ESHRE
PGD Consortium

Newsletter,
December 2007

Welcome to the 5th Consortium newsletter with an update of our activities. The consortium has achieved a lot this year by setting up four working groups to deal with specific issues, and launching the paediatric follow up and the EQA for FISH. It is hoped that in 2008 some of the working groups will publish reports, the EQA for PCR will be launched and we will have the results of the paediatric follow up. Data VII is in press and as soon as it is published on line it will be downloadable from the ESHRE web site. You will see that we have collated all the misdiagnoses in a table which will be a feature of all future papers and we aim to start collecting information on misdiagnoses as they occur so that we can alert all consortium members. Hopefully this will lead to improvements in PGD protocols and a reduction in misdiagnoses. Data VIII is almost ready to be submitted and you will see that for each indication the end point now is delivery rather than clinical pregnancy. We now have over 90 members including the majority of European centres and members from Argentina, Australia, Brazil, Egypt, India, Israel, Japan, Korea, Saudi Arabia, Singapore, South Africa, Thailand, Taiwan, United Arab Emirates, and the USA. If you have any suggestions on ways the consortium can improve, please feel free to email us. There will be a consortium report in the next Focus on Reproduction in January.

After the ESHRE meeting the steering committee tried to write a position statement on PGS but we had a lot of trouble agreeing what our position should be. The majority of the steering committee agreed that our position should be that there was currently insufficient information to decide if PGS was a valid procedure for advanced maternal age and that for all indications, further randomised controlled studies should be undertaken. However the ESHRE executive committee did not feel that this was a 'position statement' and so the paper will be published in Human Reproduction under the authors individual names. The title of the paper is 'What is next for PGS?' As you will see below, ESHRE has set up a task force to try and set up a multicentre RCT for PGS.

Joyce Harper
Chair

Genetics for ART Practitioners 2008
The next Basic Genetics for ART Practitioners course will be in Greece on 5th April 2008. This course is being organised by the Department of Medical Genetics, Athens University (Joanne Traeger-Synodinos and Emmanuel Kanavakis).

Data collection
Data VII
This will soon be available on the ESHRE web site to download.

Data VIII
This is almost ready to be submitted. We will send the draft paper to all centres whose data is included. When it is published we will put it on the ESHRE web site to download.

Working Groups Update

1. Accreditation – Karen Sermon
This working group had a meeting in Sept and have written a detailed report (see end). It is important that all PGD labs are either accredited or working towards it. All diagnostic labs should conform to ISO 15189 (International laboratory standard specific for medical laboratories).

2.PGS / Aneuploidy screening – Sjoerd Repping
The PGS working group has had a discussion on the terminology used to describe testing blastomeres for numerical chromosome abnormalities. It was decided to stick to the term PGS for aneuploidy screening since it is so commonly used nowadays. Furthermore, the working group is discussing the important (technical) aspects of future RCTs on PGS and will advise the recently installed ESHRE PGS task force on this issue. Finally, we are evaluating which factors predict the chance of pregnancy after PGS.

3. Misdiagnosis – Alan Thornhill
The working group is covering two aspects of misdiagnosis (outcomes and follow up of untransferred embryos) – and a questionnaire for each of these areas is being sent to all consortium members. Results from both questionnaires will be presented in July at the consortium meeting in Barcelona. The first draft of the manuscript describing the reported misdiagnoses to date will be distributed during the first quarter of 2008. This manuscript will include detailed analyses of the possible origins and corrective and preventative actions for case).

4. Database – Celine Moutou
The final working group is looking at the database that is used to collect data for the consortium. This group is chaired by Céline Moutou who set up the Filemaker Pro database in 2002. The aim of this group is to improve data collection and data analysis. A first meeting was held in October 2007.
It was agreed that the current database will be used for data collections IX and X but it is hoped that a new system will be developed over the next few

years. Much of the work of database development and data collection can be funded by the SANCO project (for “Santé et Consommation”, the Directorate general of Health and Consumer Protection of the EU). Tony Solomonides (Dept. of Computer Science University of West of Britain) proposed that the new system will use XML format with a Web interface. It should be more flexible than the current Filemaker Pro system (no limits in numbers, different entry possibilities). A first step will be to fill in the Filemaker Pro database of the consortium and import these data into the XML database. In a second step, data will be filled in directly to the new database. Before this, one or two centers from the database working group will test the system and fill in the data both in Filemaker Pro database and in the XLM database.
The database working group is also in charge of the development of a database for the paediatric follow-up study (see below). Since collecting the data in all the different centers is a lot of work, it has been suggested that the coordinators of the centers should back translate the answers and fill in the database themselves. Alison Lashwood has had an initial meeting with Tony Solomonides to discuss the requirements of the database and a prototype is in progress. This will be a web based package.This data collection will be a good “try out” of the database in XML-format that will have to be used for the PGD data collection.

5. Paediatric follow up – Alison Lashwood
In 2007 I contacted all member centres to confirm their interest in PGD and listed the participating centres. The questionnaire has been completed and is in the process of being translated into the last two of 5 languages.
Some funding from the monitoring strand of the SANCO bid has been secured for this work, although we are still waiting for transfer of the funds. A meeting has been held with the team setting up the database and the creation of this is underway

In 2008 the data collection will be underway and it is hoped to have this completed by April 2008. Data entry and analysis will run alongside this and follow the data collection with the hope that there will be data to present at ESHRE in Barcelona.

6. External Quality Assessment for preimplantation FISH testing – Alan Thornhill and Sjoerd Repping
The long awaited web-based pilot EQA scheme will be launched in the first quarter of 2008. The initial round of challenges will involve the multivysion probe set (commonly used in PGS) and the results presented in July. The aim is to complete 2 rounds of assessment in 2008 and publish the collected results.

Steering Committee
The members of the steering committee are:
Chair, Joyce Harper, Past Chair, Karen Sermon, Deputy Chair, Alan Thornhill. Stephane Viville (France), Christine deDie (Netherlands), Paul Scriven (UK), Gary Harton (USA), Celine Moutou (France), Alison Lashwood (UK), Sioban SenGupta (UK), Sjoerd Repping (Netherlands), Joanne Traeger-Synodinos

(Greece), Katerina Vesela (Czech Republic), Tugce Pehlivan (Spain) and Francesco Fiorentino (Italy), Maartje Van Rij (Netherlands).

Email list
If there is anyone at your clinic who would like to receive this newsletter, please send their email address to Veerle.Goossens@eshre.com quoting your centre number

Further information
If you would like to make any comments, suggestions or need any further information about the consortium please email Veerle.Goossens@eshre.com

ESHRE PGD Consortium Accreditation working group

The ESHRE PGD Consortium Accreditation Working Group (AWG) held their kick-off meeting on 7 September 2007 at the ESHRE Central Office, Grimbergen, Belgium.

The participants were Karen Sermon (Chair, Department of Embryology and Genetics, Vrije Universiteit Brussel), Mike Morris (Molecular Geneticist, LAB NAME Geneva, Switzerland), Alan Thornhill (Embryologist Bridge Fertility Centre, Single cell diagnostics, Bridge Genoma, London, UK), Paul Scriven (Cytogeneticist, Guy's and St Thomas' PGD Centre, London, UK), Jan Traeger-Synodinos (Molecular Geneticist, Athens, Greece), Katerina Vesela (Gynaecologist, Repromeda, Brno, Czech Republic), Julio Martin (Molecular Biologist, IVI, Valencia, Spain), Edith Coonen (embryologist, PGD Cytogenetics, PGD Working Group Maastricht The Netherlands), Gary Harton (Molecular Biologist/FISH, Genetics & IVF, Virginia, USA), Francesco Fiorentino (Molecular geneticist, Genoma, Rome, Italy)

Mike Morris started off the meeting with an informative introduction of the why and how of accreditation. This was followed by a round table discussion where every participant presented the situation in their own labs. Some labs are fully accredited (by local authorities, eg in the UK, or by international standards (ISO15189) and have been so for years, while others are in the process and yet others have to start. Some participants are certified (ISO 9001:2000) and see this as a stepping stone towards full accreditation. All participants are experts in PGD. Some are embedded in a larger genetics centre, others are part of an IVF centre. None of the labs are doing PGD exclusively.

The round table discussion already stirred up the discussion, with particular questions on how laboratory accreditation works, for labs in general and PGD labs in particular.

An important part of accreditation is regular participation in external quality assessment schemes (EQAS), also called proficiency testing in the US. EQAS has been demonstrated to improve results/quality of service over time, so there is value in any EQAS (even though it is not single cell specific at present).

MM gave an introduction to proficiency testing (concept/turn around time/personnel involved, etc). He stressed that there were two sides to EQAS: it is a learning process as well as a tool to police bad results.

Even if no single cell specific external quality assessment schemes (EQAS) exist it would be worth for PGD laboratories engaging in routine EQAS using DNA samples

PGD centre participants in EQAS should be able to achieve 100% results every time on genomic DNA and reporting the methodology and interpretation can be assessed which is an important part of the whole process.

MM proposes a pilot scheme whereby 1 ng of lyophilised DNA could be distributed for assessment of CFTR dF508 mutation status. Participants would be asked to dilute the sample to eg 100 pg (about 10x magnitude to a single cell) and to apply the test they use for PGD. Details on how the test was carried out must also be reported and assessed.

Obtaining accreditation itself was also discussed. Accreditation (versus ISO 9000 Certification) allows laboratories to demonstrate quality of testing they apply (i.e. competency). The recommended accreditation level is ISO 15189 (International laboratory standard specific for medical laboratories)
Some countries require government mandated licensing for laboratories to perform diagnostic testing (i.e local standards which may be equally, more or less stringent than ISO 15189). For example, testing in UK requires CPA. It may become impossible to obtain government contracts without licensing or accreditation.

A number of questions arose:

- Should PGD providers offer tests outside of the PGD test menu?
- Can you get accreditation with research personnel or alongside a research environment? Yes, but it is easiest to separate rooms and activities.
- Is accreditation per disease or per method? For CCKL and CPA (UK), accreditation covers the lab and all tests are automatically accredited (this is not true for all countries and schemes). Example: (from UK) – Design and validation of test for reciprocal translocations. Separate accreditation is not required for a new test because the methodology and approach is generic.

A number of important remarks were made:

- Different laboratories can be covered under one accreditation
- Accreditation requires a change in culture
- Accreditation needs to cover all aspects between sample (input) and report (output)
- Accreditation for a subset of specific tests allows you to state that your laboratory is accredited
- Accreditation is here to stay and likely to become a requirement
- Accreditation is a formalisation of what we (hopefully) already do
- Misdiagnosis rate may correlate with lack of accreditation (hypothetical)

Proposals:

1. FORMULATE GUIDELINES – THIS WOULD BE PREMATURE AT THIS POINT. ANOTHER POSSIBILITY WOULD BE TO COMPILE A MANUAL FOR PGD GROUPS ACTIVELY SEEKING ACCREDITATION TO SPEED UP AND SMOOTH THE PROCESS.

2. RECOMMENDED LITERATURE – SEE ALSO DRAFT LIST BELOW

3. WORKSHOP - PURPOSE TO EDUCATE SENIOR MANAGERS REGARDING THE PROCESS OF ACCREDITATION (FOCUS ON CONSORTIUM MEMBER LABORATORIES WHO ARE ACTIVELY SEEKING ACCREDITATION)

4. Develop questionnaire – to determine scope of activities and accreditation status of PGD labs (consortium members only?). Canvas groups who actively seek accreditation and wish to participate in EQAS

recommended literature

- ESTO report on QA in PGD
http://safh.jrc.es/l_study17.htm

- ISO 15189 guidelines
- http://www.acb.org.uk/docs/ISO_Stds.pdf
- http://www.acb.org.uk/docs/CPA_Stds.pdf

- New York State Accreditation Checklist (GH)

- CCKL guidance (website)
- http://www.cckl.nl/index.php?pagina=70
-
- CPA (UK) guidance (see website: http://www.cpa-uk.co.uk/)

- Eurogentest relevant documents (MM)

- OECD guidelines

- PGD/PGS Best practice guidelines (see attached ESHRE web site)