Chromosomal abnormalities and clinical outcome in patients with advanced maternal age using comprehensive chromosome screening

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Maternal Age and Infertility

• Delayed childbearing and delayed marriage age have increased in the developing countries in the last 20 years.

• The probability of having a baby decreased by 3-5% per year after 30 and even faster after 40 years.


TO ERR (MEIOTICALLY) IS HUMAN: THE GENESIS OF HUMAN ANEUPLOIDY

Terry Hassold & Patricia Hunt
### Maternal Age and Infertility

Society for Assisted Reproductive Technology 2011 (www.sart.org)

<table>
<thead>
<tr>
<th>AGE</th>
<th>&lt;35</th>
<th>35-37</th>
<th>38-40</th>
<th>41-42</th>
<th>&gt;42</th>
<th>＄38%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of IVF cycles</td>
<td>39,721</td>
<td>19,930</td>
<td>20,130</td>
<td>10,277</td>
<td>6,033</td>
<td>≈38%</td>
</tr>
<tr>
<td>Percentage of cancellations</td>
<td>6.4</td>
<td>9.5</td>
<td>12.7</td>
<td>16.3</td>
<td>20.7</td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate/retrieval</td>
<td>46.2</td>
<td>38.5</td>
<td>29.3</td>
<td>19.5</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Implantation rate</td>
<td>36.0</td>
<td>27.3</td>
<td>17.5</td>
<td>9.4</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Delivery rate/retrieval</td>
<td>42.9</td>
<td>35.2</td>
<td>24.8</td>
<td>14.5</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>
Preimplantation Genetic Screening (FISH)

13, 16, 18, 21, 22

15, 17, X, Y
### RCT Advanced Maternal Age 41-44 yrs (2009-2011)

<table>
<thead>
<tr>
<th></th>
<th>Blastocyst</th>
<th>PGS</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of PGS cycles</strong></td>
<td>90</td>
<td>93</td>
<td>----</td>
</tr>
<tr>
<td><strong>No. of transfers (%)</strong></td>
<td>74 (82.2)</td>
<td>70 (75.3)</td>
<td>(NS)</td>
</tr>
<tr>
<td><strong>% Abnormal embryos</strong></td>
<td>----</td>
<td>69.2</td>
<td>----</td>
</tr>
<tr>
<td><strong>Mean embryos transferred (SD)</strong></td>
<td>2.8 (0.8)*</td>
<td>1.6 (0.6)</td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Ongoing PR/transfer (%)</strong></td>
<td>14/74 (18.9)</td>
<td>30/70 (42.8)*</td>
<td>(p=0.0021)</td>
</tr>
<tr>
<td><strong>Ongoing implantation rate (%)</strong></td>
<td>20/152 (13.1)</td>
<td>40/114 (35.1)*</td>
<td>(p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Live birth rate (%)</strong></td>
<td>14/90 (15.5)</td>
<td>30/93 (32.3)*</td>
<td>(p=0.0099)</td>
</tr>
</tbody>
</table>

* Two-sides Fisher´s test

Rubio et al., FS 2013
To investigate the percentage and type of chromosomal abnormalities and the clinical outcome in embryos from women between 38 to 46 years of age, undergoing day-3 biopsy and Comprehensive Chromosome Screening (CCS) with array-CGH.
Materials and Methods

- **1,078 CCS cycles** in women between 38-46 years

- In 598 cycles, all oocytes and embryos came from the same stimulated cycle and the remaining ones oocytes and embryos came from mixed cycles with accumulation of vitrified oocytes, day-2 or day-3 embryos.

- Single cell biopsy was performed on **5,116 cleavage stage embryos** (mean number of analyzed embryos: 4.7 ± 2.0).
Materials and Methods

Results <24hours

Sample 1

Biopsy

Cy3

Cell (s) loading

Cy5

Sureplex DNA Amplification System (~ 3 hrs) (98.3%)

Labelling (2 hrs)

DNA precipitation (~ 1 hrs)

Hybridisation (5–12 hrs)

24sure platform

Washing (~ 1/2 hr)

Scanning

24sure
BlueGnome
2684 clones
1Mb coverage
BlueFuse Multi software
Materials and Methods

Euploid embryo

Loss of chromosome 8
Gain chromosome 21

Partial gain chromosome 2p
Materials and Methods

Complex aneuploidy

Chaotic pattern
## Incidence of chromosomal abnormalities

<table>
<thead>
<tr>
<th>AGE (yrs)</th>
<th>38</th>
<th>39</th>
<th>40</th>
<th>41</th>
<th>42</th>
<th>43</th>
<th>44</th>
<th>45</th>
<th>46</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles</td>
<td>87</td>
<td>111</td>
<td>279</td>
<td>240</td>
<td>160</td>
<td>110</td>
<td>45</td>
<td>30</td>
<td>16</td>
<td>----</td>
</tr>
<tr>
<td>No. of informative embryos</td>
<td>478</td>
<td>578</td>
<td>1388</td>
<td>1090</td>
<td>697</td>
<td>461</td>
<td>188</td>
<td>104</td>
<td>45</td>
<td>----</td>
</tr>
<tr>
<td>% Chromosomal abnormal embryos</td>
<td>74.0</td>
<td>75.6</td>
<td>79.0</td>
<td>85.8</td>
<td>88.2</td>
<td>95.0</td>
<td>95.7</td>
<td>94.2</td>
<td>91.1</td>
<td>0.001</td>
</tr>
<tr>
<td>% Embryos with complex aneuploidies</td>
<td>26.6</td>
<td>29.2</td>
<td>32.8</td>
<td>40.4</td>
<td>54.8</td>
<td>59.6</td>
<td>59.6</td>
<td>62.5</td>
<td>65.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Embryos with partial aneuploidies</td>
<td>5.6</td>
<td>3.8</td>
<td>3.7</td>
<td>2.7</td>
<td>2.7</td>
<td>2.8</td>
<td>1.6</td>
<td>3.8</td>
<td>0.0</td>
<td>0.015</td>
</tr>
<tr>
<td>% Embryos with chaotic pattern</td>
<td>16.1</td>
<td>11.8</td>
<td>15.0</td>
<td>16.3</td>
<td>15.8</td>
<td>13.7</td>
<td>18.1</td>
<td>17.3</td>
<td>20.0</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Pearson's correlation (p<0.05)
Clinical Outcome according to Age

[Graph showing the clinical outcome according to age with different age groups from 38 to 46 years]

- PR/transfer
- IR
- % Cycles with transfer
- PR/cycle
- MR

The graph illustrates the clinical outcome according to age, with a clear decline in PR/transfer, IR, and % Cycles with transfer as age increases. PR/cycle remains relatively stable, while MR shows a gradual decrease.
Conclusions

With increasing maternal age we observed:

- An increased percentage of aneuploid embryos.
- A higher rate of complex aneuploidies.
- A decreased percentage of cycles reaching embryo transfer.
- Pregnancy rates per transfer above 50% up to 44 years of age.
- Low miscarriage rates for all age groups.
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