



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

Brussels,
SANTÉ/DF

**Ad-Hoc Meeting between Stakeholders and representatives members of the
Competent Authorities on Substances of Human Origin Expert Group
(CASoHO E01718)**

16 November 2017, 13:30-17:00

BRUSSELS

This second ad-hoc meeting between selected tissue and cell stakeholders and representatives of the competent authorities for tissues and cells took place on 16 November 2017. The purpose of these meetings is to provide an opportunity for an informal exchange of views between the stakeholders, representatives of the Member State competent authorities and the Commission services on topics of mutual interest.

PARTICIPATION:

Competent Authorities from all EU-28 Member States were invited, as were competent authorities from Norway, former Yugoslav Republic of Macedonia, Serbia, Montenegro and Turkey. Observers from the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), the Council of Europe and the World Health Organisation were also invited. Sixteen Member State authorities participated, along with the Council of Europe and WHO.

Stakeholders: the European Society for Human Reproduction and Embryology (ESHRE), Fertility Europe, Donor Conception Network (DCN), Cryos International Sperm Bank, European Sperm Bank.

European Commission/DG-SANTE: Mr S. VAN DER SPIEGEL (chair), Ms D. FEHILY, Mr R. MCGEEHAN, Ms I. PUCINSKAITE-KUBIK

1 WELCOME

The Commission services presented the terms of reference for these meetings, reminding the participants in particular that the meeting would only address EU-level topics of relevance for multiple countries. Country-specific topics are to be addressed bilaterally between stakeholders and concerned Member State authorities. It was agreed to draft minutes of this meeting for publication by DG-SANTE.

The Commission services explained that they had issued a call in October 2016 for expressions of interest in participating in ad-hoc meetings with representative members of the competent authorities SoHO expert group. Following review of the applications received, a

list of approved stakeholder organisations was published in November 2016¹ and is regularly updated.

The Commission services reminded participants that in future stakeholders will be invited to the meetings depending on the agenda topics of EU-relevance. The meetings will be a focus for gathering views and information in the context of the Evaluation of the EU legislation on blood, tissues and cells that was launched at the beginning of 2017².

2 INTRODUCTION OF STAKEHOLDERS PRESENT

The representatives of stakeholder organisations each introduced their organisation and its aims.

Founded in 1985, **ESHRE** is a pan European/OECD professional organisation of 7,500 members that are clinicians, embryologists, psychologists, nurses, midwives and laboratory technicians. It also supports a European Patients Association. Its aims are to promote interest in, and understanding of, reproductive science and medicine by teaching and training, development and maintenance of data registries and research and dissemination. It also aims to inform policy makers in Europe.

Fertility Europe was founded in 2009 and has 24 member organisations from 23 countries. It is the Patient Partner Organisation of ESHRE. It launched the European Policy Audit on Fertility in collaboration with ESHRE 28th March 2017 and is a founder of the European Fertility Week held annually since 2016 in November each year. Fertility Europe advocates that all couples should have the right to access infertility treatments, noting that this has been recognised by the European Parliament but that access continues to vary widely across individual European countries. The association points to the success of IVF, noting that it has resulted in the birth of 6.5 million people. In the EU the association represents around 25 million infertile people.

The **Donor Conception Network** supports individuals and couples that rely on donors to have a child. They offer peer-support, matching with other families and signposting to experienced counsellors where required. They also organise conferences, provide books and resources for children and adults, support local groups and organise workshops to prepare members for donor conceived parenthood, as well as providing long term support to families. Although UK based, the organisation provides services to individuals and couples in many EU countries as there is no equivalent EU-wide organisation.

There is also no EU-wide organisation representing sperm banks. Two of the largest sperm banks, both providing sperm across the EU, were invited to this meeting. **Cryos International** began to operate in Denmark in 1987 and now has more than 1,000 donors and supplies to more than 100 countries. They have recorded over 33,000 pregnancies from the sperm they supply although many are not reported and, consequently, they estimate the true number to be as high as twice that. They aim to provide high quality human sperm and eggs from selected and screened donors of all ethnicities and phenotypes. **European Sperm Bank** was established, also in Denmark, in 2004 and has already provided sperm that has resulted in

¹ http://ec.europa.eu/health/sites/health/files/blood_tissues_organ/docs/2016_call_ls_en.pdf

² https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en

25,000 families in over 80 countries. They aim to contribute to the creation of healthy and dearly wished for donor children across the world.

3 GENETIC TESTING – DEVELOPMENTS AND IMPLICATIONS FOR ASSISTED REPRODUCTION TECHNOLOGIES

The topic of genetic testing was addressed in presentations by ESHRE, Cryos International and the Donor Conception Network.

The ESHRE speaker addressed the topics of genome-wide analysis, mitochondrial replacement therapy and germline genome editing, stressing that all these new developments bring challenges and require guidelines at national or international level. ESHRE plays a role in providing recommendations and guidelines for best practice.

ESHRE informed the meeting that it was collaborating with the European Society of Human Genetics to review recent developments in genetics and medically-assisted reproduction and publication was expected in the near future. *Note: Since the meeting, the review article referred to has been published³.*

On the topic of **GENOME-WIDE ANALYSIS**, the expert addressed the impact of these approaches on

- expanded carrier screening
- voiding of gamete donor anonymity
- preimplantation genetic testing, and
- non-invasive prenatal testing.

Expanded carrier screening

Preconception genetic screening for high-risk populations and gamete donors has changed dramatically in recent years. Where previously single gene testing was available, this has now expanded to testing for panels of more than 100 genes. Expanded carrier screening is available direct-to-consumers in many countries. The availability of this testing raises questions regarding the need for deciding what should be tested for and ensuring that patients understand the significance of results. It was proposed that priority should be given to testing for severe childhood-onset disorders and that it is important to minimize incidental findings that might cause unnecessary distress. Now that this testing is available, decisions will need to be made on who should be tested for what and who should pay for it. The speaker referred to a recent publication on this topic⁴.

Voiding of gamete donor anonymity

The speaker described the impact of direct-to-consumer genetic testing that allows for ancestry determination. There are already many active registries such as the Donor Sibling Registry, the Donor-Conceived Register and Family Tree DNA that allow linking donors to children/siblings, effectively making anonymity of donors impossible. ESHRE noted that this is not a problem if all parties agree, but it raises serious issues for donors that wish to remain anonymous. They note that it is not sufficient for a donor that wishes to remain anonymous to

³ Harper JC et al. Recent developments in genetics and medically assisted reproduction: from research to clinical applications. *Eur J Hum Genet* (2018) 26:12–33

⁴ Henneman L et al. Responsible implementation of expanded carrier screening *Eur J Hum Genet* (2016) 24(6):e1-e12

avoid entering genetic data in the databank because, if any family member does so, the donor can be collaterally identified. It is now considered essential that fertility centres inform donors that they will strive to protect their identity, but that their anonymity cannot be guaranteed. They must also inform couples undergoing fertility treatment with gamete donation that their children may subsequently discover their donor in this way.

Pre-implantation Genetic Testing

The ESHRE expert explained that Pre-implantation Genetic Testing for monogenic disorders (PGT-M) and Pre-implantation Genetic Testing for chromosomal structural rearrangements (PGT-SR), previously referred to jointly as Pre-implantation Genetic Diagnosis (PGD), are testing approaches that look for specific inheritable conditions. Pre-implantation Genetic Screening (PGS), now more commonly known as Preimplantation Genetic Testing for aneuploidy (PGT-A), is a testing methodology that looks for any chromosomal abnormality. The differences between these approaches are disappearing because of the use of genome-wide technologies that can detect monogenic disease, chromosomal abnormalities and incidental findings. There is still controversy on whether screening for aneuploidy improves IVF outcome. PGT-A could be used to 'rank' embryos for transfer but this will raise questions on what the criteria for ranking should be and who should decide on them. The interpretation of incidental findings is also challenging. ESHRE is working on an update on PGT guidelines.

Non-invasive pre-natal testing

It is now possible to isolate foetal DNA from maternal blood and to screen for abnormalities. There are discussions on how this testing will fit within a comprehensive prenatal screening policy, taking into account cost-effectiveness and when it should be recommended in the context of fertility treatment. The criteria for offering the test need to be agreed, particularly as it could be used for sex-selection (both for monogenic disease as for 'family balancing'). As previously, individuals will need to be made aware of the risk of misdiagnosis and incidental findings.

On the very novel topic of **MITOCHONDRIAL REPLACEMENT THERAPY**, where genomic DNA (nuclei, mitotic spindle or polar body(ies)) from an oocyte with affected mitochondria is transferred to a donor oocyte, it was explained that the result is an embryo with genomic/mitochondrial DNA from three individuals. ESHRE noted that there is, currently, virtually no knowledge on safety and that there are many ethical issues to address to ensure appropriate precautions are put in place, without hampering innovation.

On the subject of **GERMLINE GENOME EDITING** to correct genetic defects, ESHRE noted that there are still technical difficulties with this technology but that these are expected to be overcome. At this time, the clinical indications are limited and PGT provides existing and safe methods to prevent transmission of genetic disease. However, genome editing might be foreseen as appropriate for very high-risk couples (both affected by the same autosomal recessive disorder or one partner homozygous for an autosomal dominant disorder) or for situations where few embryos are expected to be transferrable after testing. The European Society for Human Genetics and ESHRE are working on recommendations and there is an ongoing ethical debate, mostly related to the argument that once genetic editing is allowed, then it might open the door to editing for other purposes beyond disease prevention.

The second presentation on the subject of genetic testing was given by Cryos International. It highlighted the challenge of differentiating between genetic variation and genetic disease. The

speaker noted that it has been estimated that all humans are carriers of at least 3-5 mutations which cause recessive diseases, including lethal diseases and that all humans harbour genetic variations which predispose for various disease traits.

Quoting the EU legislation on tissues and cells, Cryos noted that there is **NO CONSENSUS ON GENETIC SCREENING** in the EU despite the legislative reference. Directive 2006/17/EC, Annex III, paragraph 3.6 requires that *'genetic screening for autosomal recessive genes known to be prevalent, according to international scientific evidence, in the donor's ethnic background and an assessment of the risk of transmission of inherited conditions known to be present in the family must be carried out, after consent is obtained. Complete information must be provided, in accordance with the requirements in force in Member States. Complete information on the associated risk and on the measures undertaken for its mitigation must be communicated and clearly explained to the recipient.'* The speaker noted that no general requirements for genetic testing are defined by FDA nor by the American Society for Reproductive Medicine, while Health Canada suggest that sperm and ova donors who are determined to be heterozygous (a carrier) for autosomal recessive disorders, should not be excluded.

It was reported that almost all gamete donor banks screen according to Edwards et al. 2015⁵ and screen pan-ethnically. Cryos International screens sperm donor candidates according to a carrier screening panel covering 46 recessive diseases and selects according the Edwards et al., with around 15% donor rejection. Cryos called for a **TRANSPARENT SYSTEM FOR INFORMING POTENTIAL RECIPIENTS ABOUT GENETIC CONDITIONS** in children born of donor gametes which are, or are suspected, of being related to the sperm donors. The speaker noted that the system should not be static and should consider the "right not to know" and presented the new 'CON-System' implemented by Cryos where the user could choose whether or not to click on the online button and see genetic information on a condition in a donor they have selected. The information includes reports of children born from the donor's sperm, results of donor genetic testing and a risk assessment of the chances that the condition will be inherited. When accepting the declaration for donors with condition(s), the patient (or their clinic) declares that they have read the information and that they and their partner, if any, accept any risks which might be involved in using sperm from donors with conditions. They declare that they will seek the necessary medical guidance before treatment.

The director of the Donor Conception Network noted that the developments in genetic testing are important but very complex and that one of the key challenges going forward will be for clinics and gamete banks to **EXPLAIN RISKS AND TESTING OPTIONS** to individuals and couples in a manner that will be understandable for them. The speaker noted that patients contacting them regularly ask whether EU countries have different testing/screening protocols for donors and how cross-border treatment works. She stressed that it is important that differences in safety protocols between Member States must be made clear to patients.

The Donor Conception Network asked whether a problem that has a genetic component and is identified in a donor after they have donated is reported to families and offspring and conversely, whether genetic problems identified in offspring are routinely reported back to

⁵ Edwards JG et al. Expanded carrier screening in reproductive medicine—points to consider. *Obstet Gynecol.* 2015;125:653–62.

donors and to other offspring from that donor. The **IMPORTANCE OF TRACEABILITY** to the offspring to ensure these communication channels work effectively was highlighted.

4 FOCUS ON QUALITY IN ASSISTED REPRODUCTION TECHNOLOGY AND GAMETE BANKING – MEASURING AND MONITORING INDICATORS

This topic was introduced with presentations by ESHRE and by the European Sperm Bank.

The ESHRE presentation addressed three key topics: the definition of 'quality' in the context of Assisted Reproduction Technology (ART), the challenge of keeping pace with scientific and technological changes and the role of registries in monitoring quality. The speaker noted that the European Directives had put an emphasis on Quality management in the ART field. The consequence has been an improvement of standards (at least in some countries), a reduction of risk of misidentification and increased awareness of traceability issues and harmonisation of inspections (the latter is ongoing in a current Joint Action⁶). On the negative side, it has increased costs and bureaucratic workload and, as currently drafted, it reveals a degree of “misunderstanding” of the specificities of the ART field.

The ultimate measure of quality in ART was described as '**LIVE BIRTHS PER TREATMENT INITIATED**' (efficacy) although it was noted that this needed to be qualified by the number of multiple births and other criteria indicating quality. Quality could also be measured using intermediate parameters such as the following:

- Clinical pregnancy per initiated cycle, per ovarian aspiration, per embryo transfer
- Other clinical parameters such as
 - % of cancelled cycles
 - no. of oocytes retrieved
 - % of matured oocytes retrieved
- Laboratory parameters such as
 - fertilization rate
 - % of embryos of good quality

The pregnancy rate per embryo transfer has shown steady improvements in ESHRE registry data (Figure 2).

⁶ <http://arthiqs.eu/>

Monitoring clinical outcomes/efficacy - ART

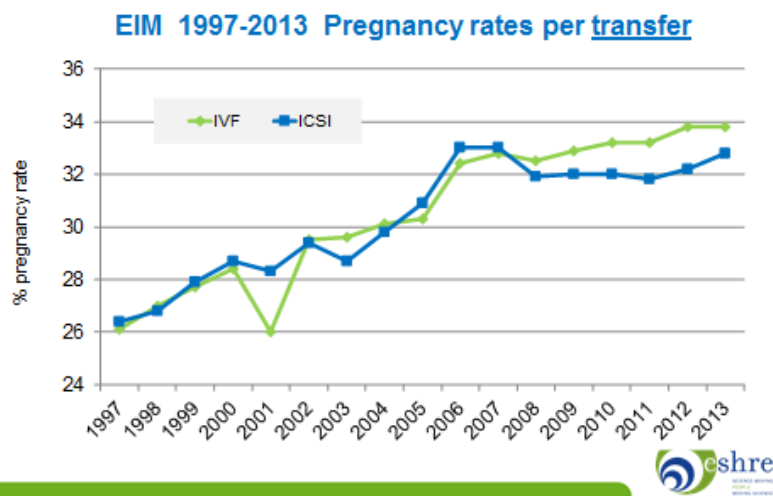


Figure 1: Monitoring clinical outcome/efficacy in ART

ESHRE pointed to specificities of the ART field that they consider differentiate it from other fields where human tissues or cells are applied to patients. These included particular issues related to the partner donation and non-partner donation contexts and the fact that the desired outcome is the birth of a (healthy) baby rather than a life-saving or function-saving objective. It was also noted that the clinical applications that can occur depend on individual Member State legislation, with diverse social and cultural implications. Treatments (oocyte retrievals) are usually repeated but the same treatment can include cryopreservation of oocytes or embryos and thereby provide multiple opportunities for getting pregnant over a long time span. In some cases, ART involves fertility preservation for medical and nonmedical reasons and some treatments include the need for surrogacy; the latter is not addressed in the tissues and cells legislation.

While keeping pace with scientific and technological changes is considered by ESHRE to be a legitimate concern, it is considered to be beyond the scope of the Directives. However, ESHRE has published a tool for assessing the degree of **NOVELTY OF NEW PROCESSES**, grading them as experimental, innovative or established according to defined criteria⁷. They consider registries of follow-up data to be essential and propose that they be made mandatory, including details on babies born. In their view, registries should collect data by cycle, in a consistent manner across Member States. They consider that **SYSTEMATIC REGISTRIES IN ART** should be implemented or improved.

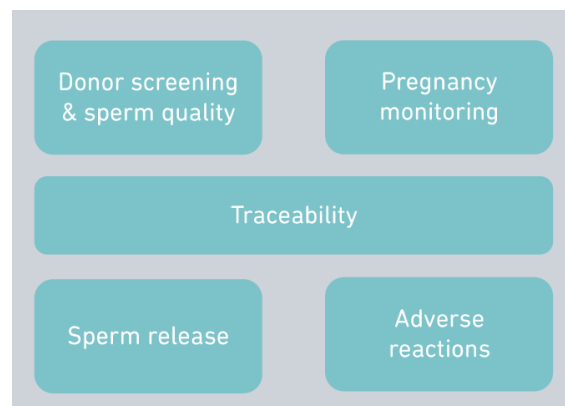
ESHRE supports and values all principles in Directives regarding quality and safety of procedures that contribute to an increase in the efficacy of treatments, the protection of patients, the protection of the future generations of children born from ART and that ensure practitioners qualifications. ESHRE stated that they see a strong need to consider ART specificities in a future legislation that would clarify the scope of EU legislation in the ART field, implement/improve systematic registries in ART, be more realistic in requirements such

⁷ Provoost V et al. Hum Reprod 2014; 29(3):413-417

as the quality of air for laboratories and reduce regulatory burden in the context of partner donation.

On the topic of quality and safety assurance in the ART field, a question was raised, whether the infectious marker testing results from a testing laboratory from another member state can be considered acceptable, if the tissue establishment receiving the gametes or embryos has no written agreement with the laboratory. It was clarified by the Commission that the requirements for written agreements between the tissue establishments and third parties as referred to in Directive 2004/23/EC Article 24, do not apply to the donor testing laboratories, but rather to the situation where tissues and cells are processed in cooperation with a third party.

The European Sperm bank presented the 'Quality' topic from the perspective of sperm banks, describing how their own **QUALITY MANAGEMENT PROGRAMME** complies with the requirements of the EU Directives and with national requirements in all the EU Member States to which they supply sperm. For their field, quality is seen as encompassing the following key areas:



The company called for greater EU regulation for sperm banks, noting that where EU regulation is not adequate, individual Member States introduce their own requirements, bringing a challenging degree of variation across the EU that does not benefit citizens and results in fertility tourism. In the stakeholder's view, the EU legislation does not adequately address requirements for the registration and distribution of donor data; donor approval requirements such as testing, transparent definition of inheritable risks with exclusion criteria and requirements for the authorisation of personnel or release rules (including blood sampling and the quarantine periods required). Specifically at the sperm bank level, the European Sperm Bank considers that there is a need for **DEFINING SPERM QUALITY MEASURES AT EU LEVEL** and for a requirement for transparency in the communication of the results of those tests. They also called for setting standards on donor, customer and staff satisfaction as part of quality monitoring.

5 CE MARKING OF CONSUMABLES, MEDIA AND EQUIPMENT – REQUIREMENTS AND CHALLENGES

An ESHRE expert presented the importance of medical devices in the field of ART and their potential **IMPACT ON THE HEALTH OF CHILDREN BORN FOLLOWING ART**. The speaker pointed to a range of products that have direct contact with the gametes, zygotes or embryos during manipulation and storage including culture media, enzyme solutions, mobilization

agents, ICSI (intra-cytoplasmic sperm injection for IVF) needles and cryopreservation solutions; some CE-marked and some not. A further list of products has indirect contact with these reproductive cells including tubes, dishes, pipettes, needles, incubators, gases (O₂, CO₂, N₂), culture oil, catheters, storage vials and liquid nitrogen.

Possibly the most important of these was identified as the **CULTURE MEDIA** in which the embryos are grown for a number of days. In animal studies it has been shown that embryo culture, including the composition of the culture media, may have a lifelong impact on the health of the offspring. ESHRE presented published evidence that this is also the case in humans. One Dutch prospective randomized multicentre trial, with 836 patients and 383 children, compared two commercial media. The results showed up to 10-fold difference in gene expression of embryos cultured in the media, along with a number of other significant differences in outcome including birth weights and weight at 2 and 9 years old⁸. The study concluded that these findings should lead to increased awareness, mechanistic studies and legislative adaptations to protect IVF offspring during the first few days of their existence. In this context, ESHRE expressed concern that, despite data showing that the composition of IVF-culture media can influence the phenotype of the offspring, the compositions are not revealed to the clinics and the manufacturing companies change the formulations without substantiation of the benefits with relevant clinical data. Although ESHRE considers that studies on the relationship between culture media compositions and phenotype and health of the offspring are urgently needed, they cannot be carried out because the media compositions are not known.

ESHRE considers that there is a **GAP IN THE EU LEGISLATION** as the 'performance' (outcome) is not regulated, allowing companies and IVF clinics to rapidly introduce new consumables, technology and procedures, without documentation of efficacy or safety for the embryos. The society considers that the CE marking procedures are not stringent enough to properly regulate these risks and are not adequately transparent for the ART professionals to assess them. ESHRE consider that ART clinics should have access to the name of the notifying body for each medium, the data provided by the media company prior to obtaining a CE mark and the composition including the concentration of each ingredient in the culture media. They would also want a notification when media composition is changed including the rationale and the new composition, together with data from post market surveillance.

6 FINAL REMARKS

All the associations present were thanked for their clear and informative presentations and for the open and constructive discussions. The issues raised will form part of the evidence base for the evaluation of the EU legislation on blood, tissues and cells.

⁸ Kleijkers H M et al. Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT. Human Reproduction, Vol.31, No.10 pp. 2219–2230, 2016