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

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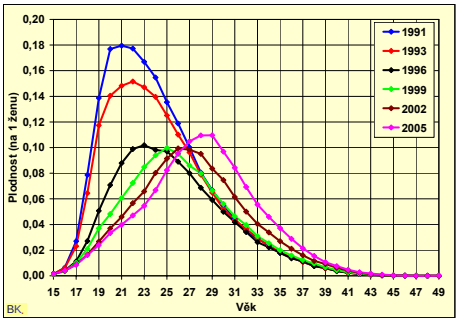
Quality management in assisted reproduction

- The number of unvoluntary childless couples seeking for help in specialized clinics is worlwide 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



Fertility Preservation Group

formed by Fertility Society of Australia (2006)

- Telephone survey of 2.400 randomly selected men and women

	1976	2006
First child < 30 %	92	27

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 personell

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 acuracy 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

National and International Quality Control Levels in Assisted Reproduction

National level

COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council

International level

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

- **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 aplicable 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 and technical requirements)

ISO 17025	ISO 15189
MANAGEMENT	**REQUIREMENTS**
4.1 Organization	Responsibilities Structure of managing and organization
4.2 Quality system	Accesibility 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

General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

ISO 17025	ISO 15189
MANAGEMENT	**REQUIREMENTS**
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 (positiveX negative)
4.8 Complaints	Policy and procedures for the resolution of complaints

General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

ISO 17025	ISO 15189
MANAGEMENT	**REQUIREMENTS**
4.9 Control of nonconforming testing and/or calibration work	Identification and management of nonconforming work, corrective measures
4.10 Corrrective 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)

ISO 17025	ISO 15189
MANAGEMENT	**REQUIREMENTS**
4.13 Internal audits	To verify that operations continue to comply with QMS and Int. standards
4.14 Management reviews	•Suitability of policies and procedures •Reports from managerial and supervisory personell •Outcome of recent internal audits •Corrective and preventive actions •Client feed back •Complaints

General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

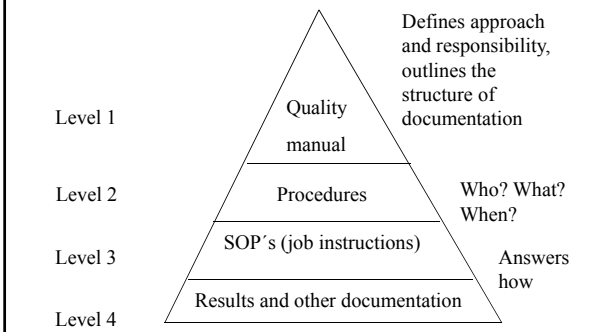
ISO 17025	ISO 15189
TECHNICAL	**REQUIREMENTS**
5.1 Generel	Factors determining the correctness and reliability of the tests
5.2 Personnel	Competence of all personell must be ensured (education, training, experience, demonstrating skills)
5.3 Accomodation and environmental conditions	Energy sources,lighting, environmental conditions, good houskeeping Separation of areas, access
5.4 Tests and calibration methods and validation	Pre-analytic steps, selection of methods, validation (confirmation and objective evidence that requirements are met). Data controlling

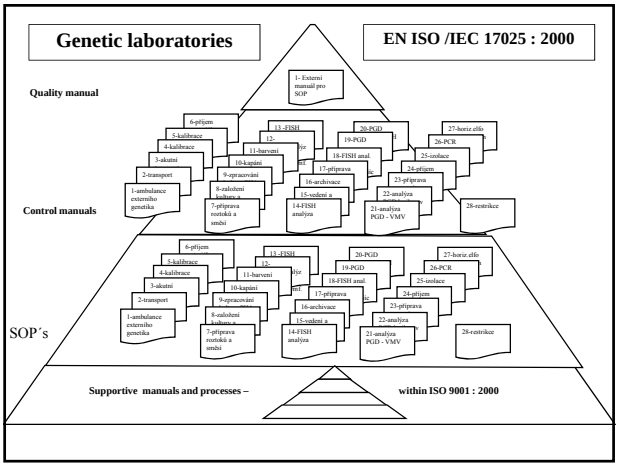
General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

ISO 17025	ISO 15189
TECHNICAL	**REQUIREMENTS**
5.5 Equipment	Capability to achieve the accuracy required, records, handling
5.6 Measurement traceability	Programs and procedurs for callibration Traceability to SI units, reference standards and materials
5.7 Sampling	Sampling procedures describing selection, sampling plan, withdrawal
5.8 Handling of test and calibration items	Policy and procedures to protect the integrity of the test Identification of tests

General requirements for the competence of testing and calibration laboratories ISO/EC 17025:1999 and medical laboratories ISO 15189 (management and technical requirements)

ISO 17025	ISO 15189
MANAGEMENT	**REQUIREMENTS**
5.9 Assuring the quality of test and calibration items	Use of certified reference materials and/or internal quality control Interlaboratory comparison programs
5.10 Reporting the results	Accurately, clearly, unambigously and objecively





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?

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

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

- PGS did not significantly improve the outcome, morover, even had a detrimental effect on the outcome of AR in couples with advanced maternal age (AMA)

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

- This paper has triggered the already late discussion on the indications, guidelines, technical standards, safety and efficacy of PGS

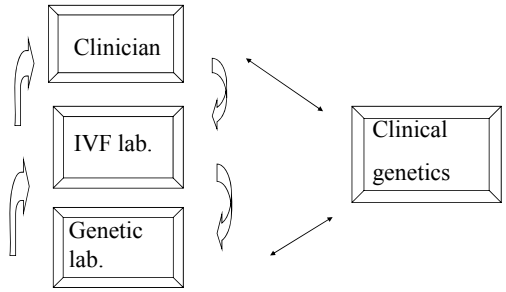
General criticism of published studies

- 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
- Restricted set of chromosomes available for dg. (refinement of current techniques, CGH)
- Mosaicism

Cooperation: basic requirement for successful PGD/PGS program



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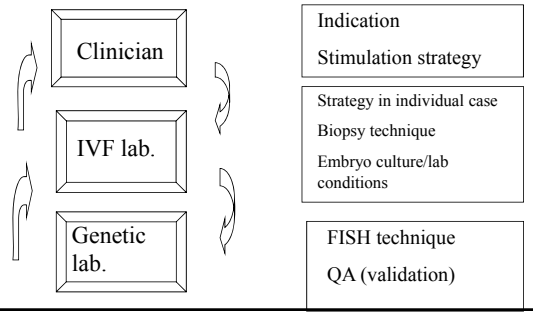

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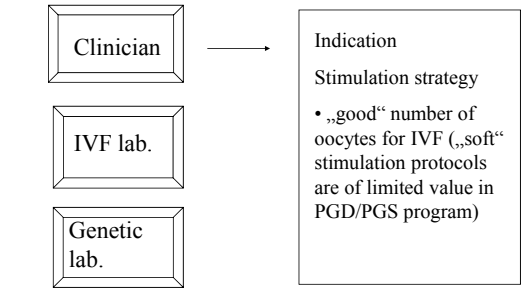

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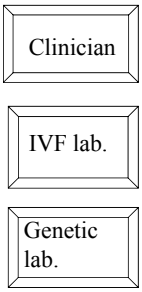
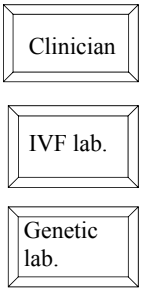


- Drilling method
- Biopsy (extrusion of a single blastomere) ⟹ Ca/Mg free medium not necesary
- Embryology is equally important!
- Culture and laboratory conditions

Cooperation: basic requirement for successful PGD/PGS program



- FISH technique
- Chromosome selection
- Selected embryos- in collaboration with IVF lab. „third round" hybdridization 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

⇒ Treshold values for each of the indicators must be given with clearly defined corrective actions

Impact of setting the tresholds

Treshold values set too low	Failure to detect lab errors and correct poor performance
Treshold values set too high	Standards are impossible to achieve, improvement efforts misdirected
Treshold values appropriately set	True view of lab performance, effective effeorts towards improvements

PGS results
Sanatorium Pronatal 2005-2007

	2005	2007	2007	Total
Biopsies	573	779	724	2076
Successful biopsy	573	779	723	2075
Diagnosed	556 (97)	763 (97,9)	702 (97,1)	2021 (97,4)

PGS results according to indication
Sanatorium Pronatal 2005-2007

Indication	No. of cycles	Cycles with ET (%)	PR/cycle (%)	PR/ET (%)
Translocations	32	26 (81,3)	8 (25)	8 (30,1)
RIF	115	92 (80)	37 (32,2)	37 (40,2)
Age	72	41 (56,9)	15 (20,8)	15 (36,6)
RPL	21	20 (95,2)	9 (42,9)	9 (45)
TESE	15	12 (80)	9 (60)	9 (75)
Egg donation	57	54 (94,7)	32 (56,1)	32 (59,3)
Sex selection	12	12 (100)	6 (50)	6 (50)

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.