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Results of the follow-up of the FCE activities 2006-2015 and comparison with European countries

Symposium of the Federal Commission for medical and scientific research on embryos in vitro
25 November 2016, Brussels
Embryo research in Belgium

- Research on embryos donated for science is allowed
- Creation of embryos for research is allowed if this is necessary to obtain knowledge

Prohibitions on

- Experiments and research for the selection or improvement of non-pathological genetic features of the human species, i.e. eugenic features or enhancement
- Reproductive cloning
- Social sexing
- Creation of chimaeras and hybrids

All projects have to be approved by a local Ethics Committee and by the Federal Commission on Research on Embryos in vitro.
Data collection

Data collection turned out to be more complicated than originally expected. The reasons will become clear in what follows.

Special thanks to Velichka Kontozova-Deutsch, Seppe Segers and the members of the working group.
Types of embryos

1. Fresh supernumerary embryos: unfit for transfer or freezing because of inferior quality, abnormal fertilisation, chromosomal abnormalities.

2. Frozen supernumerary embryos: good quality embryos, presumably healthy but no longer needed in the original parental project.

3. Fresh embryos created for research: were never part of a parental project.

[4. Frozen embryos created for research: embryos that for whatever reason could not be used directly in a research project]
Types of embryos

Attention: the numbers mentioned are the total number of embryos that were used in the research. A certain percentage will not have been actually used for research because they did not qualify (bad quality, did not survive freezing etc.)

The embryos mentioned in this report were not replaced. The research projects that were purely observational were classified as ‘clinical management’ by the FCE. See further on definition of research.
Due to the short time period it is difficult to detect trends. Nevertheless, two points:
- the number of fresh supernumerary embryos is going down, and
- the number of frozen supernumerary embryos is going up.

<table>
<thead>
<tr>
<th>Destination</th>
<th>Number of embryos in storage on 31/12/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF or ICSI</td>
<td>73802</td>
</tr>
<tr>
<td>Donation to others</td>
<td>1921</td>
</tr>
<tr>
<td>Scientific research</td>
<td>5082</td>
</tr>
<tr>
<td>Autologous storage for medical reasons</td>
<td>5941</td>
</tr>
</tbody>
</table>
About half of the IVF patients (51%) choose donation for research as the final destination for their supernumerary embryos (Provoost et al., 2012).

Important developments:

- freezing at blastocyst stage (day 5): fewer early cleavage stage embryos available.
- throphectoderm biopsy for PGD + cryopreservation: no fresh good quality genetically abnormal embryos available.

Possible consequence: more embryos will have to be created for early embryo studies.
Several projects belonged to two areas of research.
Type of embryo in combination with type of research

- fresh supernumerary embryos: 63% hESC research; 32% embryo development

- frozen supernumerary embryos: 70% hESC research; 70% embryo development (45% overlap)

- research embryos: 33% embryo development, 33% oocyte research; 31% oocyte cryopreservation
Scientific output based on researchers' reporting

- Oocyte research; 19 (37%)
- hESC; 14 (27%)
- Embryo development and implantation; 8 (15%)
- Genetic abnormalities; 7 (13%)
- Cryopreservation/vitrification /storage/freezing; 4 (8%)

Bioethics Institute Ghent
Definitional problems

Two major conceptual problems: ‘research’ and ‘embryo’

**RESEARCH**
- no clear definition could be found: activity directed at the systematic collection of scientifically new information
- distinguish research from clinical management
  ex. new incubator, new culture medium ...
- distinguish research from training (practicing skills)
  ex. biopsy, ICSI ...
- no research if testing is conducted with existing devices, according to standard methodology that is internationally recognised (established method)
  ex. vitrification
Art. 5: embryos subjected to research cannot be replaced except when the intervention has a therapeutic purpose for the embryo or when it concerns an observation method that does not harm the integrity of the embryo.

Problem: experimental intervention on a gamete (like genome editing), then creation of an embryo with these gametes and (after observation) replacement in a uterus. Not ‘research on embryos’.

ex. mitochondrial transfer to rejuvinate the oocyte
ex. genome editing

Problem: should observational studies also fall under ‘research’ and not under ‘clinical management’?
EMBRYO

Definition in the law: a cell or a bundle of cells with the potential to grow into a human being.

- parthenote? Other things might be able to grow into a human being if enough manipulations are performed.

- 0PN, 1PN and 3PN: abnormally fertilized embryos? Unfertilized oocytes?

- low quality embryos

- genetically abnormal embryos
General problem: no, little or incomplete information available

- The Netherlands: CCMO (Central Commission Human Research): some very general information on projects is available but no specific data.


- Spain: National Cellular Lines Bank & Spanish Commission on non-reproductive research on human embryos & Spanish Commission on Assisted Reproductive Technologies: 10 projects between 2006 and 2014, each with 50 to 100 embryos.
Use of supernumerary embryos for research is allowed.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of embryos frozen</th>
<th>Number of embryos for research</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>165,591</td>
<td>13,804 (8.3%)</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>17,503</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>17,667</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td>18,309</td>
</tr>
<tr>
<td>2013</td>
<td>191,845</td>
<td>19,335</td>
</tr>
</tbody>
</table>

Between 2004 and 2010: 1,087 embryos were used for research (80% hESC lines and 20% early embryo development.)
Very little research is performed and many embryos donated for research remain in the freezer. Reasons?

The Ethics Committee of INSERM (Institut national de la santé et de la recherche médicale) criticised the Agence for too many restrictions and too many barriers.

Not one single authorisation for embryo research has been given since 2008.

What will they do with the embryos donated for research? Keep them frozen indefinitely? Destroy them?

Question: is it a form of deception of the patients when they are offered to direct their embryos to research while at the same time, no action is taken to make research possible?
HFEA, 23 research projects in 2010
Around 50% of the projects are on hES cells while only around 25% in Belgium (but over 8 years).
Use of supernumerary and created embryos is allowed. Only partial data is available: 2006-2007, 2010 and 2011.

<table>
<thead>
<tr>
<th>Centre No.</th>
<th>No. of projects</th>
<th>No. of embryos donated</th>
<th>No. of embryos received / thawed</th>
<th>No. of embryos used</th>
<th>No. of embryos allowed to perish</th>
<th>No. of embryos created</th>
<th>No. of created embryos used</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL 2010</td>
<td>18</td>
<td>6462</td>
<td>6002</td>
<td>4925</td>
<td>2818</td>
<td>174</td>
<td>117</td>
</tr>
<tr>
<td>TOTAL 2011</td>
<td>17</td>
<td>4911</td>
<td>4120</td>
<td>2629</td>
<td>2719</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

HFEA, 2010; 2011.
# Embryo research in the UK

<table>
<thead>
<tr>
<th>Year</th>
<th>Embryos stored for patient use</th>
<th>Embryos stored for donation</th>
<th>Embryos stored for research</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>43467</td>
<td>168</td>
<td>&lt;5</td>
<td>43638</td>
</tr>
<tr>
<td>2000</td>
<td>47980</td>
<td>133</td>
<td>43</td>
<td>48156</td>
</tr>
<tr>
<td>2001</td>
<td>49078</td>
<td>170</td>
<td>33</td>
<td>49281</td>
</tr>
<tr>
<td>2002</td>
<td>45804</td>
<td>168</td>
<td>39</td>
<td>46011</td>
</tr>
<tr>
<td>2003</td>
<td>43597</td>
<td>144</td>
<td>20</td>
<td>43761</td>
</tr>
<tr>
<td>2004</td>
<td>44676</td>
<td>159</td>
<td>25</td>
<td>44860</td>
</tr>
<tr>
<td>2005</td>
<td>45678</td>
<td>206</td>
<td>21</td>
<td>45905</td>
</tr>
<tr>
<td>2006</td>
<td>50770</td>
<td>70</td>
<td>39</td>
<td>50879</td>
</tr>
<tr>
<td>2007</td>
<td>48687</td>
<td>98</td>
<td>352</td>
<td>49137</td>
</tr>
<tr>
<td>2008</td>
<td>51852</td>
<td>88</td>
<td>1706</td>
<td>53646</td>
</tr>
<tr>
<td>2009</td>
<td>50918</td>
<td>70</td>
<td>1597</td>
<td>52585</td>
</tr>
<tr>
<td>2010</td>
<td>51095</td>
<td>111</td>
<td>1253</td>
<td>52459</td>
</tr>
<tr>
<td>2011</td>
<td>50572</td>
<td>47</td>
<td>776</td>
<td>51395</td>
</tr>
<tr>
<td>2012</td>
<td>49755</td>
<td>73</td>
<td>535</td>
<td>50363</td>
</tr>
<tr>
<td>2013</td>
<td>60103</td>
<td>12</td>
<td>372</td>
<td>60487</td>
</tr>
</tbody>
</table>

**Totals** | **949955** | **2264** | **6814** | **959033**

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*Bioethics Institute Ghent*

*HFEA, 2015*
70% of embryos used in research are fresh embryos, compared to 66% in Belgium.
1. The number of frozen embryos donated for research goes down steadily since 2008. Explanation?

2. No information is available yet on the number of embryos used for projects for mitochondrial transfer.

3. The difference in frozen embryos and embryos used in research shows that, like in Belgium, the majority of embryos used in research are fresh supernumerary embryos.
Embryo research: conclusions

1. A number of countries (Spain, France) have legislation permitting embryo research but very little or no research is being performed. It is worthwhile to look closer to find out what the reasons / causes are.

2. In most countries, no information on embryo research is publicly available.

3. In most countries, data collection is poor or non-existent.

4. Collecting data as well as evaluating projects is a laborious process. If legislators claim that embryo research is important, they should provide the means to ensure the proper performance of these tasks.

5. Numerous problems remain to be solved in data collection but this is an ongoing process.

6. Transparency regarding research can help to increase trust by the public and the patients.