Society's foundation, when he represented Belgium on the first and second Advisory Committees (from 1986 to 1990) and, with André Van Steirteghem, organised ESHRE's second annual meeting in Brussels in 1986 (having served on the organising committee of the first meeting in Bonn in 1985). Today he remains an active member of ESHRE's SIG Ethics & Law, and of its position paper writing groups - which he has always described as some of ESHRE's most important achievements.



From the top, among an array of international and ex-Brusseliensis speakers were Bart Fauser, Peter Nagy and Filippo Ubaldi.

Twenty years this month since the world's first ICSI birth



The picture left was taken in 1993 when André Van Steirteghem reported data from the VUB's first ICSI series at ESHRE's annual meeting in Thessaloniki, three years after the first (inadvertent) fertilisation in 1990. Following trials in animal models, with ethical approval secured and pre-conditions in place (karyotyping, prenatal diagnosis), the VUB's first ICSI embryo had been transferred in 1991, and the first baby born in January 1992. The event was reported (along with four pregnancies) to the *Lancet* (by Palermo, Joris, Devroey and Van Steirteghem). Data from all subsequent patient series appeared in *Human Reproduction*, which no doubt had a lasting effect on the journal's impact factor.

Denmark reverses its decision on IVF medication co-payment

Just 12 months after introducing a patient co-payment system for ART medication and a treatment fee at all public clinics, the Danish government has gone back to its old system of free access for up to three completed IVF cycles and (almost) full reimbursement for medication. The revised system will come into force this month.

In explaining the move the government said ‘the public health system should be characterised by equal access for everybody’ and that ‘co-payment for assisted reproduction will lead to social inequality and discrimination against less wealthy patients’.

The introduction of payment in 2011 prompted protests from all health professionals, who forecast that the move would result in fewer children born in Denmark and would compromise safety and research. However, the immediate effect was a 23% drop in the number of IVF/ICSI treatments performed at the public clinics and a 30% drop in referrals. With Danish clinics now responsible for around 10% of all children born, the effect on Danish birth rates would be marked.

Whilst there was a common perception in Denmark - as elsewhere - that infertility was increasingly the result of lifestyle choices, we were able to show in arguing against the co-payment scheme that in more than 90% of all cases treated in the public system the cause of infertility was related to a disease defined as a registered diagnosis by the National Board of Health.

Further, it was shown (as described by Connolly et al in *Human Reproduction* 2011) that a decline in IVF babies would result in a net loss in tax revenue for Denmark when the perspective shifted to the long term. We were also supported in our protests by the patient organisations, who organised Facebook pages which attracted more than 30,000 friends, all objecting to the introduction of patient payment. Thus, the new Danish Government confirmed in October that ‘in order to ensure that infertility patients are not treated worse than other patients’ the system of co-payment for assisted reproduction, sterilisation and re-fertilisation would be revoked.

Søren Ziebe, Rigshospitalet, Copenhagen

. . . while Catalonia ends free access to fertility drugs for patients in the private sector

Citing Spain’s critical financial situation as an explanation, health authorities in the four provinces of Catalonia have discontinued the provision of free fertility drugs for IVF patients in the private sector. Since 1997 the cost of all drugs for fertility treatment was reimbursed by the Catalan health services, regardless of whether patients were treated in the private or public system. Free access continues in the public sector.

Policy in the Czech Republic is also to reimburse the full costs of three cycles, whether in the private or public sector, with a co-payment of around €1900. However, there are new proposals that from January this year reimbursement with co-payment will be extended to four cycles on condition that the patient accepts SET for the first two cycles.

UK’s HFEA agrees fixed sum compensation for all gamete donation

Following a public consultation and many months of public agonising, Britain’s regulator, the Human Fertilisation and Embryology Authority, agreed in October to compensate sperm donors a fixed sum of £35 per visit and egg donors a fixed sum of £750 per cycle of donation. The move, said the HFEA, was ‘a proactive approach to donor recruitment, retention and care’ which provides donors with a level of compensation ‘which better reflects their expenses’ and their inconvenience.

So far, UK policy had allowed sperm and egg donors to claim only ‘reasonable’ expenses, such as travel costs, and a modest daily amount for loss of earnings, with a limit of £250 for each course of sperm or egg donation.

In announcing the one-off fee, the HFEA was at pains to remove any hint of payment or inducement from the new policy; this was strictly compensation, based, according to the HFEA, on the precedence models of Denmark (for sperm donation) and Spain (for egg donation).

The Chair of the HFEA said that the level of compensation would ‘not deter those interested in donation’ but would ‘retain donors already in the system, without attracting those who are merely financially motivated’.

UK treatments using donor eggs had fallen to a recent all-time low in 2009 of just 1254 cycles and the HFEA clearly thought that ‘compensation’ was one way to resolve the ‘crisis’.

The HFEA’s announcement also gave its seal of approval to egg-sharing, a technique which in its consultation had been described as ‘controversial’. This system of ‘benefits in kind’, said the HFEA, which is now well established in Britain, ‘should be allowed to continue’ as before.

Almost one in five women having IVF in UK is 40 or over; but treatments continue to rise

The UK's latest report on IVF activity for 2010 shows that almost 20% of all fresh IVF and ICSI cycles performed in Britain were in women aged 40 or over. The figures represent a considerable increase, having almost doubled over the past 13 years, and are thought likely to be replicated in many other European countries.

A recent study from Maastricht found that the average age of patients attending a first consultation increased from 27.7 years in 1985 to 31.4 years in 2008, a rise of almost four years in just two decades. The proportion of women of 35 years or older almost quadrupled to 31%.

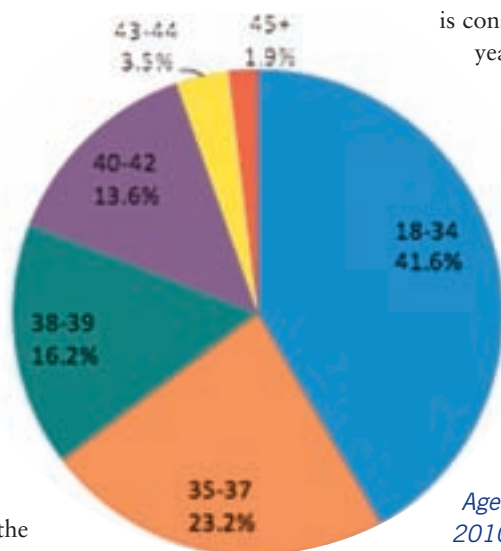
And world data gathered by ICMART for 2007 and reported at ESHRE's annual meeting last year estimated that almost 16% of women having ART were over the age of 40.

The latest HFEA report puts the

average age of women in the UK having IVF and ICSI (as well as donor insemination) in 2010 at 35 years. Twenty years ago, the average age was 33.6 years.

The report also disclosed that in 2010 a total of 45,264 women received 57,652 IVF or ICSI treatments, an increase of 5.9% on the number of cycles in 2009. This too is consistent with recent year-on-year trends calculated by ESHRE's EIM Consortium and by ICMART.

The pregnancy rate from these UK cycles was 33.4% per transfer. However, in 2009 24.9% of live births in patients aged 18–34 years were multiple, a rate only marginally lower than the 29.4% multiple rate of 2008.



Age range of IVF/ICSI patients in UK clinics in 2010, from the HFEA's latest annual report.



Netherlands poised to reduce reimbursed IVF cycles

Holland's minority government (of liberals and Christian Democrats) has been in power for little more than a year but has already announced cost-cutting measures in IVF to the tune of €30 million a year. This, they say, must be achieved by excluding a second and third cycle from the state's reimbursement scheme - which would reduce the number of reimbursed IVF cycles in the Netherlands from three to one. In announcing the measures, the government invited those involved to propose alternative ways to raise the €30 million a year.

'We calculated that the additional cost of a twin pregnancy compared to a singleton was around €5000 per pregnancy,' said Hans Evers, from the Academic Hospital of Maastricht. 'The extra costs involved in the delivery and in the first four weeks range from €2000 in the case of a healthy twin to €30,000 in the case of a twin with complications, such as prematurity.' Evers added that the long-term costs submitted to the government were only rough estimates, but ranged from €900-7000 per year per child with a minor handicap to €1800-20,000 per year per child with a severe handicap.

The Dutch calculations were based on 2009 data; 16,769 IVF treatment cycles were performed, resulting in 4386 ongoing pregnancies and 469 twin pregnancies, for a multiple pregnancy rate of 10.7%. Of these twins, 85% were born to women below 38 years of age.

'Estimating the average lifetime additional costs of a twin at €75,000,' explained Evers, 'we argued that by decreasing the number of twins to zero by performing single embryo transfer in all women below 38 years, we would save 85% x 469 twins x €75,000 per year - that's €29.9 million. We thought this would meet the government's requirements, which would leave the number of reimbursed cycles at three.'

However, despite the logic of the proposal and the clinics' promise to adopt a strategy of only SETs in all women under 38, the Minister of Health was not impressed. The cost savings would be made outside the area of IVF, and many of the cost savings were considered 'lifetime', so would not bring an immediate return. The signs are, says Evers, that the Netherlands will now lose its three cycle reimbursement policy in 2013, and become yet another example of how IVF seems the soft option when it comes to cost-cutting in health budgets.

European court now rules in favour of Austria's donation law

The Grand Chamber of the European Court of Human Rights has ruled that Austria's ban on sperm and egg donation was not in breach of the European Convention on Human Rights. The ruling was made following an appeal by the Austrian authorities and reverses a previous Court judgement which had found that the ban on gamete donation *was* a breach of the convention.



The case dates back more than a decade, to when two Austrian couples wishing to conceive a child through egg and sperm donation complained to the Court on two counts: that Austria's ban violated their right to respect for family life (under Article 8) and that the ban amounted to discriminatory treatment (under Article 14). In April 2010 the Court upheld the complaints in what appeared to be a landmark judgement.

However, at the Austrian government's request the case was referred back on appeal to the Grand Chamber, which now - in November last year - has ruled that there was in fact no violation of Article 8 in Austria's original legislation.

The Court noted that, although there was a clear trend across Europe in favour of allowing gamete donation for IVF, the emerging consensus was still 'under development and was not based on settled legal principles'. For example, the Court noted that all 'relevant legal instruments' in Europe were either 'silent' on the question of gamete donation or, in the case of the EUTCD, leaving the decision (on whether or not to use) to individual member states.

According to the judgement, the original Austrian legislation had tried 'to avoid the possibility that two women could claim to be the biological mother of the same child'. They had thus approached this controversial issue 'carefully' and 'had not banned individuals from going overseas for infertility treatment unavailable in Austria'. Thus, while the Court concluded that there had been no violation of the Convention, it still emphasised the importance of keeping legal and fast-moving scientific developments in the field of ART under review.

Of some concern to ESHRE - and as reported in the May 2011 issue of *Focus on Reproduction* - ESHRE was not allowed to submit written comment in advance of the appeal, its evidence being deemed 'inadmissible' (despite ESHRE's favourable legal advice to the contrary). The final judgement, however, notes that the governments of Italy and Germany *were* allowed to submit comment (in support of the Austrian position), along with the European Centre for Law and Justice ('a Christian-inspired organisation', see <http://eclj.org/About/>), Aktion Leben, an Austrian organisation 'for the protection of human life' (whose spokesman following the judgement said that 'egg donation is usually based on the exploitation of women'), and the Italian SOS Infertilita Onlus association.

Thirty years

Anna Pia Ferraretti

When I arrived in Norfolk in October 1981 the atmosphere was already tense and exciting. For here, at the IVF unit of the Eastern Virginia Medical School, the USA's first ongoing pregnancy from IVF was progressing nicely to term. The Norfolk group, which had been opened the year before by Howard and Georgeanna Jones after their 'retirement' from Johns Hopkins in Baltimore, at the time included Jairo Garcia, Anibal Acosta and Lucinda Veek, plus a very nice group of nurses and secretaries (who greatly helped me with my terrible English!). I was the first foreign fellow of the IVF unit, sent to Norfolk at the request of my professor, Carlo Flamigni, who hoped I would be able to start a clinical programme at Bologna University when I returned.

That first IVF baby in the USA, Elizabeth Jordan Carr, was born 30 years ago, on 28th December 1981 at the Norfolk General Hospital, delivered by Mason Andrews (then chairman of the ObGyn department). Elizabeth is now working at the *Boston Globe* newspaper, and in 2010 delivered her first baby, conceived naturally. I had held Elizabeth in my arms on the day of her birth and will never forget that moment.

Unlike Louise Brown, Elizabeth did not achieve fame as a result of her conception - she was already the 15th IVF baby to be born (12 of them in Melbourne) - and very few people now remember that she was the first successful birth using hMG for ovarian stimulation. This was important, and to understand why we must go back to the very first days of IVF, when the most controversial issue for the few people working in IVF was the natural or the stimulated cycle.

After the birth of Louise Brown (from a natural cycle) Bob Edwards had tried at least 100 hMG cycles, but without term deliveries. According to his reports, hMG (which he had used in relatively high doses) was not suitable because of its luteal phase effects.

Georgeanna Jones, a reproductive endocrinologist with huge experience of hMG in anovulatory patients, was not convinced by Bob's conclusions, but she and Howard

since the world's first hMG baby remembers the first IVF birth in the USA



Georgeanna and Howard Jones, each receiving honorary membership of ESHRE at the 1998 annual meeting in Gothenburg.

followed his natural-cycle advice when the Norfolk programme began.

During that first year of 1980, 41 Norfolk patients had IVF, but only nine reached embryo transfer and no pregnancies were obtained. This was a big disappointment, even raising doubts over the whole concept of IVF. Thus, after long discussions Georgeanna managed to convince Howard that it was crucial to return to hMG. If hMG could work in anovulatory patients, why not in ovulatory? Moreover, at the beginning of 1981, Trounson and Wood in Melbourne were already reporting their first IVF pregnancies in stimulated cycles (although with clomiphene).

But Georgeanna opted for hMG because of its more physiological nature, and at a lower dose than in Bob's approach. She chose the same dose as used in anovulatory patients - a fixed dose of two ampoules per day for three days (starting the first, third or fifth day of the cycle depending on

cycle length) and reduced to one ampoule for the next three days. The dosage was then readjusted according to response, but during the whole of 1981 no more than two ampoules per day were ever used; all that varied was the duration of stimulation. Today we would call this a mild stimulation protocol. And then the pregnancies started: seven from 55 egg retrievals and 31 transfers. All went to term,



ANNA PIA FERRARETTI:
'GEORGEANNA WAS THE
FIRST TO SUGGEST THAT
EXCESSIVE FSH ($\pm$ LH)
MIGHT HAVE A
DETRIMENTAL EFFECT ON
OOCYTE QUALITY.'

without miscarriages, and spirits rose.

So, when I arrived in October 1981, this was the protocol in use. Ultrasound was already available for monitoring, but it was difficult to interpret and the most important triggers for hCG administration were estradiol levels and biological parameters (vaginal cells and cervical mucus) as an index of oocyte maturity. My first task was a daily analysis of the cervical mucus and vaginal smear of all the IVF patients, while Jairo did the ultrasound evaluation. I remember that two or three days of coasting before hCG were considered necessary by Georgeanna, to let the oocytes complete maturation without any additional stimulus.

In the following year, 1982, Georgeanna tested several new protocols, notably increasing the amount of hMG in the first two days of stimulation, then increasing FSH (by adding Metrodin) and finally using FSH alone for the whole stimulation. We had daily meetings to discuss each case according to the different protocols, to understand the effects of FSH and LH on follicular development and oocyte viability. Georgeanna was always trying to find a physiological explanation for each observed difference, Jairo to translate into practice Georgeanna's observations, ☞

Howard to translate the statistics into data, Lucinda to describe the look of each oocyte and cumulus cell in detail, and Anibal to be the moderator of the discussion. Very often, a telephone call would be made to Bob Edwards in England, and once in a while Gary

Hodgen would come in to the meetings with updates on his animal studies. As for me, I was taking in as much as I could from these energetic debates, and getting closer day by day to the concept of IVF as seen by Georgeanna - my first paper was published with her and the rest of the group (on LH levels during stimulation with hMG) in 1983.

Reading her reports and personal notes today from this early period, I recognise that most of her observations have become routinely accepted. Some now seem obvious (but were not at all at the time!), for instance:

- 'FSH is the essential gonadotrophin for multiple follicular recruitment but FSH alone is also able to sustain complete follicle maturation.'
- 'Three different types of ovarian response can be identified: low (20%), intermediate (60%) and high (20%).'
- 'The number of follicles depends on the amount of FSH given during day 3-5 of the cycle; however, the number of



follicles that can be recruited is variable and depends on the residual store of eggs. This seems related mainly to patient age.'

But there is a recurrent observation in her early papers that was completely neglected for too many years. She wrote: 'Continuing with high amounts of FSH or hMG after the recruitment

period (after day 5) may result in an increased number of follicles but a decreased number of viable oocytes in comparison to those cycles stimulated with lower amount of FSH and LH.'

As we are now aware, more vigorous stimulation protocols were pursued in the late 1980s, particularly after GnRH agonist down-regulation was introduced. Certainly, this prompted a significant increase in the efficacy of IVF, but was also accompanied by a reciprocal increase in complications such as OHSS and multiple pregnancies. And despite these various innovations and the introduction of yet further protocols, it is still the case that only some 7-10 % of all fresh IVF oocytes actually produce a baby - and this value has remained relatively constant over the past 30 years.

Nevertheless, only in the past decade or so have investigators proposed milder forms of stimulation, as recommended by Fauser in 1999: 'Use of the lowest possible doses for

ovarian stimulation not only reduces the risk of OHSS but also increases the relative proportion of genetically normal oocytes.' Progress, however, has been very slow and only more recently has resistance to mild stimulation been noticeably reduced. Today, mild stimulation is still considered a new trend in our field, but Georgeanna was the first to suggest that excessive FSH ($\pm$ LH) might have a detrimental effect on oocyte quality.

After a year in Norfolk I returned to Bologna to set up an IVF programme with Luca Gianaroli, then returning from Melbourne where he spent time working with the late Carl Wood and Alan Trounson. Of course, we too discussed the protocol to use: Norfolk (FSH/hMG) or Monash (CC + hMG)?

We decided to test both, and in the first years of our programme 549 patients received the Monash and 979 the Norfolk protocol - with a clinical pregnancy rate of 13% in the former 18% the latter. So the clomiphene protocol was abandoned in favour of gonadotrophins. Georgeanna would have been happy with that, as she would also be knowing that for many years we have been using mild stimulation in our younger patients. But ironically the mild stimulation we are using today is the Monash protocol: clomiphene from cycle day 3 to 7 plus a little FSH on cycle days 5, 7 and 9. She may not have approved, but I can now confirm that clomiphene can work very well in IVF!

*Anna Pia Ferraretti
SISMER, Bologna, Italy*

Carl Wood, IVF pioneer: 1929-2011



The death of Carl Wood, who with Alan Trounson and John Leeton in Melbourne established the irrevocable place of stimulated cycles in IVF, was announced in September. Wood's group at Monash achieved the world's first IVF pregnancy in 1973, which was to miscarry, and several other notable firsts: in 1983 the first live birth from a frozen embryo and that same year the first birth from a donor oocyte. Twelve of the world's first 15 IVF births were conceived at Monash by Wood's team. Like Robert Edwards in Britain, Wood faced much public opposition to his work and accusations that IVF encouraged the destruction of embryos. As a Roman Catholic, Wood himself was much relieved when the techniques of embryo freezing were perfected. In the face of such opposition he always encouraged discussion, advocacy and consensus.

Something for everyone in the Italian Dolomites

A programme of lectures and debates conceived on both sides of the Atlantic

The scientific programme of the first ‘best practice’ meeting of ESHRE and the ASRM is now complete. The three-day meeting, set to be held in the Italian skiing resort of Cortina d’Ampezzo in March, is, according to ASRM chairman Roger Lobo, ‘an experiment’, but one which both societies have devised to provide opportunities for both learning and networking. Mornings will be free for social activities, while the scientific programme lasts throughout the afternoon and early evening. Subjects have been chosen for their topicality and for their relative difference in approach between Europe and the USA.

Presently, the ‘best of’ meetings are foreseen as annual events alternating between leisure venues in Europe and the USA. Cortina d’Ampezzo, this year’s venue, is located in the Dolomites in northern Italy and is considered one of Europe’s foremost skiing locations.

Details about registration, hotel accommodation and transport are presented on the ESHRE website.

Lectures

Back-to-back sessions, during which different topics and practices will be analysed from the American and European points of view

Debates, in which two experts will discuss controversial issues, illustrating different point of views and supporting different theories and approaches

Cutting-edge lectures, aiming to illustrate innovations and new findings in reproductive medicine and embryology

Thursday 1st March

14.30-15.30	The information brought by the sperm into the oocyte C. Barratt (GB)
15.00-15.30	Fertilization and unexplained failure C. Combelles (USA)
15.30-16.20	Should a single embryo be transferred in all IVF patients? K. Lundin (SE) and G.D. Adamson (USA)
16.20-16.50	PCO: Diagnosis and approaches to therapy B. Tarlatzis (GR)
17.10-18.00	Oocyte cryopreservation: standard or experimental practice? E. Van den Abbeel (BE) and G.L. Schatman (USA)
18.00-19.00	Intrauterine Insemination versus fast-track IVF: Best practices for unexplained infertility F. van der Veen (NL) and R. Reindollar (USA)
19.00-19.30	Perinatal outcome and ART techniques K. Barnhart (USA)



Friday 2nd March

14.30-15.30	The impact of oocyte quality on embryo development M. C. Magli (IT)
15.00-15.30	Environmental toxins and their impact on fertility R.Z. Sokol (USA)
15.30-16.20	POR: stimulation and oocyte quality A.P. Ferraretti (IT) and L. Schatman (USA)
16.20-16.50	PCO with hyperandrogenism is really PCOS? R. Legro (USA)
17.10-18.00	Menopause. Carcinogenesis of ovarian cancer: the incessant menstruation hypothesis P.G. Crosignani (IT)
18.00-19.00	The “timing” hypothesis revisited. R. Lobo (USA)
19.00-19.30	Who is the most important for a successful outcome in ART? The clinician or the embryologist? L. Rienzi (IT) and G.L. Schatman (USA)
	Repeated implantation failure A. Makrigiannakis (GR)

Saturday 3rd March

14.30-15.30	Culture media supplementation and culture conditions A. Sunde (Norway)
15.00-15.30	Epidemiology of reproduction Kurt Barnhart (USA)
15.30-16.20	Preimplantation genetic testing: Current technology and global experience - When to do and by what technique(s) J. Geraedts (NL) and N.Treff (USA)
16.20-16.50	Efficacy of new surgical techniques S. Gordts (BE)
17.10-18.00	Natural cycle, mild stimulation and conventional stimulation B. Fauser (NL) and R. Reindollar (USA)
18.00-19.00	Day 3 vs day 5 embryo transfer A. Veiga (ES) and US speaker TBA
19.00-19.30	Innovation in the medical treatment of Endometriosis. G.D. Adamson (USA)

The whole man, and not just his sperm, are preferred under the diagnostic spotlight

‘Low sperm count is not a diagnosis, it’s a physical sign’

A debate in the main scientific session of this year’s annual meeting in Istanbul will ask: ‘Should we treat the man or just use the sperm?’ As ever with ESHRE debates, the contest, pitching moral rectitude against practical expedience, will be enthusiastically heard - and no doubt will end without a runaway winner.

Had the same question been posed at a Campus workshop held in September in Seville, there would have been no contest. For this was an event which, from its initial planning, set out from the very premise that ‘the whole man’, and not just his sperm, was the essential focus of investigation in the infertile couple. ‘Sperm are too frequently used for the diagnosis of male infertility,’ said Australian andrologist Anne Jequier. ‘It’s a sad situation, but it’s cost effective and to some extent it works.’

Her talk - as well as those of others - was peppered with salutary anecdotes of men presenting with infertility but eventually diagnosed with testicular cancer and other malignancies. Indeed, an unpublished study of genito-urinary ultrasound findings from 1203 men attending her own fertility clinic in Perth found testicular cancers in five of them, renal lesions in 48, and testicular microlithiasis in 66. ‘Diagnosis is what we want,’ said Jequier. ‘Infertility is not a diagnosis, it’s a symptom. Low sperm count is not a diagnosis, it’s a physical sign. The diagnosis is the cause of the low sperm count.’

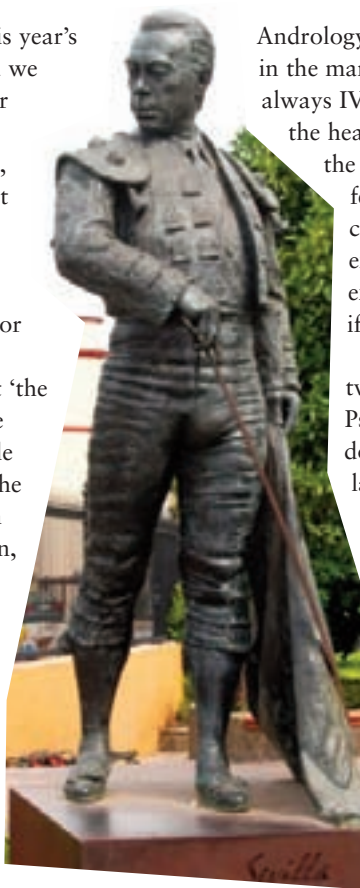
During questions and playing the role of ‘devil’s advocate’, Sheena Lewis, the new co-ordinator of the SIG

Andrology, asked how examination or investigations in the man might ever be useful if the outcome is always IVF or ICSI. Such a question, of course, lies at the heart of many charges levelled today against the treatment of infertility (both male and female) - that clinics have foresaken the classical diagnostic paradigm in favour of an exclusively prognostic model. In women, for example, why perform diagnostic laparoscopy if the treatment will still be IVF?

This Campus meeting was organised by two of ESHRE’s SIGs, Andrology and Psychology & Counselling, and there was no doubt where opinions on this sensitive matter lay. Indeed, as Uschi Van den Broeck made clear, a diagnosis of infertility can be just as devastating for men as for women and requires just as much care in delivering the news. A man’s ‘stereotype’ response to such news, said Uschi, might range from denial, to aggression and even to loss of control. But whatever the response, it nevertheless seemed clear from these presentations that men do respond to their infertility differently from women. Indeed, asked psychologist Tewes Wischman from the Institute of Medical Psychology in Heidelberg, do men ‘suffer’ less than

women, ‘or do they even suffer at all’?

Data presented by Wischman indicated that for 49% of women but only 15% of men infertility was the most upsetting experience of their lives. Of course, as Wischman readily acknowledged, men may simply respond differently to any kind of stress, whether infertility or not, but there



USCHI VAN DEN BROECK:
‘A DIAGNOSIS OF
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AS DEVASTATING FOR
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PETRA THORN: ‘MEN
CONSIDERING DI OR
ADOPTION MAY OFTEN
NEED MANY MONTHS TO
ACCEPT THE TREATMENT
AS A REAL ALTERNATIVE.’



Men need fertility preservation too

Chemotherapy may have a similarly adverse effect on semen parameters in men as on ovarian function in women. Roelof Menkveld, the Past Co-ordinator of the SIG Andrology, confirmed that both sperm function and DNA status may each be affected, with a resulting increased risk of azoospermia and poor sperm function. Fertility preservation, he said, ahead of cancer treatment will provide an opportunity for later conception through IUI or ART. Citing a study of 2005 (Agarawal and Allamaneni), Menkveld reported that sperm volume, count and motility in 205 adolescent cancer patients were almost half that of controls, and in patients with testicular cancer and leukaemia sperm concentrations were considerably lower. The most negative effect of chemotherapy appears to be on DNA integrity. In 2007 Schmidt et al showed that before treatment 91% of a study group had fathered a child, which fell to 67% after treatment.

However, while semen cryopreservation will provide a means of preserving fertility, cryopreservation itself will reduce sperm motility and reduce fertilisation potential.

So far, he added, the 'usefulness' of cryopreserved semen seems limited, with studies suggesting an uptake of around 5% following cancer treatment. Menkveld's own experience, from a pool of 64 cancer patients, has so far found an uptake rate of only 4.7% - although he and others have emphasised that the storage of sperm gives hope and confidence to many young men that they do have a future after their cancer treatment.

	Before freezing		After freezing	
	Mean (SD)	Range	Mean (SD)	Range
Volume (ml)	2.8 ± 1.5	0.5 - 7.0	-	-
Count (10 ⁶ /ml)	39 ± 29	0.1 - 100	18 ± 13	4.5 - 40.0
Motility (%)	45 ± 11	0 - 60	23 ± 12	0 - 40.0
Morphology (% normal)	5.8 ± 5.2	1.0 - 18	-	-

The effect of cryopreservation on semen parameters in 64 cancer patients (Menkveld unpublished data).

does seem to be a degree of stigmatisation about infertility for men which women don't feel. 'Women with fertility problems tend to be pitied,' said Wischman citing a 1992 study of Nachtigall et al, 'whereas men are more likely to encounter insulting slurs on their manhood.' Even the basic semen analysis, he added, has sexual connotations in its demand for a semen sample.

Despite the gender differences, Wischman concluded that

men do indeed suffer on account of their infertility, but feel they have fewer outlets than women to express their feelings - and of course counselling should recognise these differences and provide its information and support in a way which acknowledges the differences. He also showed that men felt a need to be strong for their partners, and thus tend to hide their own feelings.

This same gender gap is apparent in how men react to parenthood following treatment by donor insemination - what Petra Thorn, a former co-ordinator of the SIG Psychology & Counselling, called a 'shift from biological to social fatherhood'. She proposed that only biological fatherhood is considered by many men as 'real' fatherhood, and that men considering DI or adoption may often need many months to accept the treatment as a realistic alternative. And even as the child grows there may well remain tensions for the man - between his own role as a 'social' parent and his partner's as the 'biological' parent. Similar tensions might be played out over disclosure and donor identity. Again, said Petra, these are tensions and difficulties which counselling can help explore and resolve.

Thus, if the proper place of a man in the fertility clinic requires full investigation and the sensitive support of counselling, how important are the conventional tests of basic semen analysis? Anthony Hirsh, an andrologist from London, left no doubt that sperm dysfunction represents 'the largest defined cause of human subfertility'. But there was also evidence that many of the studies on which the latest WHO reference values for semen analysis were based were in fact methodologically unreliable - with inconsistent standards evident in laboratory methods, statistical methods and results.

And, as Sheena Lewis made clear in her presentation (and as she explains in more detail on page 27) semen analysis itself has limited diagnostic value for male infertility - and is not predictive for ART outcome. Techniques such as IMSI or tests for birefringence have sought to provide a non-invasive dimension beyond conventional semen analysis, while the latest sperm DNA tests now seem able to improve ART results in both male factor and unexplained infertility.

Of course, bubbling beneath the surface of this meeting was the fact that ICSI can now - according to Anthony Hirsh - 'treat' 98% of all cases of male factor infertility, though not always successfully. And the long-term follow-up studies of ICSI babies performed at the Free University Hospital in Brussels are accumulating 'reassuring data' in the overall health, gonadal function and psychological development of the children born. So the debate in Istanbul, that treatment should be directed at the man and not just his sperm, will not be easily won. But here was a strong case in favour, that infertility may mean to a man more than just a sperm deficiency, and that the psychological implications, as well as the physiological, require a broad interpretation.

*Simon Brown
Focus on Reproduction*

PGD CONSORTIUM

// THE PAST YEAR IN REVIEW //

Trends from a decade of PGD: ten years of data collection now seen in perspective

A manuscript summarising data collections I-X has now been accepted for publication. The paper aims to review the massive amount of data collected so far by the Consortium and to look at the data from a more distant perspective and consider trends in the whole field of PGD as they changed over the decade. Data collection XI was late being submitted for publication but should have been submitted before the end of 2011.

Working groups

Very exciting developments have taken place in the array-based PGD working group. ESHRE's Executive Committee has agreed to consider the development of a guidelines document for array-based PGD, and we are presently putting together a development group. A new external quality assessment scheme for array-based PGD is also being developed to assess testing quality around the world. This EQA, following a pilot study, will be open to any labs using array-based technology to assess aneuploidy in human embryos.

The Accreditation working group held a very successful workshop in conjunction with Eurogenetest in Athens, Greece, titled **Towards Accreditation of a PGD Laboratory**. This workshop will be repeated this year in Istanbul in the Autumn.

The Misdiagnosis and Monitoring working group continues to work on publication of the follow-up data from amplification-based and FISH-based PGD tests. This will be a landmark paper, featuring follow-up of untransferred embryos following PGD testing.

The Molecular Methods working group continues to develop a database of primers and protocols to aid Full and Transport Member laboratories in developing customised PGD testing methods for patients in need of tests for monogenic disorders.

Finally, the the Consortium Steering Committee has begun to develop a plan to help educate laboratories through a lab visitation and exchange scheme as well as offering online learning opportunities (case studies, discussion, etc). This will hopefully be a big hit.

*Gary Harton
Chair PGD Consortium*

Consortium statutes now being revised



The statutes which govern the organisation and running of the Consortium are now being revised before ratification of the Executive Committee. Following their approval, a new Steering Committee will be put in place. The current Committee (most of whom are pictured above) comprises Gary Harton (US, Chair), Joanne Traeger-Synodinos (GR, Deputy Chair), Joyce Harper (GB, Past Chair), Céline Moutou (FR), Katerina Vesela (CZ), Sioban Sengupta (GB), Georgia Kokkali (GR), Leeanda Wilton (AU), Martine De Rycke (BE), Tugce Pehlivan (TR), Pamela Renwick (GB), Edith Coonen (NL) and Francesco Fiorentino (IT).



*Participants in last year's accreditation workshop held in Athens.
The meeting will be repeated later this year in Istanbul.*

SPECIAL INTEREST GROUPS

// EMBRYOLOGY //

Culture media high on the agenda for Istanbul

Workshops

Time passes quickly, and it is again time to report our activities. Since the last issue of *Focus on Reproduction* in September, we have had a workshop in St Petersburg, Russia, in collaboration with the SIG Reproductive Endocrinology and the Paramedical group. There were almost 200 participants, and the evaluation was very positive indeed.

Joint workshops are often very successful because of the opportunity to expand knowledge to topics outside our main area of interest, to subjects that often overlap with each other. It is a great opportunity to work together with other SIGs and Task Forces.

So, for 2012 we have plans for more joint workshops. The first is an event organised with the SIG Reproductive Genetics and Task Force Basic Science, the 7th workshop on **Mammalian folliculogenesis and oogenesis** due to take place in Stresa, Italy, on 19-21st April. The course has a scientific focus, with topics covering the full circle from primordial cells, through meiosis and maturation, to the influence of maternal health and diet.

In the autumn we are planning a practically oriented course with the SIG Andrology, **The best sperm for the best oocyte** to take place in Greece in October, the exact date still to be decided. Check on the website for updates!

Culture media in Istanbul 2012

Although now cold and dark, we have a summer meeting to look forward to . . . our preconference course at the annual meeting in Istanbul, which will be focused on IVF culture media. This is a very hot topic indeed. We know that culture media are becoming more and more complex, enriched with different supplements, with compositions not fully known by the users. It has been shown that different culture media have different effects, not only on embryo quality and implantation rates, but also on pregnancy outcome such as fetal growth and birth weight. This implies that culture media affect inherent factors, possibly related to epigenetics. Our preconference course in Istanbul, **Culture media: the best environment for gametes and embryos**, will consider what oocytes and embryos need - and perhaps do not need - and how embryo culture and environment might influence early development.

Embryology certification

The clinical embryology certification exam in Istanbul is

Steering committee

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

the first for which embryologists from outside Europe have been allowed to apply. The procedure is moving along well.

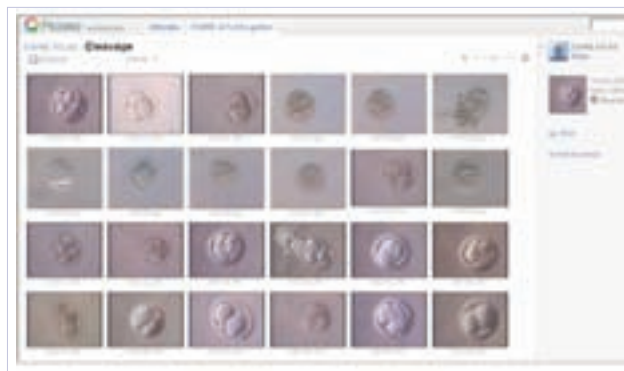
We are also pleased to announce that ESHRE certified embryologists can now renew their certification through the new CEEC (Continuous

Embryology Education Credit) system to be launched very soon. As reported on page 6, this is a voluntary scheme to stimulate continual learning by clinical embryologists, to validate their attendance at meetings and workshops and recognise publications and other activities. However, the scheme does not imply any loss of validity from a previously obtained ESHRE clinical embryology certification.

The Atlas of Embryology: from oocytes to preimplantation embryos

We are happy and proud to announce that the new embryology atlas is not far off completion. The working group, led very efficiently by Gayle Jones, has done a fantastic job, together with the ESHRE's Central Office and IT team. The atlas, in an electronic format, will contain a large number of pictures of oocytes, zygotes, cleavage stage embryos and blastocysts, fresh and frozen, grouped according to development and scoring. We believe that it will be very valuable for embryologists to share a common nomenclature as well as having a dynamic reference and learning tool.

Kersti Lundin
Co-ordinator SIG Embryology



A first glimpse of how the Atlas of Embryology will look.

SPECIAL INTEREST GROUPS

// STEM CELLS //

EU ruling bans patents on inventions whose processes involve human embryonic stem cells

The Court of Justice of the European Union ruled in October that an invention is excluded from 'patentability' where the implementation of the process requires either the prior destruction of human embryos or their prior use as base material, even if in the patent application the description of that process does not refer to the use of human embryos.¹ This ruling, which was made public in a press release dated 18th October 2011, was delivered after Greenpeace claimed that a patent held by the German scientist Oliver Brüstle was invalid because it described the differentiation of human embryonic stem cells into neuronal progenitors.

The CJEU's chain of reasoning was briefly as follows: human embryos (including embryos obtained after somatic cell nuclear transfer and parthenogenetically activated embryos) are protected by Directive 98/44/EC on the legal protection of biotechnological inventions. As hESC derivation is usually achieved through the destruction of a human embryo, hESC are thus included in the concept of 'human embryo'. The court further concluded that the uses of human embryos (and thus hESC) which are not 'patentable' should include scientific research as well as 'industrial and commercial' purposes.

The ruling has led to a flurry of reactions from distraught European scientists, supported by their American colleagues, who at times could not conceal a hint of Schadenfreude. Indeed, Googling 'stem cells EU ruling' between 18th October and 22nd November uncovered about 170,000 hits. Here, we quote a few of the comments from a wide spectrum of journals and papers, and start with the hapless Professor Brüstle, who said: 'With this unfortunate decision, the fruits of years of translational research by European scientists will be wiped away and left to the non-European countries. European researchers may conduct basic research, which is then implemented elsewhere in medical procedures, which will eventually be re-imported to Europe. How do I explain that to the young scientists in my lab?'²

Similarly and on the same website (eurostemcell.org), the well known stem cell biologist Austin Smith commented: 'This unfortunate decision by the Court leaves scientists in a ridiculous position. We are funded to do research for the public good, yet prevented from taking our discoveries to the market place where they could be developed into new medicines. One consequence is that the benefits of our

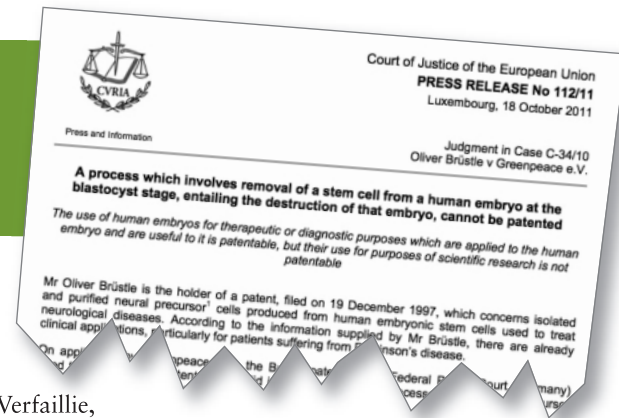
Steering committee
Karen Sermon (BE), Co-ordinator
Rita Vassena (ES), Deputy
Anis Fekis (CH), Deputy
Carlos Simon (ES), Past Co-ordinator

research will be reaped in America and Asia.'

Catherine Verfaillie, another high-profile stem cell researcher, said in *Nature Reviews Drug Discovery*: 'The decision is strange because the EU Commission allows us to do innovative research – and indeed funds such research on established ESC lines, but as a result of this decision much of this work will now not be valorizable.'³

And from across the Atlantic a comment from Robert Lanza in the *Wall Street Journal*, which we cannot help thinking was made with a wry chuckle: 'Of all the intellectual work being done in Europe, if something is successful it will now be [commercialised] by a company outside Europe. Europe is basically exporting its research—it is unfortunate.'⁴

Indignant outcries were also heard from the ethical and legal corner. In the same *Nature Reviews Drug Discovery* article as Catherine Verfaillie, Julian Hitchcock, senior life science intellectual property solicitor and regenerative medicine specialist at Field Fisher Waterhouse, London, said: 'The decision represents a dangerous expansion of the legal concept of human dignity laid down in the EU Charter of Fundamental Rights . . . But by giving the blastocysts rights that are the same as those of human beings, the dignity of patients has been seriously harmed because the mechanism by which new treatments are developed has been impeded.'⁵ However, the same Julian Hitchcock is quoted in a *Nature* news article as saying: 'Even a restrictive interpretation should allow companies to patent the technologies needed to turn human ES cells into treatments, rather than patenting procedures involving the cells themselves . . . Growth media, equipment and chemicals that help scientists to work with stem cells could all be patented in Europe without running afoul of the high court's ruling. For instance, Peter Coffey at the Institute of Ophthalmology in London and his team are working with the drug giant Pfizer to develop a human-ES-cell-based treatment for macular degeneration,



a progressive disease of the retina that causes blindness. Their patents cover the placement of their retinal cells in the eye, not the cells themselves.'

Indeed, it was even suggested that the absence of pressure for patenting might even create an atmosphere for freer research in Europe.⁵ This of course would depend on the explicit condition that research-granting agencies change their policies in favour of more and more translational research which is easily 'valorised'. As a career-long researcher, scrabbling year after year for the sustenance of granting agencies for fundamental research with ever decreasing budgets, I have doubts about this evolution.

Hearing the influential voices that have spoken out against the ruling (for example, Austin Smith in *Nature* comments,⁶) creating an environment conducive to research and development in our field of ART, embryology and stem cells in the EU remains an uphill struggle. Conservative opinions, sometimes coming from unexpected corners such as Greenpeace, seep into regulation via laws which are abused to ends different from their initial aim. Here again, as in so many places, scientists should come out of their labs as citizens, voicing their opinion in political arenas. In my lab, everyone withdrew their Greenpeace membership. A small and perhaps empty gesture, but it's a start.

Karen Sermon
Co-ordinator SIG Stem Cells

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KAREN SERMON: 'CREATING AN ENVIRONMENT CONDUCTIVE TO RESEARCH AND DEVELOPMENT IN OUR FIELD IN THE EU REMAINS AN UPHILL STRUGGLE

// REPRODUCTIVE GENETICS //

Publication planned on the dynamics and ethics of PGS

We ran three successful Campus workshops in 2011.

Building on our previously successful courses in London (2007), Athens (2008), Strasbourg (2009) and Porto (2010), a **Basic Genetics for ART Practitioners** course was held in September 2011 in Bucharest,

Romania, with a total of 82 participants registered and very positive course evaluations. This was a great opportunity to promote ESHRE (and our learning opportunities) in Eastern Europe. This same course will be run in Rome on 7th September 2012.

In October a joint meeting of the SIG RG and SIG Ethics & Law was held in Maastricht titled **Comprehensive preimplantation screening: dynamics and ethics**. There was much discussion on this rapidly advancing field of genetic testing and what it will mean for reproductive medicine. A publication is planned of the issues discussed.

Our third Campus event was held in Athens in October and was a joint meeting with EuroGentest and the PGD Consortium on **Accreditation of a Preimplantation Genetic Diagnosis Laboratory**. This is the third quality

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Ursula Eichenlaub-Ritter (DE), Deputy
Stéphane Viville (FR), Past Co-ordinator
Tania Milachich (BG), Junior Deputy

management meeting organised by the PGD Consortium, and a similar fourth workshop is planned for Istanbul in 2012.

The preconference course in Stockholm, **From genes to gestation**, was organised with the SIG Early Pregnancy. In Istanbul our course is a

joint venture with the SIG Safety and Quality in ART and is titled **Known and unknown congenital, genetic and epigenetic risks for children born following ART: basic and clinical data**, with an excellent line-up of speakers.

In 2005, a meeting jointly organised by ESHRE and the European Society of Human Genetics was held in Seville and resulted in the publication of a paper in 2006 by Soini et al (The interface between assisted reproductive technologies and genetics: technical, social, ethical and legal issues) in *Human Reproduction* and the *European Journal of Human Genetics*. We now feel it is time to revisit this important topic, so a joint ESHRE/ESHG meeting will be held in Brussels in March 2012.

Joyce Harper
Co-ordinator SIG Reproductive Genetics

SPECIAL INTEREST GROUPS

// REPRODUCTIVE SURGERY //

A possibility of certification in laparoscopic surgery

Last year we hosted two very successful, fully booked workshops in Leuven - with targeted lectures, dry lab and live surgery - and organised a collaborative meeting with the RCOG in London. The latter increased visibility of the SIG RS and proved an important platform for ESHRE to attract interest from other societies in reproductive surgery, education and important technical skills.

This year our aim is to provide the highest educational value and to increase both attendance at our meetings and interest in ESHRE. With this in mind we will hold two further training courses in 2012, both in Leuven, in February and November. In addition, we are organising a workshop in Larnaca, Cyprus, on 16-17th March on **Reproduction and the management of fibroids**, which will cover topics from basic research to operative techniques.

We have recently raised the difficult issue of managing congenital uterine pathology and have set up with the European Society for Gynaecological Endoscopy (ESGE) a task force aiming to improve diagnosis and treatment.

Our future plans

Our basic training courses in Leuven will continue into 2013 (in February and November) and we are making plans for two further workshops - one in Romania in April or May 2013 on **The importance of reproductive surgery in increasing pregnancy rates in ART**, and a second in Thessaloniki, Greece, in September on **Female genital tract congenital malformations: an update**. The former, organised

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Vasilios Tanos (CY), Co-ordinator
TC Li (GB), Deputy
Gregoris Grimbizis (GR), Deputy
Natasa Kenda Suster (SI), Junior Deputy
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by Razvan Sokolov, will review minimally invasive techniques for the diagnosis and treatment of infertility, including the treatment of uterine anomalies and the effect of myometrial pathology in successful ART. The latter, organised by Gregoris Grimbizis, will examine

the aetiology, pathophysiology and genetic background of congenital anomalies, the different diagnostic techniques, and treatments.

Certification in laparoscopic surgery

A report from the Dutch ministry of health in 2007 found training in laparoscopic surgery variable and inadequately structured, highlighting a more general concern that the standards which a future laparoscopist must meet in order to operate - either independently or under supervision - have not been adequately established.

Against this background the SIG RS has recently been considering the idea of a programme of certification in laparoscopic surgery in collaboration with the ESGE. Our idea is that ESGE would take responsibility for the basic certification, and ESHRE for subspecialty certification. It is our opinion that such an arrangement would be an attractive package, not just for the provision of systematic learning and certification at the general and subspecialty levels, but also to increase support for ESHRE's preconference courses and scientific sessions.

Vasilios Tanos

Co-ordinator SIG Reproductive Surgery

// REPRODUCTIVE ENDOCRINOLOGY //

High attendances justify integrated training programmes

The past year has continued in the pattern of 2010 with three well-attended workshops, a basic training workshop and a preconference course in Stockholm with 200+ participants. We covered a wide range of subjects, from the oncological impact of ART in Germany in February, to

periconception care in the infertility clinic in the UK in May, to the most common endocrine disorder in our field, PCOS, in Bulgaria, in December. Last year's preconference course in Stockholm was on ovarian ageing, which seems to be gradually replacing the classic causes of infertility as the main reason for referral of patients to IVF treatment.

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

Basic training workshops

Our training workshop in 2010 in Kiev and 2011 in St Petersburg attracted very high attendances - 202 and 185 participants - reflecting the need for such high-quality basic training from ESHRE. With these responses in mind, we have proposed

to ESHRE's Executive Committee the construction of a co-ordinated education strategy for basic training among all the SIGs, with at least one basic training course a year outside the EU. This would meet an undoubted educational need and increase ESHRE's influence as the major scientific representative in reproductive medicine.

An audience response system for ESHRE courses?

The SIG Early Pregnancy co-organised two meetings in the latter half of 2011. Our joint meeting with European Society of Reproductive Immunology in Copenhagen in August, on integrating clinical, epidemiological and immunological aspects of early pregnancy complications, was a great success, with 165 participants, most of whom stayed until the last session of the last day!

At the ASRM congress in Orlando we took part in a popular exchange workshop which focused on the diagnosis and management of pregnancy of unknown location, chromosome testing in patients with recurrent miscarriage, recurrent miscarriage terminology and evidence-based management of recurrent miscarriage. Diverging European and American views were discussed, and it was fascinating to experience the use of an audience response system (ARS) enabling smart phone answers to questions embedded in the presentations. ARS seems an exciting tool for activating the audience and encouraging immediate feed-back during lectures. We hope ESHRE will consider an ARS system in future pregress courses.

Future activities

Our pregress course in Istanbul will be titled **Gamete quality and ovarian reserve as markers for early pregnancy loss**. The faculty will review the evidence (or lack of) that markers of poor sperm or

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 2011 joint ESHRE/ASRM workshop faculty for early pregnancy: from left to right, Roy Farquharson (GB), Kurt Barnhardt (US), Mariette Goddijn (NL), Ole Christiansen (DK), William Kuttah (US), and Mary Stephenson (US)

oocyte quality are predictive of biochemical pregnancy/miscarriage, especially after ART. We hope that many clinicians in ART who normally do not consider early pregnancy as their main interest area will find this course attractive.

On 29-30th November our regular winter Campus course in Amsterdam will be organised by Mariette Goddijn on **Evidence based early pregnancy care**. The course will focus on the management of ectopic pregnancy and recurrent miscarriage, with a session on the organisation of early pregnancy care units and debates on RCTs in early pregnancy disorders.

For 2013 we have already made plans for a joint

ASRM/ESHRE pregress course before the annual meeting in London on risk factors for recurrent pregnancy loss. An early pregnancy session during the scientific programme has already been planned on **Gathering evidence in early pregnancy research – Making trials happen**.

During the next months procedures will begin for nominating and electing a new Deputy Co-ordinator and Junior Co-ordinator to take up their posts in Istanbul. We hope you will be there at the pregress course to meet them.

Ole B. Christiansen
Co-ordinator SIG Early Pregnancy

Future activities

The title of our pregress course in London in 2013 will be **Ovarian stimulation for ART: how to achieve efficacy and safety?** We are also asking for applications for ESHRE Campus workshops for 2013. Please send any proposals to me at griesing@uni-luebeck.de. We will need to pick the best applications in terms of originality, meeting structure, venue and accessibility.

In 2012 we have the following events:

- **Anti-Mullerian hormone: An update**, Lille, 10-12th May, a Campus workshop designed to provide an evidence-based update on the role of AMH in contemporary reproductive medicine. All aspects of AMH, from its function within the ovary, its relationship with

follicle number throughout life, and to its use for assessing ovarian reserve, defining PCOS and predicting the menopause will be featured.

- **GnRH-antagonists in ovarian stimulation**, Frankfurt, 28th September, a one-day workshop which will cover all clinical aspects of ovarian stimulation with GnRH-antagonists. The aim of the workshop is to provide participants with a comprehensive and detailed understanding of the evidence basis of ovarian stimulation with antagonists, and how to utilise them for a safer and simpler IVF treatment. Areas of debate and directions for future research will be highlighted.

Georg Griesinger
Co-ordinator SIG Reproductive Endocrinology

SPECIAL INTEREST GROUPS

// ENDOMETRIOSIS & ENDOMETRIUM //

Activities focus on the impact of endometriosis on patients' symptoms - pain, fertility and quality of life

Our Campus meeting on **Endometriosis and IVF** held in a sunny and warm Rome in October was well attended and fully booked with some 100 participants. The event was organised by the SIGEE in collaboration with local IVF specialist

Filippo Ubaldi (a past member of the ESHRE's Executive Committee) and Marco Sbracia. Excellent lecture content was accompanied by stimulating discussions. The first day focused on novel aspects of basic research in endometriosis, followed by extensive sessions on ovarian reserve in patients with endometriosis, ovarian hyperstimulation regimes and outcomes of IVF. The last lectures of the first day considered the risk of ovarian cancer in patients with endometriosis in relation to IVF - and timely observations have emerged. The second morning considered the surgeon's perspective in relation to reproductive outcomes and fertility preservation. The final lectures addressed obstetric morbidity in IVF-derived pregnancies of women with endometriosis. First feedback from the meeting has indicated a general appreciation of the high quality presentations and the opportunity for discussion of controversial topics, such as the best surgical technique for ovarian endometriomas.

Precongress courses

We will revisit the impact of endometriosis in our 2012 precongress course in Istanbul, **Pain and endometriosis**. Here we propose to address clinical issues as well as mechanistic insights and best available evidence for clinical management of this highly distressing symptom. Our target audience is all providers of care for women with endometriosis, including clinicians, nurses and scientists (and neuroscientists) with an interest in endometriosis and pain mechanisms. We also encourage attendance of those who provide multi-/ cross-discipline care.

Looking further ahead to London in 2013 we will broaden the agenda with a programme which examines the impact of pelvic pain and uterine bleeding on quality of life.

Steering committee

Hilary Critchley (GB), Co-ordinator
Anneli Stavreus-Evers (SE), Deputy Co-ordinator Endometrium
Gerard Dunselman (NL), Deputy Co-ordinator Endometriosis
Annemiek Nap (NL), Junior Deputy
Paola Vigano (I) Basic Science representative
Thomas D'Hooghe (BE), Past Co-ordinator

It has been rewarding to have received so much support from SIG members for this PCC proposal and we will endeavour to do justice to your enthusiasm for this topic.

Junior membership

Our SIGEE Junior faculty has been active and thanks are due to Annemiek Nap for driving forward this initiative. In an update from Annemiek she informs us that 'the junior faculty of the SIGEE is an enthusiastic international team of young clinicians and basic investigators from five different European countries who are active in the field of endometrial research and endometriosis'.

The goal of the junior faculty is to ensure we have a pipeline of enthusiasm with a mission to improve the care of those suffering from endometriosis and from endometrial diseases. International consensus on optimal treatment strategies may help to achieve this important goal. As a result, the junior faculty team is active in the ESHRE Endometriosis Guideline Group, which is currently updating the ESHRE Endometriosis Guidelines.

Looking ahead, there is a need for the development of more multidisciplinary treatment teams for endometriosis, consisting of gynaecologists, surgeons, urologists, gastroenterologists, nurses, pain specialists, and psychologists/counsellors. Preferably, these multidisciplinary teams would be active in networks of expertise for endometriosis. Making young doctors in these professions aware of the problem of endometriosis would be a first step towards an increase in the number of experts treating the disease.

But for the moment it is terrific to have such enthusiasm from amongst the members of the SIG Endometriosis and Endometrium

Hilary Critchley

Co-ordinator SIG Endometriosis & Endometrium

New guidelines anticipated by London 2013

New guidelines

The new Psychology and Counselling Guidelines now in development will provide best practice advice on how psychosocial care can be incorporated into daily practice to the benefit of patients and healthcare providers in the field of infertility and ART. We

aim to create a framework that takes into consideration the different ways in which healthcare is managed throughout Europe. Thus, despite socio-cultural and legal differences in Europe, the Guidelines are intended to be applicable to all countries.

Several meetings for the development of the guidelines have already taken place. The last was held during the annual meeting in Stockholm, where the scope of the guidelines was discussed. The group is now working on defining key questions, which will lead to the collection of evidence for evaluation. ESHRE's research specialist, Nathalie Vermeulen, is assisting us in this process and will conduct the evidence search. She will also train the team on how to systematise and evaluate the quality of the evidence gathered; it is from this evidence that recommendations on how to incorporate psychosocial care into daily practice will be made. We are expecting to present the guidelines at the 2013 annual meeting in London.

Budapest Campus workshop

In March we will visit Eastern Europe to deliver a workshop in Budapest, Hungary. The workshop will focus on developing competence in psychosocial care and counselling. This 1.5 day course will introduce participants to psychosocial issues present at different times and settings of the infertility experience and will provide in-depth case-discussions to deepen understanding and increase skills for providing psychosocial care. The course has two target audiences: professionals involved in the general care of people with infertility, such as physicians, nurses and administration staff; and psychologists and counsellors, who will be offered training

Steering committee

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

in specific areas, such as couples therapy or in loss and bereavement. The goal is for fertility professionals to acquire skills for improving psychosocial care and/or counselling in various settings and for various specific situations.

Istanbul

At this year's annual meeting in Istanbul our preconference course will focus on the burden of fertility treatment. The course is directed at medical doctors, nurses and paramedical staff and counsellors and others involved in psychosocial care. The aim of the course is to promote reflexion on how fertility healthcare professionals can help manage the burden of treatment, which will be addressed from different perspectives. Topics will include treatment drop-out, implications of different treatment protocols, impact on sex life, dealing with unsuccessful treatment, the use of online resources to manage the burden, patient and healthcare provider communication and quality of care. The course will end with a round-table discussion.

Following the preconference course, our SIG business meeting welcomes all members. This year we will discuss previous and upcoming Campus events and an update of the progress of the guidelines will be provided. The day will finish with our annual dinner in the city centre, held in conjunction with the International Infertility Counsellors Organization (IICO). Everyone interested in joining the dinner may contact Uschi Van den Broeck (uschi.vandenbroeck@uzleuven.be) for more information.

This is a very promising year for the SIG Psychology and Counselling and we hope to see many of you in Budapest and Istanbul.

Don't forget for your 2012 diaries:

- ESHRE Campus, **Developing competence in psychosocial care and counselling**, Budapest, 23-34 March 2012
- ESHRE annual meeting, Istanbul, 1-4 July 2012

*Sofia Gameiro
Junior Deputy Co-ordinator
SIG Psychology and Counselling*

TASK FORCES

// EU TISSUE AND CELLS DIRECTIVE //

End-of-year report: short-term targets met, and hopes high for resolution on repeat serological testing

Impact of the EUTCD in Europe

A questionnaire sent to all members of ESHRE's Committee of National Representatives in spring 2010 found that most (15/19) had by then fully implemented the three directives, but found variance in national requirements for serological testing, and even inconsistency in the definition of what a 'treatment cycle' was. Ten of the 19 member states defined 'treatment' as a single oocyte recovery procedure, but one also included subsequent frozen cycles, and two made no definition at all. One in three considered a 'chain' of egg collections as a cycle.

Collaboration with the regulators (SANCO, SOHO-V&S)

SANCO (Directorate General for Health and Consumers)

- The collaboration between the Task Force, competent authorities and the European Commission has resulted in multiple meetings in Brussels. The meetings took place under the auspices of the DG SANCO and focused on testing requirements for partner donation.
- These meetings aimed to address the risk of cross-contamination during cryopreservation and other processing and storage steps, the mix-up of gametes, the transmission of communicable diseases from the embryo to the mother and vice versa, and the reporting of serious adverse reactions and events (SARE). A final document has been produced for the attention of the competent authorities and the Commission, with the final decision still awaited. The evidence in favour of less frequent screening is overwhelming.

SOHO-V&S (Substances of Human Origin - Vigilance and Surveillance)

Task Force representatives took part in the three SOHO V&S meetings of 2010 and 2011.

- The project itself aims to identify specific issues related to vigilance and surveillance, adapt the EUSTITE V&S tools to assisted reproduction, and make recommendations for the reporting of serious adverse reactions and events. To this end, the Task Force developed a paper on triggering conditions for rapid alerts and contributed to all other ART-related topics addressed.

Aims of the EUTCD Task Force

- Ascertain the impact of the EUTCD in Europe
- Encourage best collaboration with the regulators (SANCO, SOHO (V&S))
- Provide the evidence to help ESHRE lobby for a separate ART Directive
- Establish the highest professional standards in ART
- Provide ESHRE with the documentation to help collaboration with the competent authorities.

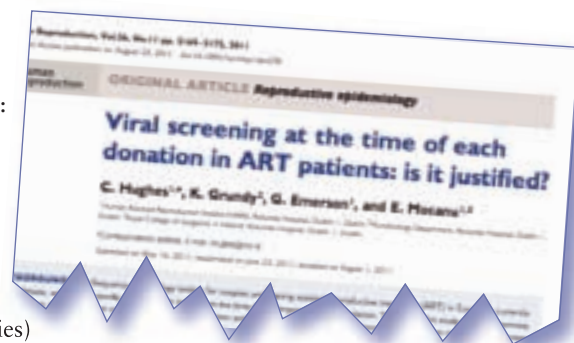
- A final document entitled 'Guidance on Vigilance & Surveillance in Assisted Reproductive Technologies in the European Union' has now been submitted to the European Commission. It covers the following areas: ART specific terminology, equipment and practices, safety in ART, reporting of SARE, triggering conditions for rapid alerts and ART-specific reporting tools.

Evidence for a separate ART Directive

Risk of seroconversion in the ART population

Data from a single centre and three European centres has been collected and submitted to SANCO as evidence that the risk of seroconversion in ART couples is negligible.

- One paper on the risk of seroconversion in ART from a single centre has just been published (Hughes C, Grundy K, Emerson G, Mocanu E. Viral screening at the time of each donation in ART patients: is it justified? Hum Reprod 2011; 26: 3169-3172). Another paper on risk of seroconversion at European level (three European countries) is in advanced preparation.



Feedback to ESHRE members

The Task Force has taken part in the member's information session at the annual meetings in Rome and Stockholm, and reported its activities in *Focus on Reproduction*.

Future tasks

The Task Force has had a significant impact in promoting a better understanding of the specific circumstances of the Directive relevant to ART. A clearer message for ART practitioners, centres, competent authorities and the European Commission has emerged based on the



ESHRE Campus at new reproductive biology world congress

The Task Force took part in the second World Congress on Reproductive Biology, held in Cairns, Australia, in October, with the organisation of a full day's Campus satellite course on **Human reproductive tissues, gametes and embryos: innovations by science-driven culture and preservation systems**. The event was greatly appreciated by participants, as reproductive biologists extend their understanding of the potential applications of their research in clinical medicine.

It is also one of ESHRE's stated priorities to enhance relationships with basic scientists in the area of reproductive biology. In the long run, this strategy aims to boost scientific research and education in our field, not only to raise practice and research standards in clinical embryology, andrology and cryopreservation labs, but also to increasingly attracting both established and young researchers to the ESHRE meetings.

The WCRB attracted more than 500 scientists from throughout the world and had the official representation of the Society for the Study of Reproduction, (USA), Society for Reproduction and Fertility (UK), Society for Reproductive Biology (AUS), and the Japanese, Chinese and Korean societies of reproductive biology. The meeting



Participants in the ESHRE workshop, including ESHRE representatives Ursula Eichenlaub-Ritter and Carlos Plancha in the near foreground.

was held in the very modern Congress Palace in Cairns and the local organisers under the leadership of Daryll Russell had prepared excellent intermezzos and social events, so that participants from all parts of the world could intermingle. The scientific programme was top quality, with participating societies delegating some of their leading performers. Speakers included Ursula Eichenlaub-Ritter, Carlos Plancha and Johan Smitz from ESHRE, and Debra Gook and Rob Gilchrist from Australia.

The next WCRB will take place in Edinburgh in September 2014 (with satellite meetings organised for 1-2nd September), hopefully with an even stronger representation of ESHRE as a world player in reproduction science.

*Johan Smitz
Co-ordinator TF Basic Reproductive Science*

published literature and as a consequence of the evidence collected. The EC continues to base its decisions on published evidence only, and articles that address ART practice covered by the Directive should receive priority in ESHRE peer-reviewed journals.

While the issue of repeat serological screening is expected to be favourably resolved in spring 2012, pending final approval of the competent authorities and European Commission, the Directive has numerous areas that still require immediate attention, notably:

- identifying areas that require further definition and amendment from an ART perspective
- the Task Force's own proposal for the establishment of a EU-ESHRE ART inspector training programme. This would provide training for inspectors in the field of ART by bringing the expertise of ESHRE and the competent authorities together. It is now opportune to use the goodwill and trust built up between the Task Force, the competent authorities and the Commission to consolidate ESHRE's leadership position in the regulation and education of ART inspectors.

To date, the short-term goals of the Task Force have all been reached. The medium-term goals - to develop an inspection curriculum with wide applicability at the European level and to organise an ESHRE workshop for competent authorities - can be achieved through pursuing the future tasks noted above. An excellent opportunity for this should be the ESHRE Campus meeting to be organised by the Task Force and SIG Safety and Quality in ART in Dublin in September this year.



*Edgar Mocanu
EUTCD TF Co-ordinator*

TASK FORCES

// DEVELOPING COUNTRIES AND INFERTILITY //

An expert workshop on the socio-cultural and ethical aspects of infertility care in poor-resource countries

In November the Social Science Study Group of the Special Task Force held an expert workshop in co-operation with the Walking Egg Foundation, the University of Amsterdam, Amsterdam Institute for Social Science Research and the WHO. During the two-day meeting, which took place in Genk, specialists from different parts of the world reviewed the various socio-cultural and ethical aspects of biomedical infertility care in poor resource areas. These included:

- Socio-cultural, political and economic barriers to access
- Counselling, patient-staff interaction, privacy and other aspects of care
- Ethical concerns at policy and clinical level
- Infertility care in times of HIV/AIDS

Sheryl Vanderpoel from the WHO explained how access to infertility care would not only help countries reach Millennium Development Goal 5b ('universal access to reproductive health care') but would also contribute to MDG 3 ('gender equality'), MDG 4 ('neonatal health'), MDG 5 ('maternal health'), MDG 6 ('HIV/AIDS') and MDG 8 ('new technologies'). Guido Pennings summarised the ethical arguments pro and contra infertility treatment in developing countries.

The first session was dedicated to sub-Saharan Africa, and S Dyer and M Patel examined how current out-of-pocket funding for ART deepens household poverty in South Africa. V Horbst and E Mariano explored how patients in Mali, Togo and Southern Mozambique cope with the barriers to infertility care. And finally, Claus Janisch talked about his own experiences and challenges in

output-based financing for maternal care in Kenya. The use of vouchers, which are strictly speaking conditional cash transfers with defined benefits, could be a promising payment model for infertility services in poor countries.

In the following session D Khalifa (Sudan), H Sallam (Egypt) and S Tremayne (Iran) reviewed socio-cultural, policy and ethical aspects of infertility care in the context of the Eastern Mediterranean region, defined somewhat by Islamic laws and culture.

The next day we turned our attention to the Asian region. P Nahar concluded after interviewing policymakers, NGOs and donors in Bangladesh that infertility is excluded from the public health discourse because of its emphasis on the epidemiological index, ie, morbidity and mortality rates. M Pashigian examined the growth of biomedical services in Vietnam and the issue of illegal trade in transnational surrogates in Asia.

In the next session, we travelled to Bulgaria where, according to Y Panyotova, resource distribution gives priority to expensive treatment for only a minority. A similar situation was found by M Makuch in the public health sector of Brazil, where the IVF centres do not provide a service for the most under privileged. Finally, in a talk on cross-border reproductive care, Z Gurtin stressed the importance of keeping an eye on the broader context of transnational flows and raised questions on how the provision of ART in low-resource countries could interact.

The final session focused on infertility care in sub-Saharan Africa in times of HIV/AIDS. N Dhont and A Bachow explored challenges in the double burden of HIV and infertility for the provision of infertility care in developing countries.

The final round-table discussion recognised the multiplicity of barriers to infertility care access and where further research is needed. The next step for the group will be the finalisation of a protocol for the assessment of newly introduced accessible infertility care in poor resource countries from a socio-cultural point of view.



The Task Force's workshop on socio-cultural and ethical aspects of biomedical infertility care was attended by 27 experts.

*Nathalie Dhont
Willem Ombelet, Co-ordinator
TF Developing countries and infertility*

The urgent need for new sperm biomarkers

Conventional semen analysis remains the gold standard for the initial investigation of male infertility. However, semen analysis is today considered of only limited value in predicting a couple's chance of pregnancy with ART. Certainly, the uptake and success of ICSI have reduced the significance and perceived need for sperm quality tests; ICSI requires only one sperm - even if morphologically abnormal and immotile - for the procedure to be around 25% successful in most European clinics. ICSI is now our most widely used means of fertilisation in ART, but can we be satisfied with this modest level of success? Will a better test than semen analysis improve our results?

Sperm DNA quality as a diagnostic test

As a diagnostic tool, sperm DNA damage has been shown to be more reproducible than conventional semen parameters and more predictive at numerous fertility check-points.¹ For example, men with sperm DNA fragmentation above a diagnostic threshold of 25% using the Comet assay or 30% using the Sperm Chromatin Structure assay (SCSA) have a high risk of infertility.^{2,3} So sperm DNA damage appears to exhibit better credentials as a novel biomarker for male infertility than a semen analysis.

Sperm DNA quality as a prognostic test for ART outcome

Sperm DNA damage is associated with longer times to pregnancy than in fertile couples, with impaired embryo cleavage and reduced implantation after IVF, and most closely with increased risk of pregnancy loss after both IVF and ICSI.

However, the lasting implications of sperm DNA damage may be of even greater significance. As sperm have few repair mechanisms and oocytes can only repair a limited amount of sperm DNA damage, such damage may remain in the germ line for generations. Nature does not prevent a sperm with oxidative DNA damage from reaching the oocyte, achieving fertilisation and thus contributing to mutations during embryonic development or even causing loss of the fetus. Damaged sperm DNA may be incorporated into the embryonic genome, thus leading to errors in DNA replication, transcription and translation during embryogenesis, and thereby contributing to a range of human diseases in subsequent future generations.⁴ In particular, sperm DNA may have an impact on both the short and long-term health of children born by ART, with some

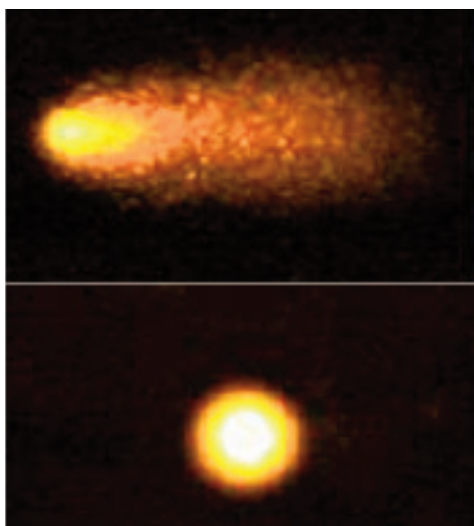
Semen analysis is of limited value but remains the gold standard of initial testing for male fertility. Will better assays improve the outcome of ICSI and IVF, asks andrologist Sheena Lewis.

studies (though not all) showing that children conceived by ICSI have a higher incidence of disease than children spontaneously conceived.⁵ Continuing into childhood, there are associations between poor sperm DNA integrity and a range of diseases, from childhood cancers to autism.

Currently available tests for sperm DNA damage

For a sperm DNA test to be clinically useful it must have strong predictive capacity for pregnancy with little overlap between fertile and infertile samples. The tests most often used today are the Comet assay, SCSA, the terminal transferase dUTP nick end labelling (TUNEL) assay, and the Sperm Chromatin Dispersion (SCD or Halo) test.

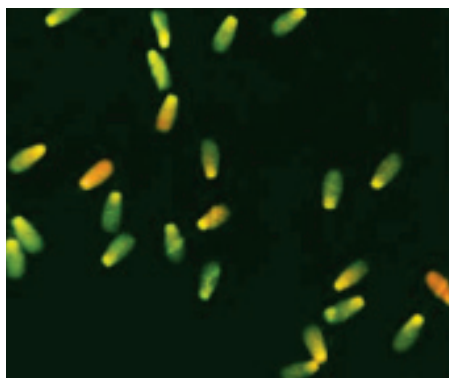
● The Comet assay



The Comet assay is a single cell gel electrophoretic test which quantifies broken strands of DNA in individual sperm cells. As the mass of DNA fragments stream out from the head of unbroken DNA, they resemble a 'comet' tail, hence the name of the assay. One major advantage of this assay is that it uses

only 5000 sperm, so is suitable for the assessment of small samples left over from clinical use, or for samples where only a few sperm are available. The Comet assay can measure both single and double strand breaks, and, with an additional step, even altered bases. This is useful, because we don't yet know which types of DNA damage are most deleterious to male fertility. The Comet is sensitive, repeatable and capable of detecting both high and low levels of damage in sperm.⁶ Since 2010, clinical thresholds for the diagnosis of male infertility and the prediction of IVF outcome have been established.

● The Sperm Chromatin Structure assay

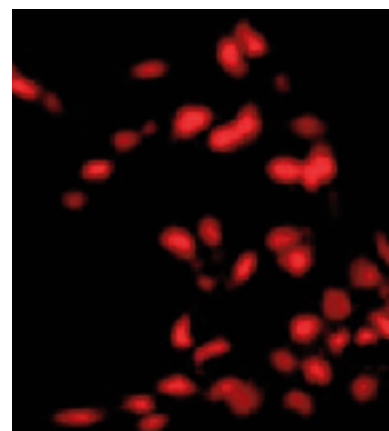


The SCSA is a fluorescence cell sorter test which measures the susceptibility of sperm DNA to denaturation after exposure to heat or acid conditions. One benefit of the SCSA is its ability to rapidly measure large numbers of cells by

flow cytometry. This gives it robust statistical power, but does make it unsuitable for samples with low counts. In addition, it measures only single strand fragments, and has demonstrated associations between native, not DGC, sperm and ART outcomes. However, the SCSA has been tested over many years and its founder, Don Evenson, has always wisely insisted on a standardised protocol for all users. This has reduced inter-laboratory variation and allowed comparison of studies from different groups.⁷

● The Sperm Chromatin Dispersion (Halo) test

The Halo test is a simple and inexpensive assay, available to fertility labs in kit form. Unlike all the other tests, it measures the absence of damage rather than the damaged DNA in sperm. The test is convenient in that it does not rely on



either colour or fluorescence intensity, and is simple to analyse in a routine laboratory with light microscopy. One limitation of the assay is that its low-density nucleoids are relatively faint, with less contrasting images. To date, correlations have been observed between DNA and other sperm parameters, although few correlations between sperm DNA damage and ART outcomes have been established with the Halo test, even in large ($n = 600$) studies.⁸ Meseguer et al in 2009 reported that sperm DNA damage as measured by Halo had a negative impact on pregnancy.⁹

● The TUNEL assay

The TUNEL assay detects 'nicks' (free ends of DNA) by incorporating fluorescently stained nucleotides. This allows the detection of single and double stranded damage. The cells can be



assessed either microscopically or by flow cytometric (FCM) analysis. This gives the assay the flexibility to be used for small numbers with microscopic analysis and in small laboratories without dedicated and expensive FCM facilities. However, the TUNEL assay can also be analysed by FCM, giving it the advantage of robust numbers with reduced time and labour. A disadvantage of the assay is its many protocols, which makes comparison between

laboratories almost impossible and explains its many clinical thresholds. Recently, Aitken's group has improved the TUNEL assay by including a preliminary step of DDT to relax the whole chromatin structure and allow access to all 'nicks'. They have also added a viability stain so that DNA damage is measured only in live sperm. This has eliminated a previous inaccuracy of measuring damage (often at high levels) in dead cells.¹⁰ Robust clinical thresholds have yet to be established.

Novel tests for oxidised bases

Oxidative stress has long been implicated as the major etiological factor in sperm DNA damage. Thus, a low physiological level of reactive oxygen species (ROS) is considered necessary to maintain normal sperm function, but ROS levels above physiological norms may cause deteriorating function or reduced survival. As a result, the measurement of oxidised bases combined with fragmentation assays may indicate the potential as well as the actual DNA damage - and thereby enhance the prognostic value of our current tests. To this end, the determination of 7, 8-dihydro-8-oxo-2'-deoxoguanosine (8OhdG) has been used as a marker of oxidative DNA bases damaged by oxidation and has been shown to be a useful adjunct to sperm DNA strand breaks, especially in men with chronic disease (eg, diabetes mellitus).

Sperm DNA in the clinical setting

Two systematic reviews from the USA in 2009 (which included only TUNEL and SCSA but not the Comet or Halo assays) have reported that the impact of sperm DNA damage on ART outcomes decreases from IUI to IVF and is least evident in ICSI.¹¹ There are currently few data relating sperm DNA damage to late fetal development or postnatal health in humans. However, although poor sperm DNA does not appear to impair early fertility outcomes following ICSI, it does seem to have an impact at a later stage, and associations between poor sperm DNA and early pregnancy loss following ICSI (and IVF) are now beginning to emerge.¹²

In the light of such results, the question I find most difficult to answer is not whether sperm DNA damage impairs the outcome of IUI and IVF, but rather, *why sperm DNA damage does not seem to affect the early stages of ICSI*. At first glance, this appears to support the belief - although counterintuitive - that ICSI appears to bypass genetic as well as functional defects.

My response to the question is speculative but I have four suggestions:

- * Up to 30% of women having ICSI have no detectable problems. They are often fertile and their oocytes may have more capacity to repair DNA damage, even if the injected sperm cell is of poor quality. This is supported by the recent findings of Meseguer et al who showed that high quality oocytes from donors could offset the negative impact of sperm DNA damage on pregnancy.¹³

- * In ICSI the gametes are not exposed to prolonged culture,

so the sperm may incur less damage than those cultured overnight, as happens in IVF procedures. The recent study from Dumoulin et al shows that even the birthweight of IVF babies can be markedly influenced by minor differences in culture conditions over that very short but influential time of early embryo development.¹⁴ In contrast, ICSI sperm are injected into the optimal environment of the oolemma within a few hours of ejaculation. This may protect them from laboratory-induced damage.

- * Evidence is emerging that embryos with high sperm DNA damage are associated with early pregnancy loss, so ICSI success rates may indeed be sometimes affected adversely, but at a later stage.¹²

- * Since we choose only one sperm for ICSI - and that choice is arbitrary except that the sperm is usually motile - we cannot assess a cohort of similar sperm. It may be that the sperm we favour is unlike the rest in its characteristics. But given that our ICSI success rates are still relatively modest, our choice appears to be still 'hit or miss'.

However, on the broader question of the clinical usefulness of sperm DNA tests, I do believe that our expectations tend to be excessive. How can we expect this single parameter (from only one of the two gametes) to provide an absolute criterion for fertility or infertility? A successful ART outcome will depend on many other traits of sperm quality and function, as well as the influences of the oocyte, uterine receptivity and maternal immune system competence.

Limitations of sperm DNA testing

The major limitation of testing for sperm DNA damage is that the assay renders the tested sperm unsuitable for clinical purpose. In an effort to overcome this problem, a number of non-invasive tests have been developed and their correlation with DNA damage assessed. If these tests can help embryologists choose sperm with low DNA damage for ART, a major step forward in sperm selection will have been achieved - but so far this is not the case.

● Birefringence

One novel tool for sperm selection has been developed using birefringence, or double refraction. This is the refraction of a ray of light into two rays, which travel at different speeds when passing through certain anisotropic materials. Sperm have natural anisotropy, so birefringence provides a non-invasive and rapid method of selecting sperm with particular properties.

Gianaroli's group in Bologna has reported a higher proportion of sperm with birefringence in normozoospermic samples, and associations between birefringence and acrosome reacted sperm.^{15,16} Further associations have been found between sperm displaying low DNA damage measured by the TUNEL assay and total although not partial birefringence. Clinical and ongoing pregnancies were also higher in sperm selected for ICSI by birefringence.¹⁵

● Intracytoplasmic morphologically selected sperm injection

A method of selecting sperm for ICSI by real-time high magnification - using a technique originally called 'motile sperm organelle morphology examination' (MSOME) - has been developed by Bartoov's group in Israel and is now more widely known as intracytoplasmic morphologically selected sperm injection, or IMSI.¹⁷ With enhanced digital imaging, magnification can be increased to x6000 such that the morphology of six sub-cellular organelles - nucleus, acrosome, post-acrosomal lamina, neck, mitochondria and tail - can be assessed. In trials, implantation rates and pregnancies were higher and miscarriage rates lower with IMSI-selected sperm than with controls.¹⁸ Investigators have again suggested that a single morphological abnormality may indicate an anomaly in nuclear DNA, though the evidence for this is circumstantial and numbers are small. ICSI based on MSOME is a very time-consuming process (taking up to five hours) and further studies are needed to assure us that this does not compromise the DNA of the sperm destined for clinical use.

● Hyaluronic acid-selected sperm for ICSI

Hyaluronic acid (HA) is present in the extracellular matrix of the cumulus oophorus of the oocyte, and in vivo mature physiologically competent sperm bind to HA receptors prior to fertilisation. The HA assay uses media supplemented with HA to select sperm that bind to HA for ICSI. A correlation between HA-selected sperm and sperm with lower levels of DNA fragmentation (using the sperm chromatin dispersion test, Halo) has also been observed in two studies. Comparisons of ICSI outcomes with HA-selected sperm and standard PVP-ICSI sperm have shown that the former are associated with better embryo quality, higher implantation rates, increased pregnancy rates and reduced miscarriage rates.

In summary, the growing interest in novel biomarkers for male infertility is a very exciting and rapidly moving area of research in reproduction. A mass of new data indicates the usefulness of many of these new tests (particularly sperm DNA testing), both in a more accurate diagnosis of male infertility and in the prediction of ART outcomes.

Alas, although some of these novel biomarkers (particularly sperm DNA testing) have increasingly robust data to support them, there is still a reluctance to incorporate them into routine clinical care. Whilst this inertia continues and our traditional tests prevail, it seems unlikely that success rates in male infertility will improve. With the wider introduction of the new tests, patients will be better informed and clinics have additional information on which to base their choice of treatment.

Sheena E M Lewis is Professor of Reproductive Medicine, Queens University Belfast, UK, and Co-ordinator of ESHRE's SIG Andrology. She is also a founding Director of Lewis Fertility Testing Ltd, a spin-off development company of her university (www.lewisfertilitytesting.com).

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GETTY IMAGES

Conception in HIV-infected couples

Antiretroviral therapy has changed the outlook for most HIV-infected couples in developed countries such that conception is now a realistic option. Augusto Semprini and Simona Fiore on behalf of the CREAThE network and ESHRE's Task Force on Fertility and Viral Diseases review the risks of transmission and the most appropriate fertility techniques.

There are no clinical guidelines for the care of fertility in those infected with HIV, and the question of how best to promote conception in HIV-infected couples on highly active antiretroviral therapy is still open to discussion. Moreover, although many fertility clinics in Europe do screen patients for HIV infection, only a few are prepared to treat them if one or the other partner is positively diagnosed - because of perceived ethical dilemmas or other concerns.

Assisting couples to conceive does not solely require a consideration of the welfare of any child born as a result of treatment. Additional concerns are the life expectancy of an

When only the female is HIV+ve: the issues for consideration

- Protection for the man against sexually transmitted infection, and to the infant from vertical transmission
- Antiretrovirals during pregnancy
- Measures to reduce the risk of vertical transmission
- Frequency of unprotected intercourse
- Self-insemination in the ovulation window should be explained
- Re-evaluate after six months of unsuccessful attempts

infected parent and the risk of viral transmission to both the uninfected partner or offspring.

However, despite such concerns, the fact is that in developed countries HIV infection has now become a chronic but manageable disease; highly active antiretroviral therapy (HAART) has substantially increased life expectancy and quality of life for both children and adults infected with HIV.¹ Thus, in the context of mother-to-child transmission (MTCT), a combination of prophylactic antiretroviral therapy during pregnancy and labour, delivery by elective Caesarean section and avoidance of breast-feeding can reduce the risk of MTCT to less than 2%.² The balance in fertility treatment decisions in HIV infection has thus shifted considerably, such that treatment has now become both feasible and appropriate.

Reproductive counselling for HIV-infected couples

Reproductive assistance to HIV discordant couples can have a significant impact on the prevention of viral, sexual and MTC transmission. Most HIV-infected people are young and fertile, and both men and women are willing to have a child at sometime in their lives.³ The marked increase in life expectancy as a result of antiretroviral therapy has removed most of the ethical difficulties in helping people with HIV become parents, and specific information and assistance can now be offered to protect the uninfected partner or child from infection.^{4,5,6}

When only the woman is infected, self-insemination with the partner's semen completely eliminates the risk of sexual infection. Semen analysis to evaluate semen quality and to rule out genital infection might be indicated, and complete infertility screening should be provided if pregnancy does not occur within six months - preliminary observations indicate that HIV-positive women might have an added risk of subfertility.⁷

When only the man is HIV-positive, the possibility of spontaneous conception carries a risk of sexually transmitted HIV to the uninfected female through infected semen. This risk is difficult to quantify, but might be

significantly higher than a theoretical 1/1000 risk per single act of penetrative intercourse; a small trial on natural conception reported four cases of seroconversion in the 94 healthy women enrolled and advised to have unprotected intercourse at the time of ovulation with their HIV-positive partners.⁸

Different reports have discussed the 'efficiency' of sexual transmission from male to female and a mathematical model has been proposed.^{9,10,11} Wilson et al put the cumulative annual risk of female-to-male HIV transmission at 0.0022 and male-to-female at 0.0043 with an average of 100 acts of sexual intercourse per year.¹² A recent review of 11 cohorts reporting on 5021 heterosexual couples and 461 HIV transmissions found no transmission in patients treated with antiretrovirals and with a viral load below 400 copies/ml.¹³

The very low risk of HIV transmission to the negative partner and to the baby if HIV-positive individuals have undetectable viraemia with HAART now lies behind an increasing interest in natural conception.¹⁴ Natural conception has also been chosen by some couples following assisted reproduction programmes. Indeed, in one Italian study up to one-third of couples did not start their insemination procedures and a further third withdrew from the programme after a number of failed attempts; half of these couples tried natural conception with unprotected sex and without medical control.¹⁵

Although some expert advice has claimed that the risk of sexual transmission is negligible when the HIV-infected partner is receiving antiretroviral therapy (with excellent adherence, undetectable viral load and no STDs),¹⁶ the mathematical model noted above would suggest that abandoning condom use could quadruple the number of contaminations and thereby have a significant effect in terms of public health. The general perception of HIV transmission by sexual intercourse is extremely low in this population, and protected sexual intercourse remains the most important means of prevention.

Anecdotal reports also suggest that periconceptional pre-exposure prophylaxis with oral antiretroviral therapy is already in limited use; if effective in reducing heterosexual HIV transmission, this too might be an option for discordant couples wanting to conceive spontaneously.¹⁷

Long-term treatment with antiretrovirals can reduce viral



AUGUSTO SEMPRINI:
'COUPLES IN WHOM ONE OR BOTH PARTNERS ARE HIV INFECTED SHOULD HAVE ACCESS TO THE SAME FERTILITY ADVICE AND TREATMENT AS NON-INFECTED COUPLES.'

replication in blood and semen, but some infected men maintain substantial viral concentrations in their semen, even in the presence of undetectable blood plasma viral load with antiretroviral treatment.¹⁸ Certain studies have shown that HIV-RNA may be amplified in semen when undetectable in plasma in 2–8% of patients on HAART, suggesting that the genital tract may represent a separate reservoir for viral replication.^{19,20} Genital tract infections account for a significant number of episodes of HIV genital shedding and their eradication is followed by a reduction in the HIV concentration in genital fluids.²¹

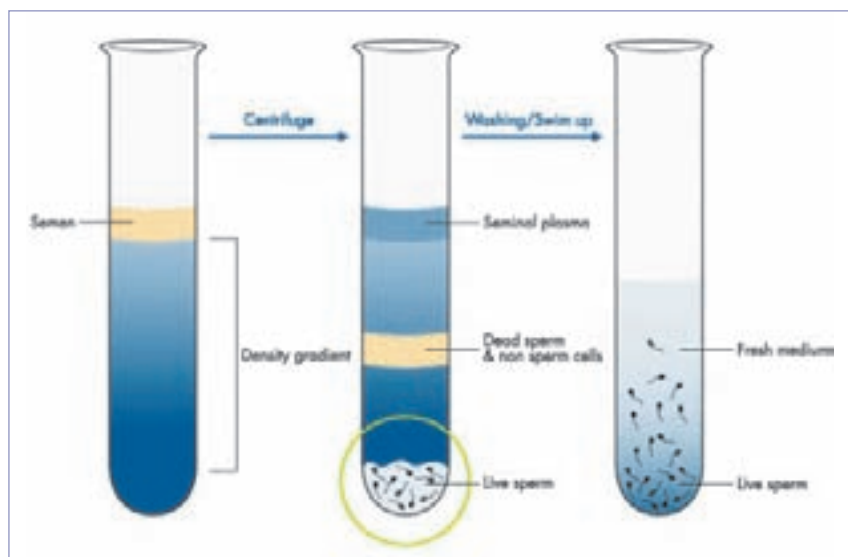
Screening for genital tract infection, for semen and ovulatory quality and for tubal patency should be performed before treatment to select the most appropriate reproductive technology and to minimise the number of treatment cycles. Some observations have suggested an increased prevalence of infertility factors in couples with HIV, which can prolong the time (and number of attempts) to achieve fertilisation; this may increase the risk of sexual transmission, or make conception impossible, as in the case of severe dyspermia or tubal disease. In the latter cases, such couples are exposed to a risk of infection without the chance of conception.

Reproductive techniques in HIV-infected couples

Spermatozoa tested for the absence of HIV contamination can be used for fertilisation by IUI or IVF/ICSI in HIV-discordant couples with male infection. The technology, used in conjunction with semen washing, should minimise potential damage to the healthy female while providing a good fertility rate.

Semen washing was developed more than 15 years ago and consists of a three-step method to remove infected seminal leukocytes and wash the spermatozoa free of seminal plasma.²² Other pioneering centres in Europe have started their own sperm washing programmes, which has now culminated in a European network of units providing assisted conception to HIV-discordant couples. These and other centres are now linked in CREATHe, a network of clinics covering Italy, Spain, UK, Germany, Russia, Switzerland, France, Belgium and Israel to optimise treatment and monitor outcomes.

A systematic review of 658 abstracts (of which only 41 were selected for analysis) and 17 full articles has just been published.²³ The review included 3900 IUI cycles in 1184 couples in 11 studies, and 738 ICSI/IVF cycles in 579 couples across ten studies. The IUI and ICSI results were, respectively: pregnancy rates per cycle 18% and 38.1%;



The risk of viral transmission from an HIV +ve male to his uninfected partner and future child can be virtually removed by ART with washed sperm. Sperm washing is based on the observation that the HIV virus cannot attach itself to spermatozoa, but can be found in the fluid and cells surrounding spermatozoa. Sperm washing allows the separation of live sperm from the surrounding fluid and cells in a three-step process: 1, a spermatozoa migration on density gradient; 2, repeated washing of the migrated pellet; and 3, a spermatozoa swim up.

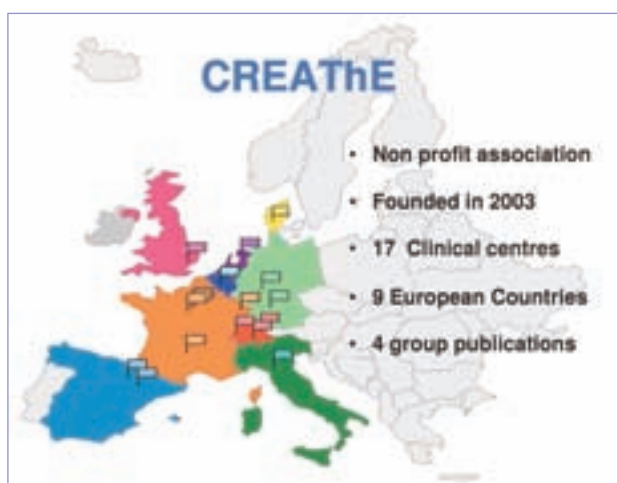
cumulative pregnancy 50% and 52.9%; and abortion rate 15.6% and 20.6%. No seroconversions in women or newborns were detectable at birth or after 3-6 months.

HIV-infected women have additional special needs in sexual and reproductive health, including information and services to protect their own health as well as to reduce the risk of mother-to-child HIV transmission. The number of specialists ready to offer these services to HIV-positive women with fertility problems has been increasing since 1993.²⁴ And today there is a general willingness to treat HIV-infected women with ART, given the low risk of HIV vertical transmission.

A reduced pregnancy rate after IVF has been observed in HIV-infected women when the patient's own oocytes were used. However, no significant reduction in pregnancy rate was found when donated oocytes were used. It has been suggested that subclinical hypogonadism mediated by immunosuppression may explain these observations. It is always important to optimise the woman's HIV immunological status before considering ART. The most recent studies report clinical pregnancy rates per cycle varying from 11-21% in HIV-1-infected women after IVF or ICSI, compared with 26% in matched controls. The paucity of data reported on IVF and ICSI cycles in HIV-1-infected women do not allow any further conclusion.²⁵

It is now well accepted that couples in whom one or both partners are HIV infected should have access to the same fertility advice and treatment as non-infected individuals to allow them to conceive, and to do so with the minimum of risk to their partners or children.

Reproductive counselling to individuals with HIV might



motivate them to ask specifically for reproductive treatment in order to limit the risk of infection to uninfected partners. The offer of reproductive care to men with HIV strengthens the message that protecting the female partner from infection makes possible a healthy mother of an uninfected child.

Reproductive options are available to HIV-infected women who positively choose to become pregnant because their own disease is well managed and interventions can minimise the risk of vertical transmission.

Dr Augusto Enrico Semprini works in clinical research at the University of Milan, Italy; he is President of the Centres for REproductive Assistance Techniques in hiv in Europe (CREATHe), and Chairman of ESHRE's Task Force on Fertility and Viral Diseases. Dr Simona Fiore is Scientific Coordinator of CREATHe.

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The European Society of Human Reproduction and Embryology
Meerstraat 60
Grimbergen, Belgium
info@eshre.eu
www.eshre.eu