Accreditation of IVF (PGD-PGS) laboratories: principles, expectations and consequences

T.Mardesic, D.Hlinka, M.Kosarova, V.Sobotka

Prague, Czech Republic

Quality management in assisted reproduction

- The number of involuntary childless couples seeking for help in specialized clinics is worldwide increasing.
- Patient expectations: treatment according to the state of the art and real chance for success (delivery of one healthy child)
- Quality=competent, intensive individualized care with personal involvement before treatment, during the treatment process and after the treatment.

Births and age structure of mothers
Czech republic 1991 - 2005

Plodnost (na 1 ženě)

BK.
Fertility Preservation Group
formed by Fertility Society of Australia (2006)
• Telephone survey of 2,400 randomly selected men and women

<table>
<thead>
<tr>
<th></th>
<th>1976</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>First child &lt; 30</td>
<td>92</td>
<td>27</td>
</tr>
</tbody>
</table>

In daily routine usually quality considers only medico-technological aspects of services (therapeutical results)

Quality means much more!
• Medico-technological aspects
• Psychological und ethical aspects
• Organisatory and economical aspects
• Fulfillment of quality expectations from the patient’s perspective
Quality in Medicine means integration of:

- Doctors and patient’s points of view
- Insurance companies points of view
- Clinic’s managements points of view
- Points of view of all other participants taking part in medical services

ART - multidisciplinary approach to infertility treatment requiring expertise from clinical personell (physicians and nurses), and from the embryologists and technicians and scientists.

The success of a clinic is similarly multifactorial.

Beginning of the 21st century in assisted reproduction in Europe

Quality control becomes a key feature
Why quality control systems (QC) are needed?

To assure the reproducibility of all methods and competence in all duties performed by the personnel.

QC – activities and operational techniques within a process that are carried out in order to meet the quality requirements.

QC-a main goal to evaluate the effectiveness of policies and procedures, identify and correct problems, assume the accuracy and precision of procedures and monitor the competency and performance of the laboratory staff.

QA – a total sum of all activities required in order to establish the confidence that the product or service meets the determined quality requirements.
Whenever a formal recognition is pursued – official standards such as developed and released by **International Organization for Standardization** should be implemented.

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National and International Quality Control Levels in Assisted Reproduction

**National level**


**International level**

- ESHRE guidelines for good practice in IVF laboratories
- EN ISO 9001 certification
- EN ISO 170 25 accreditation
- EN ISO 151 89 accreditation

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- **Certification** – result of third party inspection and verification that a product, process or service conforms to specific requirement (valid for a defined and limited time period)

- BUT does not ensure that the laboratory achieves the highest level of care for the patients
- Accreditation – a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out specific tasks

- Until 2000 – EN 45001 (general criteria for the operation of testing laboratories)
- Since 2000 – ISO 17025 (general requirements for the competence of testing and calibration laboratories)
- December 2002 – ISO 15189 (medical laboratories – particular requirements for quality and competence) ⇒ most applicable and comprehensive standard for ART labs

- Even in case of permanent short term evidence of good QC, a real decline in performance may only be identified several weeks later when pregnancy rates fall
- ⇒ establishing a minimal risk strategies in the form of a strict discipline of routines and procedures to ensure QC and QA is mandatory
### General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189

#### Management Requirements

**ISO 17025** | **ISO 15189**
--- | ---
**4.1 Organization** | Responsibilities, Structure of managing and organization
**4.2 Quality system** | Accessibility of relevant documents, Quality manual (basic document describing QMS)
**4.3 Document control** | Document approval and issue, changes
**4.4 Review of requests, tenders and contracts** | Definition of requirements, capability and resources to meet the requirements

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**ISO 17025** | **ISO 15189**
--- | ---
**4.5 Subcontracting of tests and calibrations** | Laboratory is responsible to the client for the subcontractor’s work, Register of all subcontractors
**4.6 Purchasing services and supplies** | Policy and procedures for the selection and purchasing services and supplies
**4.7 Service to the clients** | Monitoring of laboratory performance by the client should be possible, Feedback (positive/ negative)
**4.8 Complaints** | Policy and procedures for the resolution of complaints

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**ISO 17025** | **ISO 15189**
--- | ---
**4.9 Control of nonconforming testing and/or calibration work** | Identification and management of nonconforming work, corrective measures
**4.10 Corrective action** | Designates appropriate authorities for implementing corrective action
**4.11 Preventive action** | Improvement and/ and potential sources of nonconformities
**4.12 Control of records** | Identification, collection, indexing, access, filing, storage, maintenance and disposal of quality records
General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

<table>
<thead>
<tr>
<th>ISO 17025</th>
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<tbody>
<tr>
<td><strong>MANAGEMENT REQUIREMENTS</strong></td>
<td></td>
</tr>
<tr>
<td>4.13 Internal audits</td>
<td>To verify that operations continue to comply with QMS and int. standards</td>
</tr>
<tr>
<td>4.14 Management reviews</td>
<td>- Suitability of policies and procedures</td>
</tr>
<tr>
<td></td>
<td>- Reports from managerial and supervisory personnel</td>
</tr>
<tr>
<td></td>
<td>- Outcome of recent internal audits</td>
</tr>
<tr>
<td></td>
<td>- Corrective and preventive actions</td>
</tr>
<tr>
<td></td>
<td>- Client feedback</td>
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<td>- Complaints</td>
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<td><strong>TECHNICAL REQUIREMENTS</strong></td>
<td></td>
</tr>
<tr>
<td>5.1 General</td>
<td>Factors determining the correctness and reliability of the tests</td>
</tr>
<tr>
<td>5.2 Personnel</td>
<td>Competence of all personnel must be ensured (education, training, experience, demonstrating skills)</td>
</tr>
<tr>
<td>5.3 Accommodation and environmental conditions</td>
<td>Energy sources, lighting, environmental conditions, good housekeeping</td>
</tr>
<tr>
<td></td>
<td>Separation of areas, access</td>
</tr>
<tr>
<td>5.4 Tests and calibration methods and validation</td>
<td>Pre-analytic steps, selection of methods, validation (confirmation and objective evidence that requirements are met), Data controlling</td>
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<td>5.5 Equipment</td>
<td>Capability to achieve the accuracy required, records, handling</td>
</tr>
<tr>
<td>5.6 Measurement traceability</td>
<td>Programs and procedures for calibration Traceability to SI units, reference standards and materials</td>
</tr>
<tr>
<td>5.7 Sampling</td>
<td>Sampling procedures describing selection, sampling plan, withdrawal</td>
</tr>
<tr>
<td>5.8 Handling of test and calibration items</td>
<td>Policy and procedures to protect the integrity of the test Identification of tests</td>
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<td>5.9 Assuring the quality of test and calibration items</td>
<td>Use of certified reference materials and/or internal quality control interlaboratory comparison programs</td>
</tr>
<tr>
<td>5.10 Reporting the results</td>
<td>Accurately, clearly, unambiguously and objectively</td>
</tr>
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Quality manual
- Level 1: Defines approach and responsibility, outlines the structure of documentation
- Level 2: Procedures
- Level 3: SOP’s (job instructions)
- Level 4: Results and other documentation

Shows that system is operating

Genetic laboratories
- EN ISO/IEC 17025:2000
PGD vers. PGS

- General consensus that the use of PGD is acceptable for medical indications if high risk of serious genetic disorder exists
- PGS – debates regarding the safety and efficacy (few and criticized RCT’s published)

Are the results of present RCT’s reliable?

<table>
<thead>
<tr>
<th>Author</th>
<th>Criticism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staessen 2004</td>
<td>No. of embryos transferred different (2,0 vers 2.8)</td>
</tr>
<tr>
<td>(289 egg retrievals)</td>
<td>Double blastomere biopsy</td>
</tr>
<tr>
<td>Mastenbroek 2007</td>
<td>Not analyzed chrom. 15,22</td>
</tr>
<tr>
<td>(408 women with AMA)</td>
<td>FISH failed in 20%</td>
</tr>
<tr>
<td></td>
<td>Not analyzed embryos transferred</td>
</tr>
<tr>
<td></td>
<td>Low No. of embryos biopsied</td>
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</table>

Mastenbroek, S. et al:
In vitro fertilization with preimplantation genetic screening
(NEJM, 2007, 357, 9-17)

- PGS did not significantly improve the outcome, moreover, even had a detrimental effect on the outcome of AR in couples with advanced maternal age (AMA)
• This paper has triggered the already late discussion on the indications, guidelines, technical standards, safety and efficacy of PGS

General criticism of published studies

• Poor embryo biopsy technique
• Embryo damage by double blastomere biopsy
• Suboptimal FISH technique
• Poor embryo culture/laboratory conditions

Possible errors: technical aspects, biology

• „pure“ technical problems
• Mosaicism
• Restricted set of chromosomes available for dg. (refinement of current techniques, CGH)
Cooperation: basic requirement for successful PGD/PGS program

Clinician

IVF lab.

Genetic lab.

Clinical genetics

Indication
Stimulation strategy

Strategy in individual case
Biopsy technique
Embryo culture/lab conditions

FISH technique
QA (validation)

Cooperation: basic requirement for successful PGD/PGS program

Clinician

IVF lab.

Genetic lab.

Indication
Stimulation strategy

• "good" number of oocytes for IVF ("soft" stimulation protocols are of limited value in PGD/PGS program)
Cooperation: basic requirement for successful PGD/PGS program

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<th>IVF lab.</th>
<th>Genetic lab.</th>
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- Drilling method
- Biopsy (extrusion of a single blastomere)
- Ca/Mg free medium not necessary
- Embryology is equally important!
- Culture and laboratory conditions

Cooperation: basic requirement for successful PGD/PGS program

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- FISH technique
- Chromosome selection
- Selected embryos— in collaboration with IVF lab. „third round” hybridization with different probes (monosomy in „top quality” and „top history” embryos

Indicators of quality

- Objective
- Relevant to the laboratory
- Measure a broad range of specific events or aspects of treatment reflecting the quality of care

⇒ Threshold values for each of the indicators must be given with clearly defined corrective actions
Impact of setting the thresholds

<table>
<thead>
<tr>
<th>Threshold values set too low</th>
<th>Failure to detect lab errors and correct poor performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold values set too high</td>
<td>Standards are impossible to achieve, improvement efforts misdirected</td>
</tr>
<tr>
<td>Threshold values appropriately set</td>
<td>True view of lab performance, effective efforts towards improvements</td>
</tr>
</tbody>
</table>

PGS results
Sanatorium Pronatal 2005-2007

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2007</th>
<th>2007 Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsies</td>
<td>573</td>
<td>779</td>
<td>724</td>
</tr>
<tr>
<td>Successful biopsy</td>
<td>573</td>
<td>779</td>
<td>723</td>
</tr>
<tr>
<td>Diagnosed</td>
<td>556 (97)</td>
<td>763 (97,9)</td>
<td>702 (97,1)</td>
</tr>
</tbody>
</table>

PGS results according to indication
Sanatorium Pronatal 2005-2007

<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of cycles</th>
<th>Cycles with ET (%)</th>
<th>PR/cycle (%)</th>
<th>PR/ET (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translocations</td>
<td>32</td>
<td>26 (81,3)</td>
<td>6 (25)</td>
<td>8 (50,1)</td>
</tr>
<tr>
<td>RIF</td>
<td>115</td>
<td>92 (80)</td>
<td>37 (32,2)</td>
<td>37 (40,2)</td>
</tr>
<tr>
<td>Age</td>
<td>72</td>
<td>41 (56,9)</td>
<td>15 (20,8)</td>
<td>15 (36,6)</td>
</tr>
<tr>
<td>RPL</td>
<td>21</td>
<td>20 (95,2)</td>
<td>9 (42,9)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>TESE</td>
<td>15</td>
<td>12 (80)</td>
<td>9 (60)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Egg donation</td>
<td>57</td>
<td>54 (94,7)</td>
<td>32 (56,1)</td>
<td>32 (59,3)</td>
</tr>
<tr>
<td>Sex selection</td>
<td>12</td>
<td>12 (100)</td>
<td>6 (50)</td>
<td>6 (50)</td>
</tr>
</tbody>
</table>
Conclusions (1)

The goal of all QM systems is to improve patient care and satisfaction using a proactive strategy of ongoing evaluation and monitoring.

Conclusions (2)

The key elements are:
- understanding the situation
- analysing data
- improving performance

Conclusions (3)

Accreditation of IVF (PGD/PGS) lab is an efficient and effective tool to achieve and demonstrate technical competence.

It is a never ending project that shall guarantee a constant improvement of the work.