Assisted Reproduction Techniques
for avoiding inherited diseases

Practical aspects of PGD and Results

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Most clinics and registries report outcome based on the IVF and the PGD as per 1\textsuperscript{st} transfer cycle.

Figure 42: PGD treatment numbers for UK

Figure 45: PGD birth rates by age, 2016
Data from ESHRE PGD Consortium
The ESHRE PGD Consortium: 10 years of data collection
Monogenics
Chromosomal
Sexing X linked
Aneuploidy
Social sexing

REASONS FOR EMBRYO BIOPSY
ESHRE Consortium data I-XV
Based on 54,589 cycles

33,741 (58%)
PGS / PGT-A

12,885 (22%)
Monogenics

9,081 (15%)
Chromosomal

1,749 (3%)
Sexing X linked

668 (1%)
Aneuploidy

184 (0.5%)
Social sexing
The ESHRE PGD Consortium: 10 years of data collection

**Table 1 Ten years of PGD Consortium data.**

<table>
<thead>
<tr>
<th></th>
<th>Cycles to OR</th>
<th>No. embryos biopsied</th>
<th>No. embryos transferred (mean/ET)</th>
<th>Embryo transfer procedures</th>
<th>Clinical pregnancy rate (per OR and per ET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single genes</td>
<td>4733</td>
<td>27980</td>
<td>7035 (1.9)</td>
<td>3727</td>
<td>22% per OR, 29% per ET</td>
</tr>
<tr>
<td>Structural chromosome</td>
<td>4253</td>
<td>27068</td>
<td>4775 (1.7)</td>
<td>2731</td>
<td>17% per OR, 26% per ET</td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexing X-linked</td>
<td>1167</td>
<td>7317</td>
<td>1598 (1.8)</td>
<td>880</td>
<td>19% per OR, 26% per ET</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>16806</td>
<td>90404</td>
<td>21543 (1.8)</td>
<td>12071</td>
<td>19% per OR, 27% per ET</td>
</tr>
<tr>
<td>Social sexing</td>
<td>671</td>
<td>4285</td>
<td>993 (2.0)</td>
<td>492</td>
<td>21% per OR, 29% per ET</td>
</tr>
</tbody>
</table>

OR, oocyte retrieval; ET, embryo transfer procedure.
### Table IVa

Cycles performed for single gene disorders, data collection I–XIII.

<table>
<thead>
<tr>
<th>Indication</th>
<th>X-linked</th>
<th>Autosomal recessive</th>
<th>Autosomal dominant</th>
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<tbody>
<tr>
<td>Cycles to OR</td>
<td>1330</td>
<td>2838</td>
<td>3114</td>
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<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycles to ET</td>
<td>1002</td>
<td>2396</td>
<td>2402</td>
</tr>
<tr>
<td>hCG positive</td>
<td>364</td>
<td>977</td>
<td>878</td>
</tr>
<tr>
<td>Positive heartbeat</td>
<td>294</td>
<td>776</td>
<td>684</td>
</tr>
<tr>
<td>Clinical pregnancy rate (% per OR/% per ET)</td>
<td>22/29</td>
<td>27/32</td>
<td>22/28</td>
</tr>
</tbody>
</table>
Reporting Outcome of PGD

• Most clinics and registries report outcome based on the IVF and the PGD as per 1\textsuperscript{st} transfer cycle

• This does not inform patients of the likelihood of having an unaffected child when they complete a full PGD cycle (including the transfer of any tested embryos that remain frozen)

• It is important for patients to know the chance of having an unaffected child after one hormonal stimulation for PGD (intention to treat – ITT)
Cumulative Livebirth Rate

The likelihood of attaining a live birth after completing a full stimulation, IVF, and PGD cycle

– Includes fresh and related frozen transfers

– Number of frozen cycles may vary (1-6)

– Counted up to the first successful delivery
Value of Cumulative Rate

- Improves patient counselling (realistic expectations)
- Better awareness of possible reasons for a cycle not progressing or the need for multiple transfer cycles
- Better control of multiple pregnancy (one at a time)
- Clear target for funding and service provision
- Needed for comparison of other modalities of avoiding genetic disease
Likelihood of success

- Type of genetic inheritance
- Age of woman
- Response to stimulation
- Number and quality of embryos that develop
- Number of blastocysts available for biopsy
- Quality of the laboratory handling ICSI, biopsy, and cryopreservation and thaw
- Veracity of the molecular testing result
Annual number of stimulation cycles started for PGD at one UK centre
UK PGD cycles
HFEA 3 year aggregate data

ACU, Guy’s Hospital
UCH, London
CARE, Nottingham
The Bridge Centre, London
Glasgow Royal Infirmary
IVF Hammersmith, London
Oxford Fertility Unit
Edinburgh ACU
ARGC, London
UK PGD cycles
HFEA 3 year aggregate data

ACU, Guy’s Hospital
UCH, London
CARE, Nottingham
The Bridge Centre, London
Glasgow Royal Infirmary
IVF Hammersmith, London
Oxford Fertility Unit
Edinburgh ACU
ARGC, London
## Types of PGD cases

### NO PGS (PGT-A) undertaken

<table>
<thead>
<tr>
<th>No (%)</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
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<tbody>
<tr>
<td>Rearrang (FISH)</td>
<td>75 (41)</td>
<td>75 (37)</td>
<td>74 (33)</td>
<td>79 (32)</td>
<td>28 (8)</td>
<td>14 (4)</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rearrang (CGH)</td>
<td></td>
<td></td>
<td></td>
<td>73 (21)</td>
<td>73 (18)</td>
<td>90</td>
<td>102 (23)</td>
<td>84 (19)</td>
<td></td>
</tr>
<tr>
<td>Single Gene PGH</td>
<td>106 (58)</td>
<td>120 (61)</td>
<td>144 (65)</td>
<td>167 (65)</td>
<td>240 (69)</td>
<td>303 (76)</td>
<td>323</td>
<td>300 (69)</td>
<td>351 (81)</td>
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</tbody>
</table>
### Main conditions in 2011-2018

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>CF</td>
<td>39</td>
<td>28</td>
<td>29</td>
<td>28</td>
<td>25</td>
<td>44</td>
<td>39</td>
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<td>HD</td>
<td>32</td>
<td>26</td>
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<td>40</td>
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<td>44</td>
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<tr>
<td>DMD</td>
<td>5</td>
<td>9</td>
<td>16</td>
<td>12</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Fragile X</td>
<td>5</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>6</td>
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<td>5</td>
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<tr>
<td>Hb’pathy</td>
<td>4</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>22</td>
<td>29</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>MD</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>13</td>
<td>7</td>
<td>19</td>
<td>14</td>
</tr>
</tbody>
</table>
Range of SGD cases

2018: 272 biopsy cases

- Individualised SGDs: 39%
- De novo: 9%
- CF: 7%
- HD excl: 7%
- HD: 7%
- SMA: 4%
- MyoD: 3%
- ADPKD: 3%
- Sickle: 3%
- Marfan: 2%
- NF: 2%
- DMD: 2%
- FraX: 2%
- HaemA: 2%
- ADPKD: 3%
- BRCA: 6%
- DMD: 2%
- FraX: 2%
- HaemA: 2%
- NF: 2%
- DMD: 2%
- FraX: 2%
- HaemA: 2%
- NF: 2%

Centre for Preimplantation Genetic Diagnosis
Figure 43: PGD treatments by age, 2016

HFEA Report

Mean Age

Centre for Preimplantation Genetic Diagnosis

- Under 35
- 40-42
- 35-37
- 38-39
- Over 43

PGD Cycle Dislocation

1. Ovarian stimulation (GnRH agonist trigger)
2. Culture to blastocyst and biopsy
3. Blastocyst Vitrification
4. Batch genetic testing
5. Single embryo transfer

Blastocyst Thaw
SET is the norm at Guy’s
Multiple pregnancy rate has fallen dramatically
PGD Cycle Dislocation

Ovarian stimulation (GnRH agonist trigger)

1. Few eggs
   Poor quality

Culture to blastocyst and biopsy

2. Poor fertilisation
   No blastocysts
   Biopsy failure

Blastocyst Vitrification

3. Inadequate for cryopreservation

Single embryo transfer

5. Fail to survive thaw

What can go wrong

3. Inadequate for cryopreservation

Batch genetic testing

4. Test failure
   Uninterpretable result

Blastocyst Thaw

Few eggs
Poor quality

Poor fertilisation
No blastocysts
Biopsy failure
Cumulative LBR after TBx FOR SGD

In 2016, 319 couples started treatment

- 89 couples had no ET (28%)
- 82 couples had one FET
- 148 couples had two or more FET

- 20 had a LB (27%)
- 103 had an LB (70%)

Total no. of LB = 123

39% per couple starting
54% per couple reaching transfer
319 couples started
89 (28%) no ET

1. 3 no response
2. 2 no eggs suitable for ICSI

13 No fert/cleavage
28 None suitable Bx

Blastocyst Vitrification

Batch genetic testing

4. 3 no response

5. 4 Failed to survive thaw

4 Failed to survive thaw

Blastocyst Thaw

33 none suitable for ET

Single embryo transfer

Culture to blastocyst and biopsy

Ovarian stimulation (GnRH agonist trigger)
In 2016, 92 couples started treatment

- 32 couples had no ET (35%)
- 25 couples had one FET
- 35 couples had two or more FET

- 9 had a LB (36%)
- 29 had a LB (83%)

Total no. of LB = 38

42 % per couple starting
63 % per couple reaching transfer
Using Genome Editing in ART

Gene Editing Cycle

- **Ovarian stimulation (GnRH agonist trigger)**
  - 1. Few eggs
     - Poor quality

- **Culture to blastocyst and biopsy**
  - 2. Poor fertilisation
     - No blastocysts
     - Biopsy failure
  - 3. Inadequate for cryopreservation

- **Blastocyst Vitrification**
  - 5. Fail to survive thaw

- **Batch genetic testing**
  - 4. Testing / Editing failure
     - Uninterpretable results
     - Off target effects / mosaics

- **Single embryo transfer**
  - 5. Perhaps more unaffected
Balance of Editing over PGD

Advantages of editing:
• Perhaps more embryos to biopsy
• Perhaps more unaffected for transfer

Disadvantages of editing
• Efficiency of editing will have to be checked
• Reliability of the edit will have to be confirmed
• Off target effects will have to be measured and controlled
Precision & Reliability

Genome Editing
Summary: PGD vs Editing

• There are very few inherited conditions where PGD does not offer hope of an unaffected livebirth

• At present PGD can be effective if done well and using modern testing methods and without PGS

• Factors limiting PGD success generally will be the same as those encountered if gene edited ART undertaken

• The possibility of more edited unaffected embryos at the start is likely to be outweighed by the unknown or unintended effects of the edit and risks to the child and future generations