
Total Quality Management in the ART Laboratory
Basak Balaban, MSc
Filippo Maria Ubaldi, MD, MSc
gfa
Global Fertility Academy


Section 1
Introduction to ART Laboratory Management and Quality Control
gfa
Global Fertility Academy

Learning Objectives

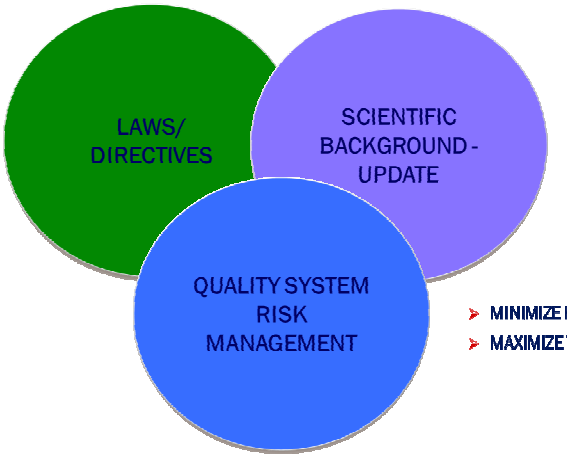
After this section, participants should:

- Better understand the importance of a total quality management system in the assisted reproductive technology (ART) laboratory to maintain stable clinical success
- More confidently incorporate quality control and quality assurance processes into their clinical environment
- Appreciate the goals of quality control and assurance in optimising outcomes

Success in ART Applications

- The ability to create an optimal environment for the culture of oocytes and embryos is important to ensure that embryo viability, and therefore pregnancy outcome, is not compromised
- Quality Control & Quality Assurance can serve at this point by monitoring the performance of clinical *in vitro* fertilisation laboratories and detecting any problems that potentially may have resulted in a sub-optimal environment

Good Management in the ART Laboratory



- MINIMIZE RISK
- MAXIMIZE TRACEABILITY

Each lab must put in place a quality management system and implement this system to continually improve the quality and effectiveness of the service provided in accordance with the guidance on good practice

gfa Global Fertility Academy

Evolution of IVF Over Nearly Four Decades

- The field of ART, which involves IVF, embryo culture, and embryo transfer (ET) has improved from >1% to 33% live birth rate (LBR)/cycle since the birth of Louise Brown in 1978
- Hence, despite improvements in the field, ART still remains relatively poor at providing the patient with demonstrably high levels of success
- Attempts to improve results and achieve a 100% success rate are required, and stability in success can only be achieved by optimisation of the procedures
- QUALITY CONTROL/ASSURANCE/IMPROVEMENT

gfa Global Fertility Academy

Total Quality Management in the ART Laboratory

Quality Control and Quality Assurance

- Quality control (QC)/assurance (QA) involves an overall view of the clinical embryology laboratory
- Main sources utilised include the following:
  - 1st QC & QA chapters in Weimer 2nd ed.
  - McCulloh DH. Quality control: maintaining stability in the laboratory. In: Gardner DK, Weissman A, Howles CM, Shoham Z, eds. *Textbook of Assisted Reproductive Techniques*. 3rd ed. London, England: Taylor & Francis; 2009:9-25.
  - Cutting R, Pritchard J, Clarke H, Martin K. Establishing quality control in the new IVF laboratory. *Hum Fertil (Camb)*. 2004;7(2):119-25.
  - Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.
  - The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

gfa Global Fertility Academy

What is Quality Control (QC)?

- Process whereby all aspects directly or indirectly involved with performing the related program (IVF) are routinely monitored and confirmed to be functional within limits previously determined to be acceptable
- Program must remain within these limits to ensure that it operates in a stable, repeatable fashion

gfa Global Fertility Academy

The Goal of Quality Control

- Confirm and document that the program maintains stable conditions
- Stability provides a constant backdrop against which all patient treatment is performed

Without this stability, it is impossible to know whether an unusual outcome for a particular patient is associated with a patient-specific issue or a programmatic failure.

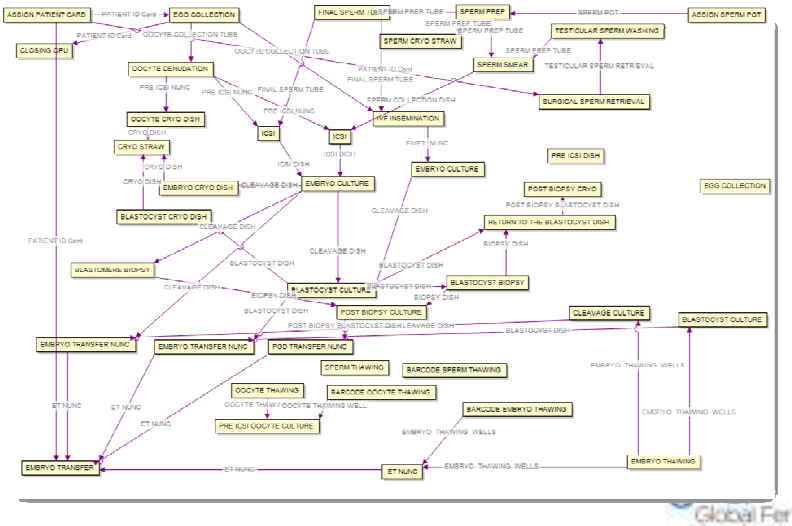
What is Quality Assurance?

- Overall process including quality control as a subset by which the program undergoes improvements and corrective actions to maintain or improve its processes

What is the Goal of Quality Assurance?

- Improve outcome: QC is a necessary part of the QA program
- It is the QC assessment of personnel, procedures, equipment, and materials that provides much of the data used in performing QA/improvement activities

Complex Procedures in the ART Laboratory



Chapter 1 Conclusions

- An ART laboratory consists of complex procedures that are closely correlated with each other
- The success of an ART laboratory is highly dependent on the control of these procedures
- In order to have accurate control on these complex procedures, it is critical to establish a total quality management system in the ART laboratory to improve patient outcomes

Learning Objectives

After this section, participants should:

- More fully understand the important features of quality control within a total quality management system in the ART laboratory
- Better adapt these feature controls into routine clinical practice

Features of QC in the Clinical ART Laboratory

- Record keeping
- QC of
  - Computers
  - Personnel
  - Procedures in clinical embryology laboratory
  - Equipment
  - Materials and supplies
  - External environment and air filtration systems

Record Keeping

- Monitored parameters in clinical embryology laboratories should be recorded and maintained for use and review in the future
- Assembled data will be useful in determining corrective actions in terms of QA/improvement in case of problems or a desire for improvements
- QC data may be maintained in paper or electronic records
  - Electronic database systems are preferred for a quicker and more practical analysis of the required data
- Off-site backup and regular QC of computers that preserve essential data are recommended

QC of Laboratory Personnel

- Employees in ART laboratories must adhere to predetermined standards; they must have appropriate training and must demonstrate competence with procedures they perform
- Although the qualification of laboratory personnel for andrology laboratories had been defined in the **United States** and some EU countries, international standards for clinical embryologists are lacking
- European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) recommendations can be followed for countries without local regulations
- Alpha Society Meeting Consensus 2014 on professional status of Clinical Embryologists: This meeting consensus and subsequent report of the Alpha International Society may be a useful guide when recommending standards for clinical embryologists

Laboratory Staffing Norms

- A sufficient number of personnel should be available to perform all IVF laboratory work without subjecting either the personnel or patients to undue risks
- Although international staffing norms are not available, it is an important QC issue to have enough staff/desired volume of laboratory services to ensure the safety and efficiency of ART laboratory procedures
- For each clinical embryologist, the desired volume ranges from 100 to 300 IVF procedures per year
- The number of personnel should be fixed for routine work, with additional personnel for more complex procedures

Recommended Staff According to Volume

Number of laboratory cycles	Minimum number of embryologists
1 - 150	2
151 - 300	3
301 - 600	4
> 600	1 additional embryologist per additional 200 cycles

The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

QC of Procedures

- Uniformity of procedures and enforcement of uniform performance are needed to ensure consistency of each procedure performed in the laboratory
- A written protocol for each procedure performed in the facility must be available near the site of performance and each protocol should be written so that anyone could perform the procedure
- International standards/guidelines for clinical embryology laboratories can be followed using ESHRE and ASRM recommendations, and detailed local guidelines can be suggested by local embryology authorities for standardisation

Preparation of a written protocol	
Principle and/or purpose of the test	Provide a general outline of the point of the procedure and how the procedure is performed
Specimen required for the test	Describe any instructions necessary to be certain that the specimen is collected in a way that will assure correct processing and testing
Reagents, standards, control, media	List any materials needed to perform the procedure
Instrumentation	List any instruments to be used and any quality control procedures needed to assure that the instrument is functioning correctly
Step-by-step instructions	Carefully describe in narrative form exactly how the procedure is to be performed
Calculations	Describe how to perform any necessary calculations
Frequency and tolerance of controls	Describe any controls that should be run to assure quality of the performance of the procedure
Expected values	List expected values for the results so that the person performing the test will know if the values are within a reasonable range
Limitations	Describe any limitations on the interpretation of the results or on the utility of the procedure
References	List sources of information that the user may wish to consult if questions arise
Effective date and schedule for review	Indicate the date that the procedure will become effective, and date(s) that it is scheduled for review
Distribution	List all persons/locations to which the procedure has been sent
Author	List the person who wrote the procedure

National Committee for Clinical Laboratory Standards (NCCLS)-US

McCulloh DH. Quality control: maintaining stability in the laboratory. In: Gardner DK, Weissman A, Howles CM, Shoham Z, eds. *Textbook of Assisted Reproductive Techniques*. 3rd ed. London, England: Taylor & Francis; 2009:9-25.

QC of Embryology Procedures in the IVF Laboratory

- Although there are no universal standard threshold limits, every laboratory should record monthly/annual/biennial verifications of all embryology procedures to ensure consistency in the success of all clinical outcome measures
- Normal fertilisation, polyspermic, ICSI degeneration, embryo cleavage, cryopreservation survival, ongoing pregnancy and implantation rates, as well as sperm concentration, morphology, and motility, should be included

Globally Referenced Morphological Grading Schemes for Standardization

The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting

Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology

ARTICLE

Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting

Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology

1. Magli MC, Jones GM, Lundin K, van den Abbeel E. Atlas of human embryology: from oocytes to preimplantation embryos. *Hum Reprod*. 2012;27 Suppl 1:i1.
2. Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

Globally Referenced Key Performance Indicators and Benchmarks

ELSEVIER

www.sciencedirect.com
www.rbmonline.com

ARTICLE

The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting

Alpha Scientists in Reproductive Medicine

gfa Global Fertility Academy

Mandatory Guidelines: Medical and Scientific Societies

- ESHRE* (Europe), FLASEF**(Latin America), and HFEA*** (Europe) mandate in their guidelines and codes of practice the permanent labeling of all labware to identify the source of the biological material it contains
- They also mandate the use of a witness to double-check and confirm the identity of the samples and the patients or donors that they are associated with at all critical points of the clinical and laboratory procedures

* European Society of Human Reproduction and Embryology
** Federacion Latino Americana de Sociedades de Esterilidad y Fertilidad
*** Human Fertilisation and Embryology Authority

gfa Global Fertility Academy

Chain of Custody

Witnessing protocols should be followed when any of the following clinical or laboratory procedures take place:

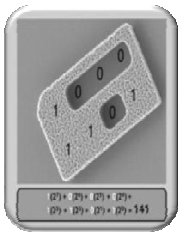
- **Collecting eggs**
- **Collecting sperm**
- **Preparing sperm**
- **Mixing sperm and eggs or injecting sperm into eggs**
- **Transferring gametes or embryos between tubes or dishes**
- **Transferring embryos into a woman**
- **Inseminating a woman with sperm prepared in the laboratory**
- **Placing gametes or embryos into cryopreservation**
- **Removing gametes or embryos from cryopreservation**
- **Disposing of gametes or embryos**
- **Transporting gametes or embryos**

****Inclusion of novel technologies**

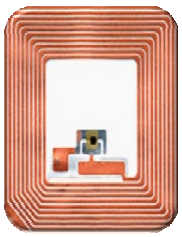
Global Fertility Academy

Labelling Systems: Available Options

Barcodes
Matcher™



Silicon-based barcodes

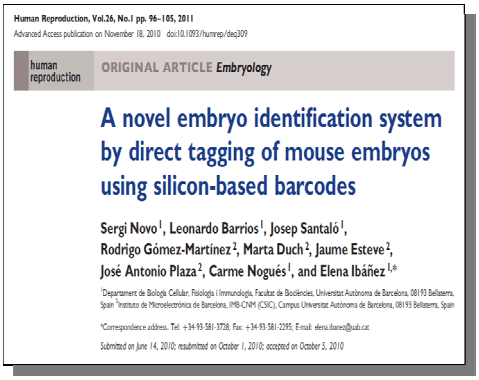


RFID Tags
RI Witness™

gfa Global Fertility Academy

Direct Labelling System: Silicon-based Barcodes

To provide a proof of concept for a direct oocyte/embryo labelling system



Human Reproduction, Vol.26, No.1 pp. 96–105, 2011
Advanced Access publication on November 18, 2010 doi:10.1093/humrep/deq309

human reproduction ORIGINAL ARTICLE *Embryology*

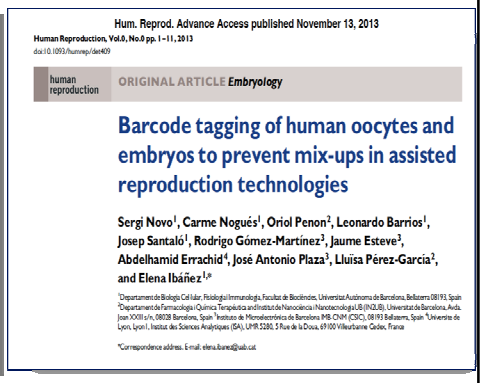
A novel embryo identification system by direct tagging of mouse embryos using silicon-based barcodes

Sergi Novo[1], Leonardo Barrios[1], Josep Santaló[1], Rodrigo Gómez-Martínez[2], Marta Duch[2], Jaume Esteve[2], José Antonio Plaza[2], Carme Nogués[1], and Elena Ibáñez[1,*]

[1]Departament de Biologia Cellular, Fisiologia i Immunologia, Facultat de Biociències, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain [2]Instituto de Microelectrónica de Barcelona, IMB-CNM (CSIC), Campus Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

*Correspondence address. Tel: +34-93-581-3728; Fax: +34-93-581-2295; E-mail: elena.ibanez@uab.cat

Submitted on June 14, 2010; resubmitted on October 1, 2010; accepted on October 5, 2010



Hum. Reprod. Advance Access published November 13, 2013
Human Reproduction, Vol.0, No.0 pp. 1–11, 2013
doi:10.1093/humrep/det409

human reproduction ORIGINAL ARTICLE *Embryology*

Barcode tagging of human oocytes and embryos to prevent mix-ups in assisted reproduction technologies

Sergi Novo[1], Carme Nogués[1], Oriol Penon[2], Leonardo Barrios[1], Josep Santaló[1], Rodrigo Gómez-Martínez[2], Jaume Esteve[2], Abdelhamid Errachid[4], José Antonio Plaza[3], Lluïsa Pérez-García[2], and Elena Ibáñez[1,*]

[1]Departament de Biologia Cel·lular, Fisiologia i Immunologia, Facultat de Biociències, Universitat Autònoma de Barcelona, Bellaterra 08193, Spain [2]Departament de Farmacologia i Química Terapèutica and Institut de Nanociència i Nanotecnologia (IN2UB), Universitat de Barcelona, Avda. Joan XXIII s/n, 08028 Barcelona, Spain [3]Instituto de Microelectrónica de Barcelona IMB-CNM (CSIC), 08193 Bellaterra, Spain [4]Université de Lyon, Lyon I, Institut des Sciences Analytiques (ISA), UMR 5280, 5 Rue de la Doua, 69100 Villeurbanne Cedex, France

*Correspondence address. E-mail: elena.ibanez@uab.cat

gfa Global Fertility Academy

Electronic vs. Barcoding Systems

	Electronic	Barcoding systems and human double-witnessing
Sample checking/forcing function	The system scans and detects all labware automatically where procedures are performed. Therefore, users cannot skip a check or perform a procedure without being checked.	The labware must be presented by the user for identification (either to a barcode reader or a human witness). Therefore, the safety of the lab relies on people remembering to perform the checks.
Prevention of mistakes	If incompatible labware is brought into the working area, the user is immediately alerted visually and audibly before any work can be carried out. A potential mistake is therefore avoided.	For a potential mistake to be avoided, the user must remember to initiate a check prior to commencing work. When using multiple dishes and tubes, great care must be taken to ensure that all labware has been correctly checked.

gfa Global Fertility Academy

Electronic Witnessing and Labelling

gfa Global Fertility Academy

Minimized Mismatch Rate with Electronic Witnessing and Labelling

Error Rate	Type of study	Author
6%	Mismatches using barcode based system (Matcher™)	Schnauffer *et al.*
0.2%	1000 drugs administration (by 2 nurses)	Krause *et al.*
7 - 10 %	Pathology studies	Elson D.
0.3 %	Mistakes in 4 hospital departments	Carraro *et al.*
0.8 %	Data input: keyboard *vs.* Barcode system	Shaw *et al.*
0.1%	Wristband mix-ups involving 2 patients	Valenstein P.

Electronic witnessing and labelling: reduces mismatch rate to ~0.1%

- Easy to implement
- Safeguard the reliability of the entire IVF process
- Allow traceability of each step
- Reduce staff workload and distractions
- Provide patient reassurance

QC of Equipment

- Periodic testing of all equipment used in the laboratory is required for proper operation within acceptable limits. Acceptable limits should be set prior to equipment use, with knowledge of biologically optimal values and instrument variability.
- ART laboratory: incubators, microscopes, heating surfaces, heating blocks, water baths, refrigerators, freezers, controlled rate freezers, etc.

List of equipment, parameters for QC, and frequency of QC			
Equipment	Parameter for QC	Frequency of QC	Comments
Incubator	Temperature CO2 Humidity	Daily Daily Daily	Annual preventive maintenance
Heating Surfaces	Temperature	Daily	
Heating bath	Temperature Water level	Daily Daily	
Heating block	Temperature	Daily	
Microscope	Image quality	Daily	Annual preventive maintenance
CASA	Sperm Count Motility(%) Motility(Velocities) Morphology(%)	Daily Daily Daily Daily	Annual preventive maintenance
Controlled Rate Freezer	Sufficient refrigerant Start temperature Seeding temperature Final temperature	Each use Each use Each use Each use	Annual preventive maintenance
Storage dewers	LN2 level	Daily	
Refrigirator	Temperature	Daily	
Freezer	Temperature	Daily	
Heating, ventilation, and air conditioning systems	Room temperature Room humidity	Daily Daily	Clean filters/humidifiers periodically
QC Equipment			
Thermometers	Temperature(accuracy/precision)	Periodically	
pH meters	Ph (accuracy/precision)	Each use(daily)	Annual preventive maintenance
Osmometers	Osmolarity (accuracy/precision)	Each use(daily)	Annual preventive maintenance
Hygrometers	Humidity (accuracy/precision)	Periodically	
Timers	Time (accuracy/precision)	Periodically	
CO2 monitor	%CO2 (accuracy/precision)		Fyrite should be changed every 300 determinations

McCulloh DH. Quality control: maintaining stability in the laboratory. In: Gardner DK, Weissman A, Howles CM, Shoham Z, eds. *Textbook of Assisted Reproductive Techniques*. 3rd ed. London, England: Taylor & Francis; 2009:9-25.

gfa Global Fertility Academy

External Environment of Gametes and Embryos - QC of Air Quality

- Each program must establish its own level of maximum air contamination, as no standardised levels are available
- Common techniques used to measure air quality are not suitable for low-level detailed analysis or may not have the ability to measure the variable composition of the air in the ART laboratory
- Measurements must be sensitive at the $\mu g/m^3$ level or better, which far exceeds the standards established and used by the Environmental Protection Agency

gfa Global Fertility Academy

Minimal Standards of an Air Filtration System in the ART Laboratory?

- Extreme measures in the ART laboratory must achieve air quality that exceeds levels found even in most surgical suites, and its direct effect on LBR has been debated for years
- Air handling systems should preferably not only remove particulate matter but also volatile gases
- Filtration systems should contain a dedicated central heating, ventilation, and air condition system (HVAC) that effectively removes 99.995% of particles 0.3 μM and larger
- AQF 2000 high efficiency gas phase filters are recommended for gas contaminant removal.
- Pre-HEPA filters and post-carbon filters can remove large dust particles
- Periodic maintenance of the air filtration systems as recommended by the manufacturing company should be performed and values recorded

External Environment of Gametes and Embryos: Cleaning of the IVF Laboratory

To be cleaned	Cleaning agent protocol	Time-table for cleaning
Incubators Surfaces	(Detergent) Dist/Water 70%EtOH	Daily
Microscopes & stages	(Detergent) Dist/Water 70%EtOH	Daily
Floors	(Detergent) Dist/Water	Daily
Heating blocks	Dist Water 70%EtOH	Weekly
Water baths	70%EtOH Water	Weekly
Incubator water pan	MilliQ Water	Weekly
Gas lines – plastic tubing	Distilled Water	Monthly
Incubators	Dist Water 70%EtOH; Or Dist Water Steri-cycle	Routine cleaning monthly; complete bunkdown-clean 2 – 4 times per year depending on use/workload
Incubator gas pre-filter		Change 6 monthly
Water, voltage, and carbon dioxide	Detergent Dist Water 70%EtOH	Bi-annually or annually
Refrigerators	Detergent Dist Water 70%EtOH	Monthly
Freezers	Detergent Dist Water 70%EtOH	Bi-annually
Centrifuges	Detergent Dist Water 70%EtOH	Weekly
Cryotanks	Allow to warm, rinse with dist water and wipe carefully with 70% EtOH. Allow to dry before re-filling	????
Video accessories	70% EtOH	Weekly
Laminar flow + filters		Prefilter monthly, HEPA filter changed annually
Air filters		Change 6 monthly or according to manufacturer's instructions

*****Embryo-safe solutions recently introduced to the IVF market are recommended**

1. Elder K, Baker DJ, Ribes JA. Infection and contamination control in the ART laboratory. In: Elder K, Baker DJ, Ribes JA, eds. *Infections, Infertility, and Assisted Reproduction.* Cambridge, United Kingdom: Cambridge University Press; 2011: 305-331.
2. Elder K, Elliot T. Cleaning protocols in the IVF laboratory. *J Assist Reprod Genet*. 2004;21(3):63-64.

Process Testing/QA

- Even if you feel certain about the education and training of laboratory personnel, that all procedures are intact, that all equipment is functioning according to predetermined standards, and that all contact materials are non-toxic, confirmation that gamete handling and embryo culture can be performed in a way that does not harm the gametes or embryos is required
- Various survival and development assays such as the hamster sperm survival test, human sperm survival test, and mouse embryo assay can be utilised despite little standardisation of these assays

Chapter 2 Conclusions

- It is of great importance to establish quality control features in the ART laboratory
- Record keeping and quality control of computers used in the laboratory should be performed periodically
- Quality control and the provision of laboratory staff with periodic training to update working knowledge is essential
- Quality control of all procedures, equipment, external environment, and air filtration systems in the ART laboratory must be performed periodically to ensure operational safety and efficiency

Learning Objectives

After this section, participants should:

- More confidently incorporate recommended guidelines from ESHRE and ASRM related to total quality control and assurance in the ART laboratory
- Better adapt these guideline recommendations into their routine clinical practice

ESHRE Guidelines for Good Practice in IVF Laboratories

- The guidelines were first published in 2000 by ESHRE Special Interest Group on Embryology (SIGE) to define minimal requirements of an ART laboratory and have been revised according to the new EU Tissue and Cell directives
- Aim: To implement a quality system for all embryologists and ART laboratory personnel, in the understanding that the embryologist has a responsibility for the correct and justified application of ART in the laboratory. The strict application and further development of these guidelines benefit all patients attending ART clinics, ART professionals, and the embryologists. It may not only respond to the need of embryologists for support and guidance in their duties, but may represent a point of reference for the national competency authorities inspecting according to the EU Tissue and Cell directives.

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Implementation

- Implementation of guidelines requires a quality management programme to be in place that integrates QC, QA, and quality improvement (QI)
- This should be done by the design of a quality policy and a consequent implementation of a quality system that encompasses and integrates the operative units, processes, and procedures that represent the core of ART clinics
- Within this framework of QA, ESHRE set up a program for the Certification of Clinical Embryologists to contribute to the assurance of good laboratory practice and to define the concept of qualified embryologists

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Staffing and Direction

- The laboratory should be directed by a qualified, experienced person with a diploma and expertise in the field of embryology and biological or medical sciences according to national rules
- The responsibilities of the laboratory director include:
  - Control and improve all laboratory procedures, manuals, data records, laboratory staff training, and orientation
  - Contact clinicians when exchanging required information

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

ESHRE Guidelines - Policies and Procedures

- All laboratory procedures must include provision for unique patient identification and corresponding gamete, zygote, and embryo identification, while retaining patient confidentiality
- Updated versions of detailed manuals for all procedures should be available in the laboratory
- Laboratory and clinical results should be regularly updated and discussed, and logbooks should be maintained to evaluate results
- Every communication with operative information should be specified in written procedures, and communication to the laboratory should be kept to a minimum

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

ESHRE Guidelines - Laboratory Safety, Design

- The embryology laboratory must have adequate space to allow good laboratory practice and be close as possible to the operating room
- New safety and design developments should be considered in equipment and facility upgrades
- Attention should be given to the comfort of the operator:
  - Bench height
  - Chair height
  - Microscope eye height
  - Efficient use of space and surfaces
  - Sufficient air conditioning with controlled humidity and temperature

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

ESHRE Guidelines - Laboratory Safety, Equipment

- Equipment must be adequate for laboratory work and easy to clean and disinfect
- Incubators and frozen sample storage facilities should be alarmed and monitored, and an automatic emergency generator back up should be in place
- A minimum of 2 frequently cleaned and sterilised incubators with gas cylinders placed outside and an automatic back up system is recommended
- Devices for the maintenance of temperature, CO_2, and pH should be in place. Regular checks and calibrations of such equipment should be documented, controlled, and retained.
- Instruction manuals for all equipment and written instructions in case of equipment failure should be in the laboratory and available for all staff

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

ESHRE Guidelines - Laboratory Safety, Infectious Agents

- ART laboratory applications involve the handling of biological material and pose a potential hazard of disease transmission to personnel and sample cross-contamination. Each unit should establish procedures and policies to ensure safety in such situations, taking local and national safety regulations into consideration
- Vaccination of the personnel against hepatitis (HEP) B or other viral diseases and the screening of patients for HIV, HEP B/C, and other sexually transmissible diseases before processing or cryopreservation should be routinely adopted
- Laboratory staff and clinicians should be informed about the risks. Class II air flow during sample preparation is recommended

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

Global Fertility Academy

ESHRE Guidelines - Laboratory Safety, Protective Measures

- All body fluids (follicular fluid, semen, etc.) should be treated as potentially contaminated
- Strict observation of staff hygiene regulations, laboratory clothing, utilisation of non-toxic, non-powdered gloves and masks, eye and face protection, cryogloves, vertical air flows, mechanical pipetting devices, fume hoods in case of fixatives, and disposable materials are preferred
- Needles and other sharps should be handled with extreme caution and should be discarded in special containers. If possible, omit glassware in the laboratory; otherwise, discard Pasteur pipettes and broken glassware in special containers
- Food, drink, cigarettes, and cigars are strictly forbidden; make-up and strong perfumes should be limited

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

Global Fertility Academy

ESHRE Guidelines - Identification of Patients and Their Gametes, Zygotes, and Embryos

- Before any treatment, the embryologist should check that the patient has signed the consent form(s) and that serological tests are completed
- Written procedures describing all laboratory and clinical procedures should be readily available
- Rules concerning the correct handling and identification of all samples should be established by a system of checks (such as double checks by a second person)
- Proper training of laboratory staff for "checking rules" is mandatory

ESHRE Guidelines - Culture Media Preparation and Quality Control Testing

- Culture media should be tissue culture grade, preferably tested by MEA (mouse embryo assay) with appropriate purity for the intended purpose
- The use of commercially produced, quality-controlled tested media is recommended
- The integrity of the packages and appropriate delivery conditions should be controlled
- Documentation of QC and assays performed by the manufacturer should be provided
- Media should be used prior to the expiration date, and appropriate refrigeration for storage is required

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

ESHRE Guidelines - Culture Media Preparation and Quality Control Testing (con't.)

- Donor serum or follicular fluid is not recommended as a medium additive; commercial protein sources are preferred
- Utilisation of mineral/paraffin oil to maintain temperature, osmotic pressure, and pH during short-term manipulations may be preferred. Documentation of the QC tests for these reagents should be provided by the manufacturer
- Each lot of culture media and oil used should be recorded in each patient's worksheet for traceability

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Handling of Embryos, Zygotes, Oocytes, and Spermatozoa

- All procedures should be performed in a Class II hood equipped with heating stages and pre-warmed heating blocks
- Appropriate measures should be taken to ensure that all samples are maintained at 37°C during handling and observation
- Tissue culture grade disposables and pipetting devices for handling samples with record of each lot number is preferred
- Each sample should be handled individually and its treatment should be completed before moving to the next sample
- Patient identification and labelling on each disposable used is mandatory. Incubators should be organized to facilitate identification of samples for each patient.
- At each stage of the procedure, date, time, and operator identity should be recorded. Before receiving samples, the identity of the corresponding patients should be confirmed
- Identical procedures are to be followed for cryo samples

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Oocyte Retrieval

- Oocyte handling procedures should be performed close to 37°C to avoid temperature-induced depolymerisation
- Detailed written procedures for oocyte pick up (OPU) and culture must be available
- Follicular aspirates are usually checked for cumulus-oocyte complex (COC) at 8-60X magnification. Exposure of oocytes to light should be minimised
- Morphological criteria for COC evaluation should be specified and documented in each patient's worksheet
- Donor oocyte utilisation and freezing should be performed according to clinic rules, and an EU code must be used

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Sperm Preparation

- Semen analysis should be performed according to the current WHO manual
- Semen samples should be preferably collected in a tissue-grade sterile container without the use of condoms, creams, or lubricants. The container should be clearly labelled with the names of the couple
- All details should be recorded, including containers, time and place of collection, etc. For donor sperm, details including donor and clinic code should be recorded.
- Written procedures for medium type, sperm preparation technique, semen-to-medium ratio, centrifugation details, incubation time, etc. should be readily available
- In cases of surgically retrieved spermatozoa, surplus sperm after insemination should be cryopreserved for further ART cycles

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - Insemination and Further Culture

- Insemination of oocytes (IVF, ICSI)
- Scoring for fertilisation
- Embryo culture and transfer
- Cryopreservation of gametes, zygotes, and embryos
- Assisted hatching
- Preimplantation genetic diagnosis

A written manual for all protocols above should be available for laboratory staff. The details should be recorded for each patient's worksheet.

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - QC

- Working in compliance with a quality management (QM) system is mandatory according to EU tissue directives
- For QC, having a validated and written procedure for each aspect of the process, ensuring that all material used is tested for quality using an appropriate assay, verifying conformance to specifications, taking any corrective action to keep procedures under conformity, and maintaining and calibrating equipment on a periodic basis is mandatory

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ESHRE Guidelines - QA

- QA: A systematic monitoring of the testing of the entire process that can be performed to make improvements by identifying problems and errors
- Internal QA results should be evaluated on a regular basis. Indicators should be objective and relevant, and adequate thresholds set up
- Indicators: Number/rates of errors and adverse events, rates of normally fertilised oocytes, rates of good quality embryos, proportion of patients with failed fertilisation, OPR (ongoing pregnancy rate) for fresh and frozen ETs (embryo transfers), multiple pregnancy rate (MPR), and implantation rates
- Analysis should be performed in collaboration with the clinical staff
- To complement the QA, participation in external QA programmes, either commercial or in collaboration with other laboratories is recommended

Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.

gfa Global Fertility Academy

ASRM Guidelines for Human Embryology and Andrology Laboratories

Organization of the Laboratory; Definition of Services

- The institutional affiliation, where appropriate, plus the history and definition of services and markets served, should be clearly defined for each embryology laboratory
- The laboratory must undergo certification and accreditation by an appropriate agency and must be in compliance with any local, state, or federal licenses and permits
- The laboratory must satisfy Institutional Review Board requirements for any investigative procedures
- All embryology laboratories must be in compliance with Food and Drug Administration (FDA) regulations
- Embryology laboratories performing only ART procedures are not referral laboratories, but maintain specific affiliation with physician groups
- Embryology laboratories must have evidence of informed consent for all procedures prior to performing ART applications

The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

gfa Global Fertility Academy

ASRM Guidelines for Human Embryology Laboratories - Laboratory Personnel

- Embryology Laboratory Director: Prior to 2006, they must have an earned doctoral degree (PhD) from an accredited institution in a chemical, physical, or biological science as the major subject or a medical degree (MD or DO) from an accredited institution. Since 2006, the additional certification of High Complexity Laboratory Director (HCLD) or American Board of Bioanalysis Embryology Laboratory Director (ABB-ELD) is also required.
  - 2 years of documented experience in a program performing IVF-related procedures
  - Other specifications as defined by ESHRE
  - Off-site director should have similar qualifications, and must be present on-site for any accreditation or certification procedures. A Laboratory Director cannot direct more than 5 laboratories.
- Embryology Laboratory Supervisors: Should either meet the qualification requirements of Laboratory Directors or have earned a Bachelor's or Master's degree in chemical, physical, biological, medical technology, or clinical/reproductive laboratory science from an accredited institution and have documented training of at least 60 ART procedures

The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

gfa Global Fertility Academy

ASRM Guidelines for Human Embryology Laboratories - Laboratory Personnel (con't.)

- Embryology Laboratory Technologist: Should either meet the qualification requirements of Laboratory Supervisor or have earned a Bachelor's or Master's degree in chemical, physical, biological, medical technology, or clinical/reproductive laboratory science from an accredited institution and have documented training of at least 30 ART procedures
- Laboratory Supervisors and Technologists operate under the supervision of the Laboratory Director and their responsibilities are defined by ESHRE

The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

gfa Global Fertility Academy

ASRM Guidelines for Human Embryology Laboratories

- Details such as laboratory design and space, equipment and procedure manuals, laboratory safety and infection control, as well as QC and QA are as defined by ESHRE guidelines
- Satellite facilities are described as a facility with an off-site laboratory director and that has a separate identification number (SART) and director
  - A satellite laboratory and its director should meet the same standards as any other embryology laboratory as defined by the ASRM guidelines

The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.

Chapter 3 Conclusions

- As the success of ART procedures improves, QC methods will continue to evolve
- When most ART programs achieve a high rate of clinical success, issues of patient satisfaction will become more important in influencing a patient's decision about which program to choose for treatment
- We must continue to perform QC and QA activities that concentrate on improving patient outcomes, and bring us closer to the promise of a viable pregnancy for all our patients

References

- ALPHA Scientists In Reproductive Medicine. The Alpha consensus meeting on cryopreservation key performance indicators and benchmarks: proceedings of an expert meeting. *Reprod Biomed Online*. 2012;25(2):146-167.
- ALPHA Scientists In Reproductive Medicine, ESHRE Special Interest Group Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Reprod Biomed Online*. 2011;22(6):632-646.
- Cohen J, Alikani M, Gilligan A, Schimmel T. Laboratory procedures: setting up an ART laboratory. In: Gardner DK, Weissman A, Howles CM, Shoham Z, eds. *Textbook of Assisted Reproductive Techniques Laboratory and Clinical Perspectives*. 2nd ed. London, England: Taylor & Francis; 2004:27-35.
- Cutting R, Pritchard J, Clarke H, Martin K. Establishing quality control in the new IVF laboratory. *Hum Fertil (Camb)*. 2004;7(2):119-25.

References

- Elder K, Baker DJ, Ribes JA. Infection and contamination control in the ART laboratory. In: Elder K, Baker DJ, Ribes JA, eds. *Infections, Infertility, and Assisted Reproduction.* Cambridge, United Kingdom: Cambridge University Press; 2011: 305-331.
- Elder K, Elliot T. Cleaning protocols in the IVF laboratory. *J Assist Reprod Genet*. 2004;21(3):63-64.
- Magli MC, Jones GM, Lundin K, van den Abbeel E. Atlas of human embryology: from oocytes to preimplantation embryos. *Hum Reprod*. 2012;27 Suppl 1:i1.
- Magli MC, Van den Abbeel E, Lundin K, et al. Revised guidelines for good practice in IVF laboratories. *Hum Reprod*. 2008;23(6):1253-1262.
- McCulloh DH. Quality control: maintaining stability in the laboratory. In: Gardner DK, Weissman A, Howles CM, Shoham Z, eds. *Textbook of Assisted Reproductive Techniques*. 3rd ed. London, England: Taylor & Francis; 2009:9-25.

References

- Novo S, Barrios L, Santaló J, et al. A novel embryo identification system by direct tagging of mouse embryos using silicon-based barcodes. *Hum Reprod*. 2011;26(1):96-105.
- Novo S, Nogués C, Penon O, et al. Barcode tagging of human oocytes and embryos to prevent mix-ups in assisted reproduction technologies. *Hum Reprod*. 2014;29(1):18-28.
- The Practice Committee of the American Society for Reproductive Medicine, The Practice Committee of the Society for Assisted Reproductive Technology. Revised guidelines for human embryology and andrology laboratories. *Fertil Steril.* 2008;90(5 Suppl):S45-S59.
- World Health Organization Department of Reproductive Health and Research. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. Geneva, Switzerland: World Health Organization; 2010.