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New Laboratory Techniques in Reproductive Medicine

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New Laboratory Techniques in Reproductive Medicine

M. Montag, B. Toth, T. Strowitzki

Worldwide the routine IVF laboratory still relies on technology and instrumentation which is in principle the same as in the time when IVF started. However, the advances in instrumentation and micro-engineering as well as the increasing knowledge on oocyte and embryo biology will have an impact on how we will perform IVF in the near future. New laboratory techniques will enter the routine in assisted reproduction and lead to a shift in treatment possibilities. This overview summarizes some of the ongoing developments and tries to give a look into the next decade. **J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 33–7.**

Key words: human ART, automatization, time-lapse, biomarkers, omics

■ Introduction

During the last decade innovations in controlled ovarian stimulation (COS) have culminated in myriads of protocols, physicians can choose in order to meet the needs and requirements of an individual patient. The term i-COS (for individualized COS) is not only a synonym for this new approach, it also reflects the upcoming generation of patients and their demands in a world driven by modern technology.

However, there is a general agreement that despite the best patient-tailored stimulation protocols ever, an increase in the overall success rates in assisted reproductive treatment (ART) does also depend on the developments and innovations in the embryologic laboratory. This may eventually lead to an individualized laboratory scheme (i-lab) for each patient or even for individual oocytes from a single patient.

But are we yet there? The aim of this article is to summarize the present state of ART technology in the IVF laboratory and to highlight those technologies which are at the cutting edge from bench to routine application.

■ To Reach Out For the Best Gametes

In the past gametes (sperms as well as oocytes) were primarily chosen based on

their structural as well as their functional integrity by light microscopy.

■ Spermatozoa

The introduction of ICSI somehow changed the view on what is a “perfect sperm”, as several studies showed that neither morphology nor motility seems to play a major role [1]. This has recently been challenged by a more detailed look on sperm morphology using high magnification microscopy [2]. The first studies were very enthusiastic and promising and consequently intracytoplasmic morphologically-selected sperm injection (IMSI) attracted a lot of interest in the ART community [3, 4]. However, the results of a randomized study were not in favor of applying IMSI to unselected patients [5]. The present consent is, that only selected patient groups may benefit from IMSI. However, IMSI is still a matter of debate, especially as gross morphological aberrations and also nuclear vacuoles can be detected up to certain extend by conventional Hoffman modulation contrast microscopy, too [6]. Therefore experienced embryologists may select morphological good sperm even prior to IMSI, thus the beneficial effect is not apparent.

At present, apart from IMSI, numerous other technologies for the selection of spermatozoa in ART are under investigation. Some focus on markers of the sperm surface like Annexin V [7] and hy-

aluronic acid binding [8], others on detecting DNA damage and fragmentation (reviewed by [9] and more recent technologies apply RAMAN spectroscopy [10] or atomic force microscopy [11]. Some of these topics, like DNA fragmentation [12], are controversially discussed, and major trials in order to proof the benefit of certain selection criteria and classify the subgroup of patients which will benefit are still missing. Nevertheless, we may expect within the next couple of years that there will be innovative approaches in andrology which may impact ART laboratory procedures.

■ Oocytes

Morphology

In contrast to spermatozoa, oocytes are not constantly generated in the ovary from stem cells. Instead all oocytes for the entire lifetime are present in the female fetus at 6 months of gestation and get less from that time on. The long exposure until a woman decides for children, makes them extremely sensitive to internal and external influences, which may affect oocyte quality as well. Since the beginning of assisted reproduction, selection of good oocytes was mostly based on morphology. Nowadays, numerous studies proved that oocyte morphology is not a reliable predictor (reviewed by [13]) and a recent consensus workshop from Alpha and ESHRE [14] concluded, that the only morphological feature in oocytes which should be taken

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seriously, is the aggregation of smooth endoplasmic reticulum [15]. This does not mean that oocyte morphology *per se* is not important; it rather underlines the problem that morphology *per se* is not a strong classifier to exclude oocytes from fertilization and further use in ART as these might still have a considerable chance to result in an ongoing pregnancy.

Chromosomal Integrity

The quality of an oocyte is mainly determined by three aspects: chromosomal integrity, nuclear maturity and cytoplasmic maturity. Chromosomal integrity is mainly dependent on the age of the woman. The decrease of pregnancy rates beyond the age of 35–37 as well as the concomitant increase in miscarriage rates and the possibility to investigate the genetics of oocytes [16] or embryos [17] has led to the concept of pre-implantation genetic screening (PGS). Until recently, PGS was mainly performed by embryo biopsy at the 8-cell stage and analysis of 5 to 10 chromosomes by fluorescent in-situ hybridization (FISH). The enthusiasm at the very beginning was followed by the discouraging results of several studies which all showed that PGS in combination with FISH did not give better success rates (reviewed in [18]). Consistently, professional societies uniformly recommended not applying embryo biopsy on day 3 in combination with FISH for PGS [19, 20]. The ultimate proof was presented recently, showing that if two embryos are transferred at the same time of which one was biopsied and the other not, it was predominantly the non-biopsied embryo which did implant [21].

Another major point regarding the benefit of PGS was that chromosomal mosaicism present in day 3 embryos makes these cells not a suitable target for PGS. A recent systematic review and meta-analysis reported that mosaicism was found in up to 70% of the investigated embryos [22]. Consequently the concept of doing PGS with polar bodies or trophoblast cells was taken up again [23]. Together with the introduction of robust protocols for screening of all chromosomes by array-comparative genomic hybridization (CGH) this leads to the enrollment of several new studies. Especially the European Society for Human Reproduction and Embryology (ESHRE) has initiated a prospective randomized multi-centre study which aims to give an answer if PGS by polar body biopsy and array-CGH (Fig. 1) will decrease the time to pregnancy and ameliorate the outcome. In preparation for the multicentre trial a feasibility pilot study was undertaken which clearly showed that 80% of all oocytes from women with a mean age of 40 were chromosomally aneuploid [24, 25].

Nuclear and Cytoplasmic Maturity

Although nuclear oocyte maturity seems to be such an easy characteristic to look at, it is actually not. Polarization microscopy revealed, that the presence of the 1st polar body does not necessarily predict the metaphase-II stage [26, 27]. The presence of spindle fibers between the polar body and the ooplasm characterizes an oocyte in the transition state from anaphase to telophase. The underlying physiology is the meiotic cell cycle and the course of this has been evaluated

in oocytes matured in vitro as well as in vivo [27, 28]. A recent investigation showed, that the presence of the metaphase-II spindle is dependent on the time after hCG trigger and that this may have an impact on the timing of fertilization and even on further development up to the blastocyst stage [29]. Based on this, nuclear maturity seems to play an important role and the actual state of an oocyte within the meiotic cell cycle may sometimes been easily overlooked.

Looking at cytoplasmic maturity is much more difficult. There is actually no direct approach to do so; rather the discussion is on indirect measures which may allow for identifying the follicular background of an oocyte. The two most prominent methods are zona birefringence imaging and cumulus gene expression studies.

Zona imaging has initially been investigated in a retrospective study comparing the birefringence in the zona pellucida of oocytes which later resulted in embryos leading to pregnancy and in embryos which failed to implant. Embryos competent for implantation showed higher zona birefringence compared to others [30]. Subsequently this approach triggered several studies which proved the applicability of this concept [31, 32]. It finally resulted in the development of an automatic zona detection module which calculated online a zona score and allowed for the objective selection of oocytes [33]. Selection of oocytes by automatic zona imaging allowed excluding oocytes which have no potential to develop to blastocysts in one study [34] and other studies reported on higher implantation and pregnancy rates [32, 35] and lower miscarriage rates [36].

Another possibility to assess oocyte maturity is the analysis of the gene expression pattern in cumulus cells. As cumulus cells are important in coordinating oocyte growth within the developing follicle, analysis of their transcriptome allows for an indirect assessment of oocyte quality as well as embryo quality [37]. Several studies have shown the feasibility of cumulus transcriptome analysis in the field of human IVF, however, at present the technique still needs to be developed further to be applicable in routine practice [38].

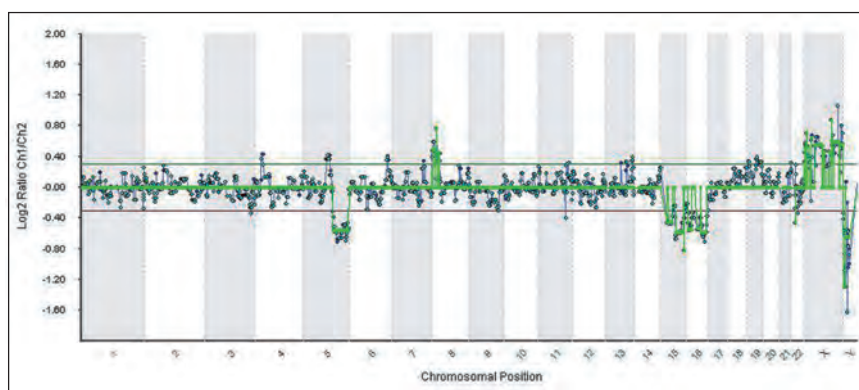


Figure 1. This example shows the result of an array-CGH analysis of the 1st polar body from an oocyte taken from a patient with a maternal reciprocal translocation 46,XX,t(5;8)(q22;p11.2). The possibility to detect numerical (loss of a chromatid 15 and 16) and structural chromosomal aberrations (gain of a chromatid 8p and loss of a chromatid 5q) by array-CGH is obvious. Reprinted in part with permission from [Montag et al., J Reproduktionsmed Endokrinol 2010; 6: 498–502].

■ From Subjectivity to Objectivity in Embryo Classification

The major problem of most selection strategies in the ART laboratory is the impact of subjectivity. This is obviously the case with every decision based on morphology and especially appearance of embryos can deceive us. Hence there is a clear need for objective parameters which allow identifying at whatsoever stage the one embryo among others which will have the best chance to implant. Naturally such an approach must be non-invasive and the analyzed embryo should survive the diagnostic procedure and hence be still available for embryo transfer thereafter. The problem of using PGS at the early embryo stage has already been discussed. Accumulating data on PGS and array-CGH by trophectoderm biopsy at the blastocyst stage may change this and first monocentric studies show, that PGS in combination with comprehensive chromosome screening does give high implantation and pregnancy rates in infertile patients [39, 40]. However, PGS as well as any other selection method can only be applied if there is something to select, meaning that sufficient oocytes or embryos are available.

Metabolomics

A very appealing idea is the use of metabolomics in order to assess the implantation potential of an embryo. This concept is based on the uptake from or the release of products to the surrounding culture medium by the growing embryo. The analysis of these products should give a picture of the metabolic activity of an embryo. This has been applied for glucose [41] and amino acids [42], however, until to date these strategies have not reached the clinical routine and are still considered experimental.

A very promising approach was based on a viability score which has been established for an algorithm calculated on the absorption spectrum of unspecific functional groups in the near infrared in spent culture medium from human embryos. Changes in the concentration of these functional groups in the culture medium due to the metabolic activity of the embryo would directly change the viability score [43]. The applicability of the viability score was proven in a pilot

study, however, a randomized multi-centre follow-up study was terminated pre-term because the study group showed no benefit from the diagnostic intervention [44] and as a consequence the device is no longer on the market.

Oxygen Respiration Measurement

Another approach which is somehow linked to metabolomics is oxygen respiration measurements in the culture medium of oocytes and embryos. This technology was first explored in the bovine [45] and later applied in experimental settings in human ART. The overall results were very encouraging, as oxygen respiration correlated to oocyte maturity [46]. Even more important, oocytes which generated embryos which implanted showed clearly different levels of oxygen respiration compared to embryos which did not implant [47]. The drawback of this technology at present is that it is not available for routine application. Although there was a device which combined oxygen respiration with time-lapse it had only one oxygen sensor. This is acceptable in research setting or in animal studies but not in therapeutic IVF where cross-contamination is a severe issue. Therefore the use of this technology is at hold until another sensor strategy has evolved.

■ Morphokinetic Analysis

Conventional Morphokinetic Criteria

For the identification of implantation competent embryos also criteria other than embryo morphology were investigated in the last decade, like pronuclear scoring [48] and early cleavage [49]. More recently, the benefit of these techniques was controversially discussed and especially the introduction of time-lapse imaging has brought new insight into the kinetics of the underlying processes [50, 51]. Based on this one can conclude, that these criteria still have a certain value, provided that they are applied in a very strict and timely coordinated way.

Time-lapse Imaging: The Big Step Forward?

In view of all the different approaches which were described above, the most prominent and promising technology at present, time-lapse imaging, sounds

very simple. The principle of time-lapse imaging is the assessment of morphological changes in developing embryos over time (Fig. 2). Hence it is a combination of morphology and cleavage kinetics and can be best described by the term morphokinetics.

The two prominent time-lapse systems which are in use at present can be classified according to their working principle: one is based on a camera device which is placed in a standard incubator, whereas another one is an integrated unit of an incubation device with build-in time-lapse capabilities. Several studies have shown that the principle of continuous observation does not harm embryos [52] and at least one study reported improved blastocyst rates in a closed time-lapse incubation system compared to a standard incubator [53].

Time-lapse imaging was applied in a retrospective study to identify the morphokinetics of implanting embryos compared to non-implanting embryos and several criteria with a high predictive value were described [51]. Besides, time-lapse imaging helps to explain some aspects of early development which were expected to be like that but for which the exact nature of their kinetic course was unknown, like pronuclear morphology [50]. In view of this, the time-lapse technique can be used for objective classification of embryo quality using software which identifies those patterns giving rise to implanting embryos. However, the overall benefit of achieving improved pregnancy and live birth rates with time-lapse imaging is still missing and further studies are needed in order to reveal the potential of this highly promising technology.

■ What is On the Horizon?

In general, the way how we perform IVF in the laboratory today has not changed much since the early days. But given the fast progress in computer technology and in engineering, new ideas and concepts do enter the field of ART and will impact in the near future laboratory as well as medical practice.

New IVM strategies

Despite all efforts to identify the one and only embryo out of a large cohort following controlled ovarian stimula-

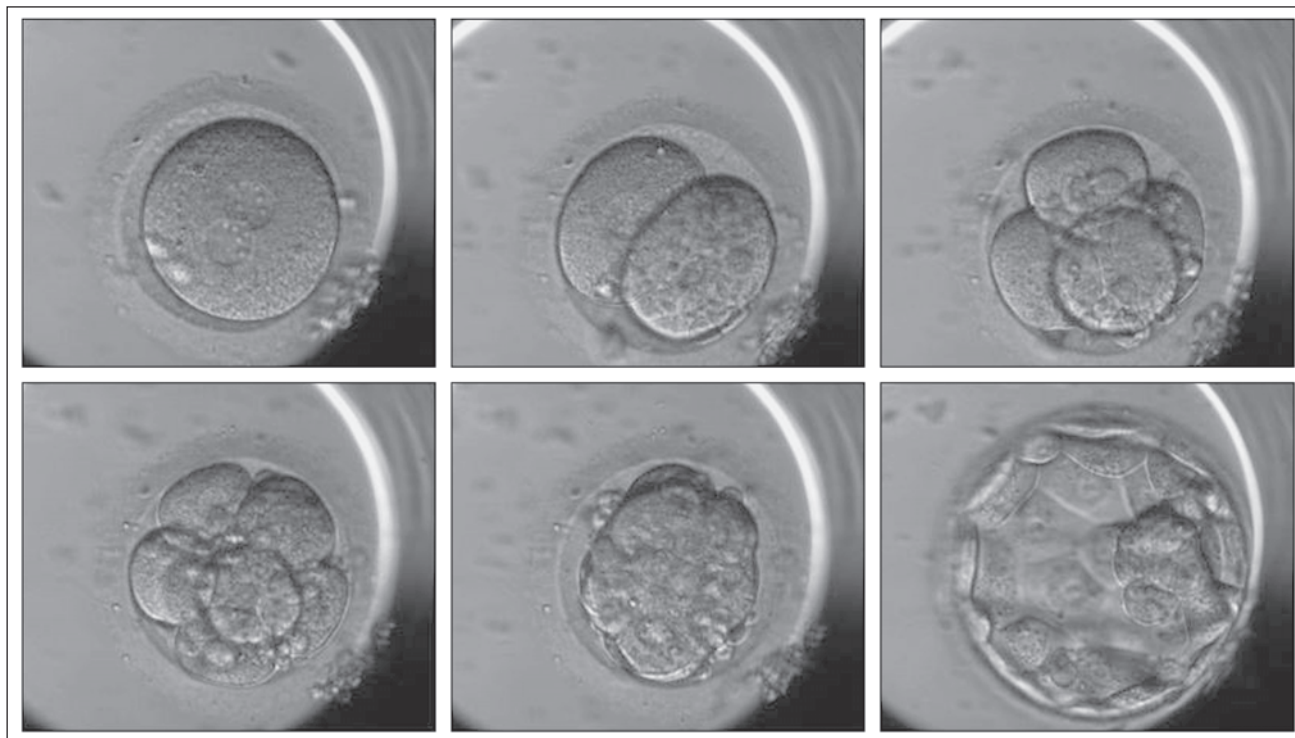


Figure 2. Series of time-lapse images taken from one embryo starting at the 2PN stage (upper left) up to the expanded blastocyst stage (lower right). Images were taken at 19.1, 33.1, 47.1, 70.3, 89.3 and 114.1 hours after ICSI and following transfer this embryo implanted and gave a pregnancy. Analysis of cleavage times and intervals between cleavages allows for subtle differentiation between individual embryos and helps choosing the one with the most synchronous and timed development.

tion (COS), there are some old concepts which may be revived within the next decade. One example is in vitro maturation (IVM). This technique was implemented a decade ago but today is only applied by few laboratories and far away from being an alternate to COS [54]. However, the better understanding of oocyte physiology and in particular of the final steps of maturation from GV to M-II does throw a new light on IVM and at present new concepts are investigated in pre-clinical trials [55]. This might lead to a change at least for some patients and in combination with the more objective selection technologies described above it will give a new stimulus to further investigate the effects of COS on oocyte and embryo quality.

Robotic Concepts

Automatization of laboratory procedures is upcoming in IVF. This does include strategies to perform robotic ICSI [56] as well as the use of microfluidic devices for embryo culture [57, 58] incorporating automatic exchange of culture media, sampling of media aliquots for diagnostic purposes and time-lapse imaging [59]. Although one or the other of these aspects has been realized under

experimental conditions, the combination of all of them in a single device is a very ambiguous project and not yet around the corner.

Conclusions

Within the last decade we have seen a constant rise of innovations in the IVF laboratory and this development is still ongoing. Although some very promising innovations like metabolomics have failed in clinical trials, the underlying concept remains interesting and has to await the proper devices which will probably solve the issue. Industrial sponsoring will become a driving force in the IVF lab as new approaches do get quite complicated, require huge financial investigations and are not easy to implement without having a strong back-up which will help solving pre-clinical trial work as well as regulatory and legal issues. For the time being we have to rely on those procedures which are proven to be safe and to be applicable in the daily routine.

Conflict of Interest

No potential conflict of interest to this article was reported.

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