Chapter

Quality Management System in Medical Assisted Reproductive Technology (MART)

Delia Hutanu and Ioana Rugescu

Abstract

A quality management system (QMS) refers to an organization's broader approach to minimize deficiencies and errors, to meet regulatory compliance standards, and to satisfy a specified set of inherent characteristics during the health care services provided to patients. According to the European directives and recommendations (European Commission, 2006a, c, 2012; Council of Europe, 2013), working in compliance with a QMS is mandatory. The requirements cover the organization, management, personnel, equipment and materials, facilities/premises, documentation, records, and quality review. The IVF clinics should consider total quality management (TQM) as an option, especially in these days when escalating regulatory scrutiny increases the pressure for professional accreditation. TQM is an integrative philosophy of management for continuously improving the quality of services and processes and includes quality assurance (QA), quality control (QC), quality improvement (QI), and risk assessment and risk management. QMS must become an essential topic for those who are working in MART.

Keywords: quality management system, total quality management

1. Introduction

Medical assisted reproductive technology (MART) represents the sum of medical procedures used by healthcare providers in order to help infertile patients to achieve a pregnancy. It is a complex process, and the success depends on various factors such as patient-related and some other not patient-related. The present chapter focuses on the quality management system involved in assisted reproductive facilities. Taking into account all European directives and recommendations, as well as the national laws/regulations, the present material wants to summarize the present status of the quality management system.

2. Quality management system

A quality management system (QMS) refers to an organization's broader approach to minimizing deficiencies and errors, meeting regulatory compliance standards, and

satisfying a specified set of inherent characteristics during the health care services provided to patients.

According to the European directives and recommendations (European Commission, 2006a, c, 2012; Council of Europe, 2013), working in compliance with a QMS is mandatory. The requirements cover the organization, management, personnel, equipment and materials, facilities/premises, documentation, records, and quality review. Moreover, in vitro fertilization (IVF) clinics should consider total quality management (TQM) as an option, especially in these days when escalating regulatory scrutiny increases the pressure for professional accreditation. TQM is an integrative philosophy of management for continuously improving the quality of services and processes and includes quality assurance (QA), quality control (QC), quality improvement (QI), and even risk assessment and risk management. QMS must become the essential topic for those who are working in MART.

In the following pages, this chapter will bring together the most important information and tools that will allow the reader to start, implement, and maintain a QMS in his own unit, searched in literature, guidelines, and several consensuses. This chapter is intended to be a condensed pill of quality management information that will treat the reader's acute need for information on this topic.

The concept of "quality" has been defined over time in many ways and viewed from many angles and points of view, probably precisely because it has been and continues to be a topic of great importance and relevance. Any organization that respects itself and wants to be part of modern accreditation schemes has the entire activity based on the principles of a quality system. In 1979, Crosby defined five stages in the development of a quality management system and Garven in 1988 proposed a four-stage development model, so there it has been more than four decades since organizations are focused on good quality products or services. As a definition, although it seems simplistic, quality management; means coordinated activities to lead and control an organization in the field of quality.

2.1 Quality management principles

As an approach initially, eight principles were proposed as follows:

1. Process-based approach
2. Leadership
3. Staff involvement
4. Customer/patient orientation
5. Management approach as a system
6. Fact-based approach to decision making
7. Continuous improvement of performance
8. Mutually beneficial relationships with suppliers

In medically assisted human reproduction units, but especially in terms of testing, processing, cryopreservation, storage, distribution of reproductive cells and reproductive tissues in embryology and/or andrology laboratories it is imperative that the organization be based on ISO 9000 standards principles and other relational standards. In particular, the embryology part is especially important for the risk management and the minimization of errors.

As a result of the MART activity expansion and also taking into account the globalization that is taking place in the healthcare services sector, quality and risk management have become a necessity. In this context, in order to provide medical services that are intended to have the expected result in conditions of maximum safety, it was necessary that all licensed IVF units that offer such services operate in accordance with international standards, such as ISO 9001 [1], thus reflecting the current awareness of these services not only from a medical point of view but also from a commercial point of view.

The structure and organization of a licensed IVF unit may vary depending on a several number of factors, such as its size, and various types of organizational structures have been described in the literature by Dale, 1998; Heller and Hindle, 2003 [2, 3].

2.2 Legislation, certification, accreditation/licensing

Even if may vary from country to country, legislation, certification, and accreditation/licensing are often confused with each other or are seen as points of view in the management of an IVF unit, in fact, they are completely different concepts and all three work together for an integrated management system.

Legislation or the legislative requirements that an organization (IVF unit) must comply with in order to have permission to offer healthcare services. Compliance with legislative requirements is verified by an individual inspection of the unit and is confirmed by licensing/accreditation.

Generally, the legislative requirements are of the restrictive indicative type and provide precise indications regarding what an organization must comply with in accordance with the legislation in force.

The accreditation/licensing is the set of requirements and the process by which an organization must meet and is identified as complying, in order to be licensed / accredited and that they must maintain throughout the license/accreditation period. In EU member states, usually, this accreditation/licensing is issued by the Health Ministry and/or National Competent Authority. In other countries, the process may vary.

In addition, there is a certification that can be defined as a process by which an organization is identified as complying with and meeting certain criteria. In the case of IVF units, the ISO 9000 standards family applies (ISO 9001: 1994, ISO 9002: 1994, ISO 9003: 1994) with revised editions, for example, ISO 9001: 2002.

It is also possible to consider ISO 19011: 2002, as well as ISO 15189: 2003, and last but not least the ISO 17025: 2005 standard. The certification system implemented by ESHRE (European Society for Assisted Human Reproduction and Embryology-ARTCC) can also be considered. Regarding the legislative requirements for EU member states, the European Directives for Tissues and Cells and their implementation in the member state's national legislation must be taken into account. From this point of view, in the case of IVF clinics, we must consider the following:

- EUTCD Directive 2004 23 EC
- EUTCD Directive 2006 17 EC
- EUTCD Directive 2006 86 EC

In October 2020, the commission adopted its work program for 2021. The work program includes the revision of EU directives for tissues and cells. This revision comes after an evaluation of available translations of the preceding of the legislation, published in October 2019, confirming that the legislation had improved the safety and quality of blood, tissues, and cells used for transfusion, transplantation, or medically assisted reproduction. The evaluation also highlighted a number of gaps and shortcomings, which will be addressed to ensure the framework is up-to-date, fit for purpose, and future-proof. The initiative aims at updating the legislation in the direction of a more flexible alignment with scientific and technological developments tackling the re- emergence of communicable diseases, including lessons learned from the COVID-19 pandemic focusing on the increasing commercialization and globalization of the sector removing from legislation many technical provisions, which will allow a faster update of standards possibly merging the basic acts into a single instrument. The revision is planned to be adopted in the second quarter of 2022. The legal basis is provided by Article 168(4)(a) of the treaty on the functioning of the European Union [4].

Although the field of medically assisted human reproduction is very well known, quality management is much more used and implemented in embryology laboratories and it is based on monitoring cellular activity in terms of monitoring parameters in the workspace, equipment, etc.

It is well known that as a result of the action of some physic-chemical agents, the embryos are greatly affected, so that for correct implementation of a quality system all the parameters that can bring/produce changes regarding the embryonic development must be monitored.

Within an efficient quality management system, it is known that the performance indicators of the system play an important role, in our case the performance indicators of the activity.

In the quality management of an IFV unit, it is very important to be aware of the proactive tools in terms of risk management and to use these tools in a designed system in order to optimize the processes.

If we discuss the embryology or andrology laboratories, we must also standardize as much as possible the evaluation of oocytes, sperm, and embryos because they are considered to be essential components in the qualitative monitoring of the laboratory's processes.

Quality management is summarized as:

1. Quality control
2. Quality assurance
3. Quality improvement

From the point of view of risk management, the most important aspects to consider are:

1. Elimination of risk

2. Avoiding risks

3. Risk minimization

4. Risk transfer

5. Accepting risk

Regarding the management system:

1. Schematic of the processes

2. Analysis systems

3. Indicators and reference criteria

At this point, risk management is considered to be an integral part of proactive quality management [5, 6].

2.3 Indicators and benchmarks

Indicators: (we cannot control something we cannot measure).
That is why the indicators must be:

- Reliable- in order to measure something useful that is defining for the process to be monitored;

- Robust- in order to minimize foreign effects in the idea of measuring only the process to which it refers;

Routine data collection should not be difficult without a lot of extra work.

In order to optimize the activity and the results, it must be taken into account that the whole process is governed by the biology of gametes and embryos; therefore, it must ensure optimal conditions for gametes and embryos; protect gametes and embryos from physiological stress; and protect gametes and embryos from adverse external factors.

Cellular stress is a high-energy consumer and can also lead to altered gene expression and/or, for example, imprinting. Suboptimal embryonic culture may lead to irreparable changes that may affect the future conception product.

Another important step in quality management is the recognition of all the factors of influence that affect the processes in the embryology/andrology laboratories.

Possible sources of influence can be derived from the patient but also derived from clinical processes: ovarian stimulation, ovarian puncture during oocyte pick-up, embryo transfer, and luteal support.

The environmental design and construction of space, design of the workflow, equipment, work circuit, and air can influence the procedures. Among other factors that can have an influence on the process are: temperature, Co_2/pH, equipment calibration, and faulty operation.

The materials used in the IVF lab should be suitable for use, not to be embryo or cytotoxic, to be manufactured by a certified manufacturer in terms of quality (CE marking), or to be validated. All the methods used during the process have to be appropriate for the purpose, correctly chosen, SOP (documented), and lastly, the staff of the facility should be trained and skilled.

From the point of view of the sources of influence, the optimization of the system in the (embryology/andrology laboratories) for each component of the process must take into account the following:

1. Identify processes accurately.

2. Identifying the necessary pro factors to ensure the operability of the processes in optimal parameters.

3. Ensuring all of them as well as optimal control of these factors.

4. Identifying all the factors that can negatively influence the processes.

5. Ensuring that all possible interference is controlled, minimized and, if possible, eliminated.

6. Monitoring all processes and outcomes.

2.4 Key point indicators in IVF laboratory

Another important step for an efficient quality management system is the selection of key indicators for the medically assisted human reproduction process. In this case, the Vienna consensus on performance indicators in medically assisted human reproduction laboratories must be taken into account.

Performance indicators (PIs) are objective measures for assessing critical areas (patient safety, efficacy, fairness, patient fairness, timeliness, and effectiveness of medical treatments). In the activity of medically assisted human reproduction, quality indicators are needed for the systematic monitoring and evaluation of its contribution to patient care (ISO15189-2012), and it is a vital element in the quality management system (QMS) [6].

Any performance indicator must be reliable and robust, and the collection of data for tracking the indicator should be straightforward. In addition, the biological or technical process that we want to monitor must be defined with certainty. Key performance indicators (KPIs) are indicators that are considered essential for evaluating the introduction of a technique or process; setting minimum standards of competence; monitoring ongoing performance in a quality management system (for quality control (IQC), external quality assurance (EQA)); and benchmarking and quality improvement.

In general, the results of a series of key performance indicators (KPIs) will provide you with an adequate overview of the most important steps in the medically assisted human reproduction process [7].

The requirement for defining a process within quality management are:

1. Defining the process to be monitored,

2. Measuring only the desired process.

3. Minimization of external influences.

KPI	Competency	Benchmark
ICSI damage rate	≤10	≤5
ICSI normal fertilization rate	≥65	≥80
IVF normal fertilization rate	≥60	≥75
Failed fertilization rate IVF	<5	<5
Cleavage rate	≥95	≥99
Day 2 embryo development rate	≥50	≥80
Day 3 embryo development rate	≥45	≥70
Blastocyst development rate	≥40	≥60
Successful biopsy rate	≥90	≥95
Blastocyst cryosurvival rate	≥90	≥99
Implantation rate (cleavage stage)	≥25	≥35
Implantation rate (blastocyst stage)	≥35	≥60

Table 1.
KPIs in IVF lab.

In accordance with Vienna consensus [8], for a high-quality management system, three types of indicators have been identified that can be monitored:

a. Benchmarks - refer to the input indicators for assisted human reproduction activity and represent the connection between clinical and laboratory indicators.

b. Performance Indicators - this data should be documented and stored even if it is not currently reported in the control charts.

c. Key performance indicators - refer to the basic activity of the laboratory and always appear in the control diagrams (**Table 1**).

Considering the cryopreservation, the Alpha consensus on cryopreservation key performance indicators and benchmarks divided these into the following categories:

1. Cryopreserved oocytes KPI

2. Cryopreserved zygotes KPI

3. Cryopreserved embryos KPI

4. Cryopreserved blastocysts KPI

2.4.1 Oocytes

2.4.1.1 Morphological survival

This KPI was defined as the proportion of morphologically intact oocytes, based on the intention to inject, at the time of ICSI. Oocytes with oolemma or abnormal ooplasm at the time of ICSI should not be excluded (**Table 2**).

KPI		Competency	Benchmark
Morphological survival	Freezing	⩾50%	75%
	Vitrification	70%	85%

Table 2.
KPIS for morphological survival of cryopreserved oocytes.

As this KPI may be affected by the number of cases and/or the experience of the practitioner, different values have been assigned to achieve competence for both slow freezing and vitrification. Competency values are those that should be achieved by any practitioner, while reference intervals are aspirational targets.

2.4.1.2 Fertilization rate

The fertilization rate indicator was defined as the proportion of oocytes with two pronuclei at the time of fertilization verification (17 ± 1 h after insemination). The fertilization rate should be no more than 10% lower than that for the fresh oocyte in the center.

2.4.1.3 Embryonic development rate

The embryonic development rate indicator is defined as the proportion of embryos in the developmental stage that reach the stage of development specifically for the time of observation (2-cell stage at 26 ± 1 h after ICSI, 4-cells stage at 44 ± 1 h after insemination, 8-cells stage at 68 ± 1 h after insemination, morula stage at 92 ± 2 h after insemination, and the blastocyst stage at 116 ± 2 h after insemination).

The rate of embryonic development for embryos from vitrified oocytes should be the same as for the comparable population of fresh embryos from the bank of reproductive cells and tissues. For embryos from cryopreserved by slow freezing oocytes, some developmental delays may occur, but no more than 10–30% lower than that for the fresh embryos at the center.

2.4.1.4 Implantation rate

The implantation rate indicator was defined as the proportion of ultrasound-confirmed pregnancies with fetal heartbeat relative to the number of embryos transferred. The implantation rate for embryos from cryopreserved oocytes should be at most 10–30% lower than a comparable population of fresh embryos from the laboratory.

2.4.2 Zygotes

For zygotes produced by ICSI, the observations made during the ICSI procedure regarding the oocyte quality should always be recorded. This would allow a possible further analysis of the prevalence of oolemma/ooplasm abnormalities that could have been caused by the cryopreservation procedure.

2.4.2.1 Morphological survival rate

This KPI was defined as the proportion of morphologically intact zygotes immediately after thawing/devitrification compared to the number of morphologically

preserved zygotes. A morphologically intact zygote is one that is similar in appearance to a fresh zygote. The same survival rate should be achieved by slow freezing as well as vitrification.

2.4.2.2 Cleavage rate

This KPI was defined as the proportion of thawed/devitrified zygotes that divide to form a cleavage embryo. The rate of division should be the same as for the comparable population of fresh embryos in the bank of reproductive cells and tissues.

2.4.2.3 Embryonic development rate

The embryonic development rate indicator is defined as the proportion of embryos in the developmental stage that reach the stage of development specifically for the time of observation.

2.4.2.4 Implantation rate

The implantation rate indicator was defined as the proportion of fetal ultrasound-confirmed pregnancies with fetal heart rate relative to the number of embryos transferred. The implantation rate for embryos from cryopreserved zygotes should be no more than 10–30% lower than that for the comparable population of fresh embryos at the center (**Table 3**).

2.4.3 Embryos

For the KPI calculation, the embryos selected for cryopreservation should meet the criteria for an optimal embryo at the cleavage stage.

2.4.3.1 Indicators - post-freezing survival rate from a morphological point of view

The KPIs that assess the post-freezing survival rate for embryos are based on the proportion of thawed/devitrified embryos with 100% and ⩾50% of the total intact embryos. For the first category, embryos thawed with 100% of the total intact embryos, the competence value is 40% and the benchmark is 55%, and for the devitrified embryos, the competence value is 70% and the benchmark is 85%. For the category with embryos thawed with ⩾50% of the total intact cells, the competence value is 60% and the benchmark is 85% and for the devitrified embryos, the competence value is 85% and the benchmark is 95%. It should be noted that KPI values do

KPI	Competency	Benchmark
Morphological survival	70%	85%
Cleavage rate	The same as for the comparable population of fresh embryos at the center.	
Embryo development rate	The same as for the comparable population of fresh embryos at the center.	
Implantation rate	No more than 10–30% lower than that for the comparable population of fresh embryos at the center.	

Table 3.
KPIs cryopreserved zygotes.

not prevent the transfer of embryos with suboptimal morphology, as this may be the only opportunity for patients.

2.4.3.2 Development rate indicator after thawing/warming

For the calculation of this key performance indicator, only the embryos with 100% intact morphological structure will be considered after thawing/warming. Post-cryopreservation development includes cleavage and further development at the blastocyst stage, as well as implantation rate, defined as the proportion of ultrasound-confirmed pregnancies with fetal heartbeats relative to the number of embryos transferred.

The competence value for the rate of embryo development after thawing/warming should be at most 10% (relatively) lower than the comparable population of fresh embryos in the laboratory and the benchmark value should be the same as for the comparable population of fresh embryos at the center.

2.4.4 Blastocysts

As the in vitro growth rate is substantially affected by exogenous factors, no key differences were made between the performance indicators of post-freezing/ vitrification blastocysts and blastocyst stages (early, full, expanded blastocyst, hatched). Similarly, there is no recommendation on blastocyst collapse. The decision will be made by each lab accordingly. Regarding the reported results for cryopreserved embryos cryopreserved in the blastocyst stage, they are substantially better after vitrification than after slow freezing.

2.4.4.1 Survival rate

The blastocyst survival rate indicator after cryopreservation is defined as the proportion of surviving blastocysts relative to the total number of thawed/devitrified blastocysts and applies to blastocysts with at least 75% intact morphology.

2.4.4.2 Transfer rate

This KPI has been defined as the proportion of thawed/warmed blastocysts that are of sufficient quality to be transferred. This parameter assumes that the transfer decision is not subject to legislative limitations in terms of the number of embryos transferred per patient and does not take into account the transfer decisions of some suboptimal blastocysts. No matter the type of embryo transfer (single, double, or multiple).

2.4.4.3 Implantation rate

The implant rate indicator was defined as the proportion of ultrasound-confirmed pregnancies with fetal heartbeats relative to the number of blastocysts transferred (**Table 4**).

KPI		Competency	Benchmark
Survival rate	Freezing	70%	85%
	Vitrification	80%	95%
Transfer rate	Freezing	70%	85%
	Vitrification	80%	95%
Implantation rate		⩽10% lower than that for the comparable population of fresh embryos at the center.	The same as for the comparable population of fresh embryos at the center.

Table 4.
KPIs for cryopreserved blastocysts.

2.4.5 Sperm

The performance indicators for sperm are related to:

1. Sperm recovery rate

2. Sperm motility post-wash

The expected proportion of motile spermatozoa in the final washed preparation showed values of 90% for competency and 95% for the benchmark.

Sperm recovery rate, defined as the percentage recovery of progressively motile sperm after washing as compared to pre-washing, can be used as a laboratory KPI, providing useful information for inter-operator comparison and proficiency testing.

2.5 Clinical KPI

Performance indicators (PIs) are a valid method to be sure that the medical facility is of high quality and it operates within acceptable limits. In order to reach these goals in 2019 was published the Maribor consensus [9]. The paper recommends six PIs to be monitored in clinical work in ovarian stimulation for ART: cycle cancelation rate (before oocyte pick-up), rate of cycles with moderate/severe ovarian hyperstimulation syndrome, the proportion of mature oocytes at ICSI, complication rate after OPU, clinical pregnancy rate, and multiple pregnancy rate.

1. Cancelation is an unexpected event that can occur before the oocyte pick-up. The values depend on the population and is ranging from 3% in high responders, 20% in the general population, and up to 40% in poor responders

2. Rate of cycles with moderate/severe ovarian hyperstimulation syndrome: The excessive ovarian response is characterized by the growth of a large number of follicles. Several follicle thresholds have been proposed as critical for predicting the occurrence of OHSS. For example, 14 follicles larger than 11 mm in the general population or > 20 follicles larger than 11 mm for patients with PCOS

(polycystic ovary syndrome) [10]. The value of the rate of cycles with moderate/severe ovarian hyperstimulation syndrome is 6.43% and 10.61% in regular and PCOS groups.

3. The proportion of mature oocytes at ICSI. Oocyte retrieval rate (ORR) or the proportion of oocytes recovered is defined as the number of oocytes retrieved during oocyte pick-up over the number of follicles on the day of trigger (**Table 5**). The proportion of MII (metaphase II) oocytes at ICSI or the rate of mature oocytes was categorized as a reference indicator in Vienna consensus and it is the number of mature oocytes at ICSI over the number of cumulus-oocytes complexes retrieved.

4. The complication rate after oocyte pick-up: Complications of oocyte pick-up include bleeding (severe vaginal, intra-abdominal, or intra-peritoneal bleeding), infections (pelvic or ovarian abscess, pelvic infections), and severe pain or injury of pelvic structures. Vaginal bleeding appears the most common complication, with a reported incidence ranging from 0.01–0.1%. Peritoneal bleeding is a more serious complication of oocyte pick-up and has an incidence of 0.05–0.35%. Pelvic organ (bladder, bowel, and ureters) injury ranges from 0.04–0.77%. Severe pain requiring hospitalization is reported to occur in 0.065to 0.7% of the cases [11, 12].

5. Clinical pregnancy rate: Clinical pregnancy rate (CPR) is a commonly used criterion for measuring the effectiveness of ART, even though is not the final objective of the procedure. However, CPR is associated with clinician skills; therefore, it is relevant to be used as the main PI for ET. Clinical pregnancy is defined as a pregnancy confirmed on ultrasound by visualization of one or more gestational sacs. The benchmark value for CPR is problematic due to a lack of standardization. The Maribor consensus proposed that CPRs competency and benchmark values should be defined at the local level.

6. Multiple pregnancy rate: Multiple pregnancy or gestation is defined as a pregnancy with more than one embryo [13]. Multiple pregnancy is the most frequent and serious iatrogenic complication in ART. The value of it is ranging from 1.1 to 35.7%. lowering the occurrence of multiple pregnancies or deliveries is a desirable goal in ART to increase the safety.

A well-developed system in terms of quality management in the ART clinic must be taken into account the moment when following the monitoring and evaluation of the processes we find that there are problems. That is why an evaluation and correction process must be identified and developed. For a good administration of a scheme for the evaluation and solution of a nonconformity, it is absolutely necessary the root cause analysis (RCA). Such an analysis is the basis of a process that must take place after a problem has arisen.

RI	Benchmark value
Proportion of oocytes recovered	80–95% of follicles measured
Proportion of MII oocytes at ICSI	75–90%

Table 5.
Oocyte retrieval rate and proportion of mature oocytes at ICSI.

In this case, it is necessary to identify the factors that led to the appearance of a nonconformity; therefore, we will classify the factors as follows:

a. No contribution

b. Contributors

c. There is not enough data to establish

In the latter case, the need arises to create or access the necessary data in order to run a new classification. If we identify a number of factors, it is necessary to prioritize them in order to build a risk mold. Following the identification and ranking of contributing factors, an action plan must be developed and implemented. In general, in an ART clinic, the appearance of nonconformities is due to an accumulation of contributing factors and less to a single cause.

Also, the literature recommends that the term "cause" not be used in the reports prepared due to the possible psychological and/or legal impact.

In order for a noncompliance process to be effective, it must be effective and:

1. Leads to the normalization of operations in the shortest time.

2. Leads to a better understanding of the processes, including the performance we want within them.

3. It provides us with both previous and current information about these processes, we must be able to establish at least one key performance indicator, if not more, and be able to make control charts.

4. It offers us the possibility to analyze the processes in depth, using (ideally) additional data that we already have.

5. Leads to minimizing the possibility of similar situations in the future.

Due to technological progress, it has been possible for four decades to get from the first cultures of animal embryos to the culture and transfer of genetically tested human embryos. All these advances require quality control and also quality assurance methods in assisted human reproduction laboratories precisely to ensure repeatable processes. If progress is constant all specialists recommend the introduction of a total quality management system (TQM).

Quality control (QC) in the activities of the bank of reproductive cells and tissues is essential for its smooth running. Quality control must work in parallel with the specific activities of the bank. Recording the temperature of the equipment is an example of a quality control activity. All these control activities have been specially planned to be able to demonstrate and verify if, for example, that equipment produces the same results every time.

In terms of quality assurance (QA), this consists of complex methods of monitoring and evaluating all the processes in a bank. While quality control is concomitant with banking activities, quality assurance is a retrospective process. Also, for good quality management, we have to take into account the qualitative improvements (QI) through which we raise the performance of the activities in the ART clinic.

QI is different from QA and QC and is specifically designed to identify and correct problems or errors in the processes and activities of the ART clinic.

An example of QI is to adapt the laboratory's procedures to new zygote evaluation technologies precisely to improve the criteria for selecting embryos for transfer.

Total quality management (TQM) is a combination of all three of these topics.

This orientation does not change the structure of authority in the organization, nor does it diminish the essential role of top management. The inverted hierarchy emphasizes "service delivery" relationships and the importance of the consumer to the organization, which is why it is the perfect model for healthcare organizations.

An important part of QMS is the environment in the processing space: Laboratory staff must inspect the equipment to ensure that it is in good working order. Instruments used to determine temperature, gas concentration, and relative humidity must be recalibrated at the latest within 1 year.

If the manufacturer recommends another interval, the manufacturer's recommendation will be followed. The maintenance of all equipment must also be considered (according to the manufacturer's instructions and in accordance with the organization's policy).

The recommended monitoring parameters documented measures of continuous evaluation, correction, and monitoring of the activity, as well as, but not limited to:

1. Temperature in incubators (continuous and at three months measurement with separate equipment),

2. Temperature on heated surfaces (daily and at six months measurement with separate equipment),

3. Air temperature in the processing area and/or storage area (continuously and at three months measurement with separate equipment),

4. Temperature in refrigerators (daily and once a month measurement with separate equipment),

5. Temperature in containers of liquid nitrogen (or nitrogen level), (weekly or more often, depending on the evaporation rate of each container);

6. Determination of the level of CO_2 (or mixture, as the case may be) in incubators by direct or indirect measurement—continuous and at three months measurement with separate equipment;

7. Determination of positive pressure (continuous and at 12 months measurement with separate equipment).

2.6 Air quality

The first references to this topic appeared in the 1990s when the first correlations between various toxic agents (bacteria, dust, and VOC = volatile organic components) and embryonic development were reported. Johnson published a study on the influence of VOCs on embryonic culture [14] and Boone published studies on this topic [15]. Other authors published similar findings [16, 17]. Kao published a study that showed improved results based on air quality in the processing area [18]. At

present, it is mandatory in most countries to have purified air in the ART laboratory. Most laboratories use HEPA-type ventilation and purification systems (0.3 μm is the average of airborne particles found in measurements). Some of the ART laboratories that process reproductive cells have added ULPA filters, which bring improvements in air quality. It is recommended to have ISO class V regarding the number of airborne particles (grade A). It is also important to monitor the level of VOCs both in the air in the cell processing space and the level inside the incubators [19]. In any case, the HEPA/ULPA filtration system does not exclude the occurrence of VOCs neither in the air in the processing area nor in the incubator environment.

During the measurements carried out in various laboratories, aromatic hydrocarbons like (benzene, toluene, and xylene) were found, probably from the paints used as well as isoflurane due to the fact that the reproductive cell processing space is located in the immediate vicinity of the puncture room. Other VOCs found were propane and hexane, as well as aldehydes, probably from perfume and/or deodorants used by staff [20]. Incubation gas monitoring revealed benzene in CO2 cylinders, which leads to the recommendation to use special filters on the gas transport system [21].

Due to reports of ethylbenzene and benzaldehyde emissions from plastic consumables, special consumables that do not eliminate VOCs are currently being used [22]. Since VOCs are oil-soluble, even the closed culture system (under oil) does not protect embryos from these toxic substances.

Because over time, a number of VOCs from the outside air have been reported, taken over by the HEPA/ULPA ventilation system [23] or the air to be partially recirculated in case the outside air does not correspond to the norms. Fresh air supply of 30% is recommended to use, and also an active charcoal filtration system.

The quality system in an ART clinic is a component part of the total quality management system (TQM). The quality assurance system when performing the tests is formulated in the quality manual and can be developed according to the provisions of SR EN ISO/CEI 17025: 2002.

ISO 17025 is the standard that specifies the requirements for proficiency testing and/or calibration. This standard includes 15 quality management requirements and 10 technical requirements. These requirements show what an ART laboratory needs to do to be accredited.

2.7 Risk analysis

Risk analysis is a process that incorporates three components:

1. Risk evaluation

2. Risk management

3. Risk communication

The person in charge of the reproductive cell and tissue bank has, among other responsibilities, the one related to the implementation of a risk management and prevention policy. According to European Directives and recommendations (European Commission, 2006a, c, 2012; Council of Europe, 2013), work in accordance with a quality management system (QMS) is mandatory. Requirements cover organization, management, personnel, equipment and materials, facilities/premises, documentation, records, and quality assessment. It includes, but is not limited to:

- Providing risk assessment analyses for all activities in the ART clinic.

- Proactive risk assessments and preventive measures must be taken to minimize noncompliance.

- Organize the workspace carefully for the comfort of the operator to provide a safe working environment that minimizes the risk of distraction, fatigue; therefore, the occurrence of an error.

- Informing staff about how viral-positive patients to be treated and awareness of the risks of handling infected biological material.

- Ensuring easy identification of all PTAs (ancillary therapeutic products) to avoid misuse—risk analysis.

- Minimizing any risk of transmitting possible contamination through LN2.

Risk assessment is used to describe the general process or method of identifying hazards and risk factors that have the potential to cause harm (identifying hazards), and analyzing and assessing the risk associated with that hazard (risk analysis and risk assessment).

A danger is anything that can cause harm; these can be physical health hazards, such as chemicals, electricity, working on stairs, an open drawer, or mental health.

The risk is high or low that someone will be injured by these or other hazards, along with an indication of how serious the injury may be.

There are five steps in risk assessment:

1. Hazard identification.

2. Identification of the recipient of the possible injury (staff, patient, embryos, visiting equipment, relatives, etc.)

3. Risk assessment (what is the probability that each identified hazard will cause harm. Also, determine whether to reduce the level of risk. Even after all precautions have been taken, a certain risk usually remains. It must be assessed for each remaining hazard if the risk remains high, medium, or low).

4. Recording all the steps performed.

5. Regular reassessment of all hazards/risks and/or possible new hazards/risks.

For ease of use for biological reproductive material, the Euro-GTP II Guide has been created, which provides structured guidance on how to use the tools and methodologies developed by the EuroGTP II project, namely, the use of a systematic mechanism based on risk analysis from the point of view of the degree of novelty as follows:

- Assessing whether a new or modified process, service, or product has a significant degree of novelty.

- Determining the general risk arising from novelty.

- Determining an appropriate level of preclinical and clinical assessments to address and assess risk.

- Implement the result of risk assessment in routine practice and follow-up the results.

The general process requires to identify specific risks related to potential risk factors and the consequences of the risks. Each of these must be assessed individually to determine the residual risk of implementing the change. Assessment taking into account:

i. The probability of occurrence of the risk.

ii. The severity of the consequences if the risk arises.

iii. The probability that the source of the hazard for the consequences of the risk will be detected before the use of the product/provision of the service.

iv. The instrument does not cover the consequences of risk after embryonic implantation.

v. Any existing evidence that can be used to mitigate the risk.

The instrument shall take into account the number of individual risks assessed to calculate the percentage value of the overall risk.

The result of this risk analysis will be a single global risk score (on a scale of 0 to 100)the final risk score, which can be used to define the extent and/or need for preclinical and clinical assessment needed to support the proposal to change or introduce a new type of product or service [24].

3. Conclusion

Due to the fact that infertility is a growing problem in our society, the natality being on a downward trend, medical assisted reproductive technologies have an important role. The success rate depends on numerous factors, patient and non-patient-related. Among the latest, quality management systems with all the components of it play a crucial role in the whole process. The chapter summarizes this part of MART, emphasizing how and why the QMC can and does influence the final result.

Author details

Delia Hutanu[1*] and Ioana Rugescu[2]

1 West University of Timisoara, Biology-Chemistry Department, Timisoara, Romania

2 National Transplant Agency, Bucharest, Romania

*Address all correspondence to: delia.hutanu@e-uvt.ro

IntechOpen

References

[1] Alper MM, Brinsden PR, Fischer R, et al. Is your IVF programme good? Human Reproduction. 2002;**17**:8-10

[2] Dale B, Menezo Y, Cohen J, Di Matteo L, Wilding M. Intracellular PH regulation in human ovocyte. Human Reproduction. 1998;**13**:964-970

[3] Heller R, Hindle T. Essential Manager's Manual. New York: DK Publishing; 1998

[4] Available from: https://ec.europa.eu/health/blood-tissues-cells-and-organs/overview/revision-eu-legislation-blood-tissues-and-cells_en

[5] Leape L. L - A systems analysis approach to medical error. JAMA. 1997;**277**:307-311

[6] Mortimer D, Mortimer S. Quality and Risk Management in the IVF Laboratory. UK: Cambridge University Press; 2015

[7] Salinas M, Lopez-Garrigos MG, Lugo J, Sirvent JV, Uris J. Achieving continuous improvement in laboratory organization through performance measurements: A seven-year experience clin. Chemical Lab Medical. 2010;**48**:57-61

[8] The Vienna consensus: Report of an expert meeting on the development of art laboratory performance indicators; ESHRE Special Interest Group of Embryology 1 and Alpha Scientists in Reproductive Medicine

[9] Veljko Vlaisavljevic, Susanna Apter, Antonio Capalbo, Arianna D'Angelo, Luca Gianaroli, Georg Griesinger, Efstratios M Kolibianakis, George Lainas, Tonko Mardesic, Tatjana Motrenko, Sari Pelkonen, Daniela Romualdi, Nathalie Vermeulen, Kelly Tilleman, The Maribor report of an expert meeting on the development of performance indicators for clinical practice in ART, ESHRE Clinic PI Working Group. 2019

[10] Griesinger G, Verweij PJM, Gates D, Devroey P. Prediction of ovarian hyperstimulation syndrome in patients treated with corifollitropin alfa or rFSH in a GnRH antagonist protocol. PloS One. 2016;**11**(3)

[11] Levitt T. Production line approach. Harvard Business Review. 1972:41-52

[12] Özaltın SK, Savan K. Evaluation of complications developing during and after transvaginal ultrasound—guided oocyte retrieval. Ginekologia Polska. 2018;**89**:1-6

[13] Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, Mouzon J, Sokol R, et al. The international glossary on infertility and fertility care. Human Reproduction. 2017;**32**(9):1786-1801. DOI: 10.1093/humrep/dex234

[14] Johnson JE, Boone WR, Bernard RS. The effects of volatile compounds (VC) on the outcome of in vitro mouse embryo culture. Fertility and Sterility. 1993;**60**(suppl. 1):S98

[15] Boone WR, Johnson JE, Locke AJ, Crone MM IV, Price TM. Control of air quality in an assisted reproductive technology laboratory. Fertility and Sterility. 1999;**71**:150-154

[16] Cohen J, Alikani M. The time has come to radically rethink assisted reproduction. Reproductive Biomedicine Online. 2013;**27**:323-324

[17] Von Wyl S, Bersinger NA. Air quality in the IVF laboratory: Results and survey.

Journal of Assisted Reproduction and Genetics. 2004;**21**:347-348

[18] Kao YK, Higdon HL III, Graves-Herring JE, Boone WR. Where do mouse embryos thrive best? Comparation of mammalian embryo development under varying laboratory environments. Journal of South Carolina Academy. 2009;**7**(2):29-30

[19] Warrilow KC, Huynh HT, Gwozdziewicz JB, Schillings WA, Peters AYA. Retrospective analysis: The examination of a potential relationship between particulate (P) and volatile organic compound (VOC) levels in a class 100 IVF laboratory cleanroom (CR) and specific parameters of embryogenesis and rates of implantation (IR). Fertility and Sterility. 2001;**76**(suppl. 1):S15-S16

[20] Geisthovel F, Ochsner A, Gilligan AV. Environmental Evaluation of Assisted Reproduction Techniques Laboratories in Germany and the USA. Narasa Publishing Hause; 2001. pp. 184-198

[21] Merton YS, Vermeulen ZL, Otter T, Mullaart E, de Ruigh L, Hasler JF. Carbon activated gas filtration during in vitro culture increased pregnancy rate fallowing transfer of in vitro – Produced bovine embryos. Theriogenology. 2007;**67**:1233-1238

[22] Richardson ME, Trapp AC, Bernard RS. The effect of residual paint fumes on murine embryonic development. Bulletin Academic Science. 1997;**59**:131

[23] Lichtenfels AJFC, Gomes JB, Pieri PC, El Khouri Miraglia SG, Hallak J, Saldiva PHN. Increased levels of air pollution and a decrease in the human and mouse male to female ratio in Sao Paulo, Brasil. Fertility and Sterility. 2007;**87**:230-232

[24] Available from: https://tool.goodtissuepractices.site/