Novel Home-Based Devices for Male Infertility Screening

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Key Points

- Approximately 30% of infertile couples fail to proceed with a male fertility evaluation prior to proceeding with ART.
- Many men struggle with providing a semen sample in a laboratory setting and believe it to be stressful and difficult.
- Home-based semen testing typically only provides users with sperm concentration, but it may facilitate a formal evaluation and potentially avoid unnecessary diagnostic and medical treatment for the female partners.
- Conventional laboratory semen analysis evaluates pH, volume, concentration, motility, morphology, viability, and markers of oxidative stress. Continued comparison between laboratory and smartphone-based screening should be performed.
- The YO Home Sperm Test provides accurate and precise results of motile sperm count when compared to computer-assisted semen analysis.

66.1 Introduction

Infertility is the inability of a couple to conceive after 12 months of unprotected sexual intercourse. Of the total infertility cases, 50% are attributable to male factor alone or combined with female factor [1, 2]. Both male and female partners should seek evaluation and treatment to optimize their chances of achieving a pregnancy. However, men are more hesitant to seek medical evaluation when compared to their female counterpart [3]. In a survey of men aged 25–44 years, only 9.4% underwent a fertility assessment compared to 13% of age-matched women [4]. Moreover, roughly 30% of infertile couples entirely forgo a male fertility evaluation prior to proceeding with assisted reproductive techniques, which has its own limitations [5]. The semen analysis has been the primary screening test to evaluate male fertility potential, and recent evidence suggests that infertile men may be at higher risk for adverse health later in life. Further research is necessary to elucidate the nature and etiology of the association between male infertility and its possible long-term impact on health. However, increasing interest and development of commercially available, affordable at-home semen analysis screening tests is aimed to screen male fertility parameters at home and serving as guide to further screening at specialized andrology laboratory [6].

Semen analysis provides useful information to clinicians and patients, but natural conception is an intricate process, and conventional semen analysis may not truly predict the fertility outcome [7–9]. Among standard sperm parameters, total motile sperm count (TMSC) is more predictive of fecundity when compared to concentration, motility, and morphology [10, 11]. Low motility is also inversely associated with the sperm DNA damage [12]. Manual microscopic semen evaluation and computer-assisted semen analysis (CASA) are both acceptable methods to perform conventional semen analyses. Both technologies have limitations such as human error, relatively expensive equipment, and inadequate accessibility to patients [13, 14]. Formal testing also requires trained andrology lab personnel and dedicated

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equipment, both of which are not readily available in many parts of the world. Also, many men struggle with providing a semen sample in a laboratory setting and cite it to be stressful and difficult [15].

In order to overcome these limitations and prevent unnecessary interventions on the female side in couples with male factor infertility, home-based semen screening tests were devised. At-home semen analysis offers a convenient, rapid, and cost-effective solution to this issue. This approach facilitates identification of men with subfertility who may otherwise be hesitant to seek medical evaluation, prompting a more formal assessment [3–5]. Men interested in assessing their fertility potential or those who live in areas with limited andrology services may also find at-home tests useful. Furthermore, these devices may be of interest and helpful in easy screening post vasectomy and after radiation/chemotherapy in cancer patients. This chapter reviews the evolving landscape of home and smartphone-based semen analysis. We discuss the limitations and future directions of these devices.

66.2 Conventional Semen Analysis

Since 1980, the WHO has endeavored to standardize how laboratories analyze and report semen parameters globally. The WHO manual is currently in its fifth edition which was published in 2010 [1]. The reference values for semen parameters have evolved over time and are not without controversy. For results that fall outside of the reference values, the American Urological Association recommends a clinical and/or laboratory evaluation of the male [16]. Semen analyses provide valuable information for clinicians and patients but are only a surrogate for male fertility and do not guarantee fecundity. It is unclear why some men with "normal" semen analyses may be unable to conceive and those with "abnormal" semen analyses may remain fertile [17].

The Clinical Laboratory Improvement Amendments (CLIA) has specific guidelines for laboratories to ensure quality and accurate semen analysis results [18]. Despite these guidelines, there is still a wide variability in techniques used, and inter-observer/laboratory variations and standardization are difficult. Semen testing can be performed either manually or via automated testing systems. Automated testing systems refer to computer-assisted semen analysis (CASA) or sperm analyzers such as SQA-Vision and Integrated Visual Optical System (IVOS) [19]. Although manual semen analysis results are subjective, they are considered accurate when performed by trained medical andrology technicians [1, 19]. Automated systems are also not inoculated from challenges such as costly equipment, inadequate sample preparation, optics, or poorer performance with low sperm concentrations [20]. Macroscopic and microscopic semen parameters are analyzed to determine quantitative aspects of the semen. Once the semen liquefies, typically within 20–60 minutes, a macroscopic assessment of the semen sample is performed which includes volume, pH, color, and viscosity. Subsequently, microscopic examination determines the concentration, motility, morphology, and vitality of the sperm [11].

It is important for clinicians to understand that semen parameters can vary with time in different samples taken from the same man [21, 22]. This issue can be related to many factors, such as differences in the duration of abstinence and physiological variation [23]. As a result, analysis of at least two separate semen samples is usually advised [1]. In an effort to avoid multiple visits to the laboratory as well as reducing health-care related expenditures, home-based screening tests have been developed.

66.3 Home-Based Semen Tests (Fig. 66.1)

There are several home-based semen tests that have been approved for use by the US Food and Drug Administration (FDA). They allow men to perform and interpret the test in the comfort of their own home. This can be valuable for patients who are reluctant to seek medical evaluation or lack access to andrology services. Currently available at-home semen analysis tests include SpermCheck Fertility (Princeton BioMeditech), SwimCount Sperm Quality Test (MotilityCount ApS), Micra First Step (Micra), and the Trak Male Fertility Testing System (Sandstone Diagnostics) [24–27]. Many of these products only provide users with sperm concentration, which is only one aspect of the semen analysis used to assess fertility potential. However, a simple assessment may help determine when a more formal evaluation should be obtained and potentially avoid unnecessary diagnostic and medical treatment for the female partners.

66.3.1 SpermCheck Fertility

This device is FDA-approved and commercially available with price $39.99. This product is an immunodiagnostic test that works similar to a pregnancy test. It uses a sperm concentration greater than 20 million/ml (M/ml) as its threshold for a normal result which is higher than the current WHO standard cutoff of 15 M/ml. However, it carries some limitations as it does not calculate a numerical sperm count nor provide information regarding motility or morphology. It utilizes monoclonal antibodies to detect a surface antigen,

Fig. 66.1 Home-based semen tests: (**a**) SpermCheck Fertility kit with SpermCheck device, semen transfer device, semen collection cup, and SpermCheck solution bottle. (**b**) SwimCount Sperm Quality Test with plastic cup, syringe, and test device. (**c**) Micra First Step kit with slides and microscope. (**d**) Trak Male Fertility Testing System with engine and props. (**a**: Courtesy of SpermCheck Fertility (Princeton BioMeditech), **b**: Courtesy of MotilityCount ApS, **c**: Courtesy of Micra First Step (Micra), **d**: Courtesy of Trak Male Fertility Testing System (Sandstone Diagnostics))

SP-10, located on the head of spermatozoa. SP-10 concentration has been shown to correlate with sperm concentration [24]. The SpermCheck Fertility kit consists of SpermCheck device, semen transfer device, semen collection cup, and SpermCheck solution [25].

The semen is mixed with the SpermCheck solution thereby releasing the SP-10 protein from the sperm. The mixture is transferred to the sample wells where SP-10 binds to a colloidal gold protein, forming gold-SP-10. When the newly formed gold-SP-10 complex traverses the test membrane, a red line will appear in the results window if the sperm concentration is greater than 20 M/ml. If the sperm concentration is less than 20 M/ml, there will be no red line. The test results are available in approximately 10 minutes. The manufacturers report that the test was accurate in detecting normozoospermia, oligozoospermia, or severe oligozoospermia in 96% of patients [24, 25].

66.3.2 SwimCount™ Sperm Quality Test

This product is an easy to use home test device that reports progressively motile sperm cells (PMSCs) per mL [28]. The European CE-marked version of the SwimCount™ Sperm Quality Test kit contains a plastic cup, syringe, instructions for use, and test device. Once the patient has provided a sample, they must wait 30 minutes to allow for the semen to liquefy. The syringe is used to draw 0.5 mL of the sample (avoiding bubbles, which will affect the volume). The sample is transferred onto the device where there are three distinct chambers. Only PMSCs are capable of moving from the first chamber (sample chamber) into the second chamber (separation chamber). The PMSCs are stained with a dye in the second chamber, which produces the blue color in the third chamber (detection and result window). The more PMSCs in the semen sample, the darker the color in the detection and results window. After approximately 30 minutes and pulling the slider back, the user must compare the shade of color in the results window to the reference colors on the device. The result is characterized as <5 million progressive motile sperm/mL (light color which means "low" sperm quality), 5–20 million progressive motile sperm/mL (medium color which means a "normal-mid" sperm quality), and >20 million progressive motile sperm/mL (darkest color which means a "normal-high" sperm quality). An accuracy of 95% was determined after comparison with traditional semen analysis [28]. The sensitivity and specificity of the test is 88.1% and 93.3%, respectively [28]. It is currently pending FDA approval and is available in Europe for €49.99 [14] and countries outside of Europe including Brazil and New Zealand.

66.3.3 Micra First Step

This product is a home microscopic kit that assesses semen volume, concentration, and motility [14]. The kit consists of a plastic microscope, pipette, and slides. The user transfers their ejaculated sample onto the slide using the pipette. The microscope lens contains an "analysis grid" that assists the user in calculating the sperm concentration and motility in specified visual fields. The process is similar to a manual semen analysis performed in a laboratory. However, the equipment is of lower quality, and the user is unlikely to be as highly trained as laboratory technicians for analyzing cells under a microscope. This allows for more user error and poorer accuracy when interpreting the results. The device is FDA-approved and is available for approximately $85 [14].

66.3.4 Trak System

This product was developed based on principles of centrifugal microfluidics and provides sperm concentration only [29]. The Trak System includes an instrument (the Trak engine), disposable cartridges (the Trak props), and a mobile app to record and monitor results. The user collects their ejaculate and transfers it to the liquefaction cup. A pipette is used to place 0.25 ml of the liquefied sample onto the disposable test prop which is loaded onto the Trak engine. Once the lid is closed, the engine will centrifuge the sample for approximately 6 minutes. The spermatozoa will form a pellet in the channel at the bottom of the test prop. The height of the pellet corresponds with either optimal (>55 M/ml), moderate (15–55 M/ml), or low (<15 M/ml) sperm concentrations for conception. The accuracy of typical users was determined to be 93.3%, 82.4%, and 95.5% in the low, moderate, and optimal categories, respectively [25]. The authors also demonstrated that device had a positive linear relationship with CASA (r ¼ 0.99) [25]. The product is FDA-approved and retails for $124.99 [29].

66.4 Smartphone-Based Semen Testing Devices

It is estimated that there were 2.1 billion smartphone users in 2016 and that number is expected to grow to 2.5 billion in 2019. At the time of publication of this book, over 35% of the global population use a smartphone [30]. With much of this growth stemming from developing countries with limited resources and poor accessibility to health-care services, smartphones are emerging as a powerful tool in the search of point-of-care diagnostic testing [31]. Advances in smartphone technologies have allowed for rapid processing and transmission of data through user-friendly interfaces called "apps." Additionally, smartphones provide secure memory storage, high-resolution cameras, and built-in sensors that can be used for the detection and assessment of a variety of human biosignals [31]. Smartphones can communicate this data between the user and a centralized laboratory for professional guidance [32, 33]. Several groups have developed devices compatible with smartphones that have the potential to provide affordable and convenient home-based semen testing [34–36].

In 2016, Kobori and colleagues [33] constructed an economical single-ball lens that attaches to a smartphone in order to assess semen concentration and motility. The device consists of a polyethylene sheet and 0.8 mm in diameter single-ball lens, which provides 555 times magnification. It costs roughly $7 to produce. A small fraction of the ejaculate is placed onto the polyethylene sheet which attaches to the single-ball lens microscope device by magnetic force. The smartphone is then connected to a personal computer where the user can manually assess sperm concentration and motility from a 3-second movie clip of the sperm. The sensitivity and specificity of the device to measure oligozoospermia ($<15 \times 10^6$ spermatozoa/mL) when compared to CASA was dependent on the type of smartphone used and varied between 75.5% to 90.9% for sensitivity and 87.8% to 90.9% for specificity [34]. This device is not currently FDA-approved, and the need for a personal computer to interpret the results coupled with the potential for user error is a limitation of this device.

Another point-of-care smartphone semen testing system was designed utilizing microfluids and a wireless weight scale system [35]. This device consists of an optical attachment for the smartphone and disposable microfluidic slides. The developers analyzed 350 semen specimens which were compared to CASA testing and determined the device had an accuracy of 97.71% [35]. The smartphone app associated with this product analyzes the stored video clip to calculate sperm concentration and motility. The mean reporting time is less than 5 seconds and can be reviewed by the user or clinician. Another significant advantage is that the cost to produce this device is less than $5. However, limitations of this device include misidentifications of nonsperm objects of a similar size to a sperm head and a saturation point for sperm concentration >100 million/ml [34, 36]. It is currently in the prototyping phase and is not FDA-approved.

66.4.1 Yo Home Sperm Test (Fig. 66.2)

The YO Home Sperm Test (Medical Electronic Systems) was approved by the FDA in 2016 and is the first commercially available smartphone-based semen testing device [36]. The YO measures motile sperm concentration (MSC) utilizing the smartphone's camera and flash to record a video of the sperm. The YO kit contains the YO device, collection cup, pipettes, liquefaction powder, and YO slides to complete two YO sperm tests.

Instructions (Video 66.1):

1. Collect semen specimen in the collection cup via masturbation (no lubricants). Pour one vial of the red powder into your sample and let it "rest" for 10 minutes.
2. Place the YO clip on your smartphone (2019 version of the YO device will replace clip with an external testing module which plugs into phone).
3. Use the pipette to transfer a drop of your sample onto the red dot on the YO slide.
4. Insert the YO slide into the YO clip and press "start testing."
5. Results are typically ready within 3 minutes.

The YO device utilizes the smartphone camera to capture the light fluctuations caused by movement of sperm. The device determines the sperm concentration and motility to ultimately calculate MSC. The YO test results will report whether MSC is "low" or "moderate/normal," using six million/mL motile sperm as its threshold [37]. Agarwal and colleagues [38] performed a double-blind trial comparing the YO Home Sperm Test and an automated laboratory analyzer (SQA-Vision). They analyzed 144 aliquots of semen samples from 24 healthy donors and demonstrated that the YO device provided good correlation when compared with SQA-Vision. The Pearson and concordance correlation coefficient was above 0.92. The YO exhibited an accuracy of 97.8%. The YO device yielded a precision of 16%. The manufacturers cite an accuracy and precision of 97% and 20%, respectively [38].

The device is currently available for $59.95 [36]. Like the aforementioned home tests, point-of-care semen tests can provide the concentration of motile sperm, but do not evaluate all of the parameters commonly used to evaluate male fertility.

66.5 Limitations

Identifying men with subfertility who may otherwise be hesitant to seek medical evaluation and preventing unnecessary interventions for the female partner will certainly improve patient care, but point-of-care screening also has several limitations. The smartphone-based sperm testing devices provide only basic semen parameters such as sperm count or MSC, whereas a laboratory semen analysis evaluates significant sperm parameters such as pH, volume, concentration, motility, morphology, viability, and markers of oxidative stress. Continued comparison between laboratory and smartphone-based screening should be performed to ensure

Fig. 66.2 2019 The YO® Home Sperm Test kit. (Courtesy of Medical Electronic Systems)

accuracy and reproducibility with varying clinical conditions. In some cases, user error or potentially lack of quality control may lead to false-negative results, which could delay the actual diagnosis or treatment process. A thorough history and physical examination is a cornerstone of the male fertility assessment, and a home-based screening test cannot replace an office visit with a physician.

66.6 Conclusion

Novel smartphone-based semen screening devices are a step forward in the right direction and may overcome some of the limitations of laboratory testing including convenience, cost, access to lab, and hesitation to ejaculate in the lab. There is continuous need to devise an ideal low-cost, easy-to-use, reliable screening test which could provide substantial information on more standard sperm parameters. Current and future advancements in smartphone and point-of-care technologies will enable more men to assess semen parameters at home which will ideally facilitate identification of men with subfertility who may otherwise be hesitant to seek medical evaluation or indicate when a more formal assessment should be obtained. A reliable and more accurate home-based male infertility screening test will potentially reduce the undue female investigations and financial and psychological pressure on the couple.

66.7 Review Criteria

We extensively searched Google Scholar, PubMed, Medline, ClinicalKey, and ScienceDirect for articles focusing on semen analyses, male infertility, and home semen testing. We began our literature search September 2018 and completed it by January 2019. The following keywords were utilized in our search: "semen analysis," "microfluidics," "SpermCheck Fertility," "SwimCount Sperm Quality Test," "Micra," "Trak Male Fertility Testing System," and "YO Home Sperm Test." We reviewed only English language articles. Images were obtained with written consent.

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