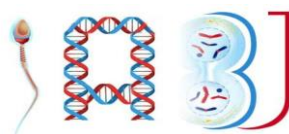


## Indonesian Andrology and Biomedical Journal



### Literature review

## Technology Updates in Male Infertility Management

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### Abstract

**Background:** Technologies are replacing manpower many fields including medical field. Several devices have been marketed for replacing/reducing manpower in the medical field including male infertility. Here we reviewed several technologies that developed in male infertility.

**Review:** Computer assisted sperm analysis (CASA), Automatic assessment of biochemical marker of seminal plasma, B-mode ultrasound, and automatic sperm cryopreservation can be applied routinely. Several updates i.e. automatic histopathology assessment, ultrasound strain elastography, magnetic resonance imaging (MRI) stronger than 3.0 T, Artificial intelligence for predicting the presence of sperm in azoospermia cases, automatic sperm selection, and automatic intracytoplasmic sperm injection (ICSI) need more studies before their application.

**Summary:** Prudent choice based on valid studies is needed in order to give a comprehensive management to patient with male infertility without using useless technology.

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## 1. Introduction

Technology continues to develop in all fields including medicine. Automation and artificial intelligence are replacing manpower in medical field. Some technologies have been applied routinely while others still need further development. It is important for health professional and hospital to collect information in order to understand the benefits, compare the value of these technology and decide to use them or not. Here we review some medical technology updates related to the field of Andrology with focus on imaging, automation, and artificial intelligence.

## 2. Diagnosis of male infertility

### 2.1 Computer Assisted Sperm Analysis (CASA)

The first commercial Computer Assisted Sperm Analysis (CASA) system was the CellSoft™ system, which first distributed in 1985. The CASA cannot analyze sperm flagellar beating directly and must rely on tracking the movement of the sperm head. Brownian motion of immotile objects with similar size to sperm head can be counted as motile sperm. Immotile spermatozoa also can be stirred by the flagellar beating of nearby motile spermatozoa and classified as motile spermatozoa.<sup>1</sup>

Nowadays, CASA has progressed greatly. Higher resolution digitizer, higher number of frame captured, software improvement such as advanced Brownian motion and drift filtering, tail detection, give a better result than what we got in the earlier version.

Recently, more compact CASA has been available. It can be used as screening tool because it gives reliable results for diagnosing oligozoospermia and asthenozoospermia. However, when the clinicians need more accurate results such as detail concentration, motility in very low number of sperm, or want to confirm the azoospermia, manual method gives more reliable results.<sup>2</sup>

CASA has several advantages through its ability to count more detail parameters, but there are some potencies of misinterpretation. Using CASA doesn't mean that operator only needs to put the sample and receive the result. He/she should keep the temperature of the semen, perform seminal plasma examination, homogenize the sample well prior to examination, and cross check the result before it's printed.<sup>3</sup>

### 2.2 Automatic assessment of biochemical marker of seminal plasma

Several seminal plasma contents are important for infertility diagnosis. The role of fructose and neutral alpha glucosidase for discriminating obstructive and non obstructive azoospermia are well documented.<sup>4,5</sup>

The methods for semen biochemical marker of seminal plasma have been develop from manual, semi-automatic, and fully automatic. The automatic method has several advantages such as simple reagent preparation, smaller amount reagents needed for each test, few errors, reduction manpower, simple calibration, and quality control procedure.

At present, automatic method is applied in the detection several seminal plasma markers such as neutral alpha glucosidase, acid phosphatase, fructose, and zinc.

Several manufactures offered their manual and automatic blood analyzer as seminal plasma biochemical marker. The negative displacement method for semen aspiration using these analyzer should be studied more since it is recommended to use positive displacement pipette for handling viscous sample like seminal plasma.<sup>6,7</sup>

It also should be noted that the usefulness of biochemical plasma for discriminating obstructive and non obstructive azoospermia can be replaced with ultrasound imaging. Moreover, biochemical assessment is not able to differentiate whether distal obstruction is caused by ejaculatory duct obstruction, congenital absence of vas deferens, or seminal vesicle hypoplasia as ultrasound is capable.

### 2.3 Histopathology assessment

The Johnsen score has widely used for evaluating histological specimen of the testis. Johnsen scores were arranged for quantifying spermatogenesis in seminiferous tubule section. The score is given according to the presence of cell arranged in the order of maturity. Score 10, 9, and 8 are given for the presence of spermatozoa in tubule. Score 7 or 6 for the presence of spermatids with no further mature cells are presence. Scores 5 or 4 describe that spermatocyte are presence with no presence of further mature cells. Score 3 is given when spermatogonium is the only germ cell presence in the tubule. Score 1 is given when

Setoli cells is the only cell presence in the tubule. While score 1 describes all cells are absence in the tubule.

Ito et al develop a toll for determining Johnsen scores automatically using artificial intelligence. Promising result with the average precision 99.5% has been reported for the first time in 2021.<sup>8</sup> More studies are needed for determining the benefit of this artificial intelligence tool.

### *Imaging:*

#### 1. Ultrasound

Ultrasound have been improved significantly in the last few decades. It is well known that Ultrasound (US) B-Mode offers greater accuracy in testicular measurement than orchidometer especially in specific clinical conditions (i.e. hydrocele, inguinal testis, etc), several pathologies in the testis and epididymis. Color Doppler US may asses vascular characteristic in the testis and plexus pampiniformis. While transrectal ultrasonography (TRUS) are useful for assessing obstructive azoospermia.

Ultrasound strain elastography has been developed to asses tissue stiffness as an image. Compression produces strain within the tissue. The strain resulted would be low in stiff tissue while the strain would be high in softer tissue. Based on this principle, the stiffness of tissue can be quantify using the strain value. K $\ddot{u}$ c $\ddot{u}$ k $\ddot{u}$ durmas et al found that strain ratio are significantly different between patients with normal and abnormal semen parameters. They also found that there is a negative correlation between strain value of testicular tissue and sperm concentration in abnormal semen parameters group.<sup>9</sup>

Moreover, Li et al conducted a study evaluating strain ratio between obstructive and non obstructive azoospermia patients and revealed that average or low strain was seen more in NOA patients (81.7%) compared to OA patients (16.3%).<sup>10</sup> Briefly, it can be stated that strain elastography may be more sensitive and objective than palpation for determining testicular consistency.

#### 2. MRI

MR imaging is better than transrectal US for examining male infertility patients. It's better soft-tissue contrast and multiplanar abilities can portray the detail anatomy of male reproductive tract including seminal vesicles, prostate, and ejaculatory ducts. It is recommended to use MRI

in patients with inconclusive TRUS finding.<sup>11</sup> The minimal magnetic field strength for pelvis imaging is 1.5 T.<sup>12</sup> Higher field strength facilitates higher signal-to-noise ratio. MRI using 3.0 T may reduce the use of uncomfortable endorectal coil for prostate examination.<sup>13</sup> The strongest magnetic used for MRI is 10.5 T, but no publication the use of this highest magnetic field for male infertility.

### *Artificial neural network for predicting the presence of spermatozoa in azoospermia cases*

The prediction of spermatozoa presence prior testicular biopsy is remain a challenge. The processes is clinician dependent until now. Samli and Dogan developed an artificial neural network for predicting the presence of spermatozoa prior to surgical sperm retrieval in men with non obstructive azoospermia and compared it to standard logistic regression model. The model which using age, infertility duration, hormonal levels, and testicular volumes had a clinically acceptable sensitivity as they reported significantly higher sensitivity than the logistic regression model (68% vs 28%,  $p < 0.0001$ ).<sup>14</sup>

### 3. Treatment

#### *3.1 Automatic sperm selection*

One potential sperm selection technique that could be used for automated system is sperm electrophoresis. Electrophoresis able to separate spermatozoa based on their surface charge. It has been known that spermatozoa with negative surface charge (NCS) seem to be more mature and having more intact chromatin or lower DNA damage.<sup>15-17</sup> NCS sperm also give better IVF outcome including fertilization rate, blastocyst rate, implantation rate and clinical pregnancy rate.<sup>17</sup> Interestingly, it also reported that more female embryos are resulted by this zeta method combine with DGC compared to DGC only.<sup>15</sup> There are two methods of sperm electrophoresis: electrophoretic and microelectrophoresis sperm separation. Using both methods, motile, and morphologically normal spermatozoa could be isolated automatically. We have found 4 prospective studies that support the benefits of the zeta method of sperm selection in increasing pregnancy rates and no study has revealed any disadvantages of this method to date. However, a meta-analysis is still needed to further confirm the

benefits of this method.<sup>15,18–20</sup>

Individual sperm should be remained chosen directly by the operator based on morphology and motility assessment for ICSI. Javadi and Mirroshandel developed an artificial intelligence for detection of abnormal sperm morphology that work well for unstained sperm and low-resolution images. Their study reported that their algorithm had achieved F0.5 scores of 84.74%, 83,86%, and 94.65% for detection of abnormality in acrosome, head, and vacuole.<sup>21</sup>

Image analysis software for highlighting of the most fertile sperm by color automatically has been marketed (see: <https://www.radicalindia.com/life-ICSI.php>). However, no publication found about the result of the ICSI result between this computerized and manual sperm selection.



**Figure 1.** Sperm selection for ICSI using RI ICSI (taken from: <https://www.radicalindia.com/life-ICSI.php>).

### 3.2 Robotic ICSI

The first paper reported robotic intracytoplasmic sperm injection (ICSI) is published in 2011. The system developed require minimal human involvement (a few mouse clicks).<sup>22</sup> However, no report about the application of this system for human until now. One of the reasons is the oolemma penetration before sperm injection using image processing algorithms remain unreliable. Electrical resistance increase is reported can be used for confirming oolemma penetration and would become one important step for developing a more reliable robotic ICSI in the future.<sup>23</sup> More studies are needed for the application of robotic ICSI in the future.

### 3.3 Automatic sperm cryopreservation

Programmable freezing provides a precise step of cooling rates through the use of automated programmable liquid nitrogen freezers. Sperm samples which mixed with cryoprotectants are put into cryovial then arranged on a plate. Samples are frozen using a freezing rate of decreasing the

temperature from room temperature to a first temperature set point. Next, the freezing rate is increased until second temperature set point. Once the second temperature set point is achieved, samples will be plunged into liquid nitrogen (-196 °C).

Manual sperm ultra-rapid freezing using cryovial showed significant decrease of motility compared to slow programmable freezing. However, no difference in DNA damage in both results.<sup>24</sup> Meanwhile, Kalludi et al showed no significant different in term of motility, viability, and DNA damaged between manual rapid freezing with slow freezing with programmable device.<sup>25</sup> It can be concluded that programmable device is not superior to manual method if the cooling step is near to similar.

The usefulness of automatic sperm cryopreservation is also limited in conditions when a high number of samples are required to be cryopreserved at the same time. It may be explained why this machine is more commonly used in veterinary field. Furthermore, programmable sperm freezing is not as efficient as it thought because of latent heat released by the sample leading to delays in freezing rates, thus being detrimental for spermatozoa.<sup>26</sup>

## 4. Conclusion

Several devices have been marketed for replacing/reducing manpower in the medical field including male infertility. Several technology updates can be applied in male infertility field while the others need more studies before their application. Prudent choice based on valid studies is needed in order to give a comprehensive management to patient with male infertility without using useless technology.

## Conflict of Interest

The authors state there is no conflict of interest.

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