LEARNING OBJECTIVES

At the conclusion of this session, participants should be able to:

● Summarize the strengths and weaknesses of semen analysis.
● Characterize the biological significance and clinical utility of past and current sperm function tests.
● Determine the appropriate use of semen analysis and other tests for their clinical practice.
DISCLOSURE

- No relationships or conflicts to disclose

A USA perspective ...

Semen: What it is and what it isn’t

- Admixture of germ and non-germ cells, and secretions primarily from the seminal vesicles (coagulating) and prostate (liquefying).
- Spermatozoa heterogeneous in structure and function despite same ancestral origin
- Spermatozoa influenced by male and female secretions
- These attributes and more make semen distinctly dissimilar to other clinically evaluated body fluids.
Seminal Origins of Semen Analysis & Reference Values:

"The spermatozoa count. Its value in the diagnosis, prognosis and treatment of sterility."

Macomber and Sanders, 1929

Seminal Origins of Semen Analysis & Reference Values:

"The male factor in fertility and infertility. II. Spermatozoon counts in 1000 men of known fertility and in 1000 cases of infertile marriage."

MacLeod and Gold, 1951

WHO Manuals 1980 – 2010: Global model for semen analysis standards
WHO Reference limit comparisons

Table 1. Cut-off reference values for semen characteristics as published in successive WHO manuals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>N.D.</td>
<td>≥2</td>
<td>≥2</td>
<td>≥2</td>
</tr>
<tr>
<td>Sperm count (10^6/mL)</td>
<td>30,000</td>
<td>≥30</td>
<td>≥50</td>
<td>15</td>
</tr>
<tr>
<td>Total motility (1%)</td>
<td>N.D.</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
</tr>
<tr>
<td>Viable sperm (%)</td>
<td>≤95</td>
<td>≤80</td>
<td>≤50</td>
<td>≤50</td>
</tr>
<tr>
<td>Morphology (% normal)</td>
<td>≤50</td>
<td>≤50</td>
<td>≤50</td>
<td>≤50</td>
</tr>
<tr>
<td>Ejaculate volume (mL)</td>
<td>≥1.5</td>
<td>≤1.5</td>
<td>≤1.0</td>
<td>≤1.0</td>
</tr>
</tbody>
</table>

*WHO = World Health Organization; N.D. = not defined.

Table 2. Characteristics of reference studies used to establish new limits for human semen characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>TTP &lt; 12 mm Staged</th>
<th>Sperm Morphology Evaluation</th>
<th>Overdiagnosing Authorship &amp; Classification</th>
<th>Age at biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bojes et al., 1998</td>
<td>Denmark</td>
<td>N.D.</td>
<td>No</td>
<td>Modified David</td>
<td>Yes</td>
</tr>
<tr>
<td>Alger et al., 2001</td>
<td>France, Denmark, United Kingdom, Finland</td>
<td>No</td>
<td>Yes</td>
<td>David</td>
<td>Yes</td>
</tr>
<tr>
<td>Jorgensen et al., 2001</td>
<td>Denmark, United Kingdom, Finland</td>
<td>N.D.</td>
<td>No</td>
<td>Tt!ogsgnweg</td>
<td>Yes</td>
</tr>
<tr>
<td>Jensen et al., 2001</td>
<td>Denmark, United Kingdom, Finland</td>
<td>No</td>
<td>Yes</td>
<td>David</td>
<td>Yes</td>
</tr>
<tr>
<td>Buens et al., 2002</td>
<td>France, Denmark, United Kingdom, Finland</td>
<td>Yes</td>
<td>Yes</td>
<td>David</td>
<td>Yes</td>
</tr>
<tr>
<td>Smart et al., 2003</td>
<td>United States</td>
<td>No</td>
<td>Yes</td>
<td>Tt!ogsgnweg</td>
<td>Yes</td>
</tr>
<tr>
<td>Hough et al., 2006</td>
<td>United Kingdom, Australia</td>
<td>Yes</td>
<td>Yes</td>
<td>Tt!ogsgnweg</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TTP = time to pregnancy.

Origin of WHO 2010 reference values

Table 3. Characteristics of reference studies used to establish new limits for human semen characteristics

WHO 1999 vs WHO 2010

Figure 4. Illustration of the relative effect of moving a reference limit to lower values based on the distribution of results from limits.

WHO = World Health Organization; N.D. = not defined.
The effect of the new 2010 World Health Organization criteria for semen analyses on male infertility


Sperm morphology, motility, and concentration in fertile and infertile men.

Semen Analysis & Diagnosis

- The semen analysis neglects composition of seminal plasma
- Semen analysis principally surveys the quantity and not the quality, per se, of manufacturing.
- The semen analysis essentially evaluates a single parameter of sperm function – motility
- The reference limits are derived from a very limited population
- Therefore, the reference limits have questionable value for a large segment of the global male population

How then can the semen analysis on its own possibly be used to correctly diagnose fertility?
Functional attributes of fertile spermatozoa

Attributes of fertile spermatozoa

- Normal structure of vital functional components
- Functional metabolic pathways for motion, maintenance of membrane potentials, ionic microenvironment, pH or other cellular functions
- Ability to penetrate/pass-through all reproductive tract barriers
- "Survival proteins" to protect sperm while in female tract
- Appropriate receptor-mediated entry/activation of sperm to female tract
- Functional membrane receptor proteins for migration and binding to zona and vitelline membrane
- Acrosomal enzymes maintained inactive until appropriate time
- Fusible plasma and acrosomal membranes
- Precise timing in sequence from spermiogenesis to syngamy
- Properly packaged and stable DNA that is capable of decondensation when appropriate (De Jonge, 1999)

Sperm function tests of old

Attributes
- Motion
- Shape
- Survival proteins
- Capacitative proteins
- Binding/penetration proteins
- Zona-lysing enzymes
- Properly packaged and stable DNA

Tests
- Manual/CASA
- Morphology – criteria?
- N/A
- Acrosome reaction ionophore challenge
- Sperm penetration assay
- Hemi-zona assay

Why did the dinosaur die?

- Complexity of materials and methods
  - Failure to standardize materials and methods
    - Creates diversity in results and interpretation
    - Prevents comparison of results between different test locations
    - Prevents amalgamation of results for deriving clinically meaningful reference values
  - Staffing
    - Training
    - Time
  - Financial
Commercialization of sperm function tests

- Patient demand drives innovation
- Innovation starts at the research bench
- Translation from benchtop to bedside satisfies patient treatment needs

Sperm function tests today

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motion</td>
<td>Motility – manual/CASA</td>
</tr>
<tr>
<td>Shape</td>
<td>Strict criteria</td>
</tr>
<tr>
<td>Survival proteins</td>
<td>N/A</td>
</tr>
<tr>
<td>Capacitative proteins</td>
<td>Cap-Score™</td>
</tr>
<tr>
<td>Binding/penetration proteins</td>
<td>Hyaluronan Binding Assay (HBA*)</td>
</tr>
<tr>
<td>Zona-lysing enzymes</td>
<td>Cap-Score™ - indirect</td>
</tr>
<tr>
<td>Properly packaged and stable DNA</td>
<td>SCSA®, COMET, TUNEL, Halosperm®</td>
</tr>
</tbody>
</table>

Cap-Score™ (Androvia LifeSciences – North Amer.)

- The Cap-Score Assay measures, on a molecular level, the percentage of sperm capable of undergoing capacitation, i.e., sperm fertilization potential.
Cap-Score™ (Androvia LifeSciences)

- Semen analysis measures for men who were and were not successful in generating pregnancy (Mol Reprod & Dev. 2018;85:pp654-664)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Motile (%)</th>
<th>Vitality (%)</th>
<th>Motility (%)</th>
<th>Sperm Count (M/mL)</th>
<th>Sperm Morphology (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>18</td>
<td>1.100.2</td>
<td>88.393.5</td>
<td>88.404.9</td>
<td>94.301.2</td>
<td>82.516.0</td>
</tr>
<tr>
<td>Not pregnant</td>
<td>75</td>
<td>3.489.2</td>
<td>88.393.4</td>
<td>90.404.8</td>
<td>90.301.5</td>
<td>72.516.4</td>
</tr>
</tbody>
</table>

Prospective Test of Cap-Score (Mol Reprod & Dev. 2018;85:pp654-664)

SCSA® (SCSA Diagnostics - International)

- The SCSA measures the level of DNA fragmentation after denaturation by using acridine orange staining and flow cytometry.
- Double-stranded (native) DNA stains green and single-stranded (denatured) DNA stains red.
- SCSA also detects immature sperm that have increased histones rather than protamines.
- High levels of DNA fragmentation correlate with pregnancy loss after natural conception and IUI.

https://www.scsadiagnostics.com
• SpermComet® is a single cell gel electrophoresis test that measures the amount of single- and double-strand DNA fragments present in individual sperm, generating a picture of the extent of DNA fragmentation throughout a sample.
To detect DNA fragmentation sperm are immersed in an agarose matrix on a slide, treated with an acid solution to denature DNA that contains breaks, and then treated with lysis buffer to remove membranes and proteins. The agarose matrix allows working with unfixed sperm on a slide in a suspension-like environment. Removal of nuclear proteins results in nucleoids with a central core and a peripheral halo of dispersed DNA loops.

Sperm nuclei with elevated DNA fragmentation produce very small or no halos of DNA dispersion, whereas those sperm with low levels of DNA fragmentation release their DNA loops forming large halos.

Nucleoids with small halo, without halo, and without halo and degraded, contain fragmented DNA. Sperm cells with fragmented DNA are indicated by an asterisk.
Hyaluronan is found in the cumulus oophorous and the ability of sperm cells to bind to hyaluronan is a biomarker for sperm maturity and quality. Only fully mature sperm that have completed the last crucial stages of spermatogenesis have developed receptors for hyaluronan.

Less mature sperm, e.g., retained cytoplasm, have increased aneuploidy, dysfunctional ability to bind to HA and greater risk for increased oxidative stress, and DNA damage.

HBA primarily being used for selecting sperm for use in ICSI.

Sperm function tests on the horizon

- Epigenetics
- Metabolomics
- Proteomics
- High-throughput screening
  - Potential for individualized diagnosis

Conclusions

- Semen analysis is an essential component when assessing male reproductive capacity.
- Semen analysis incompletely provides a comprehensive assessment of male fertility potential.
- Sperm function tests add to the semen analysis by providing important critical data regarding sperm function for:
  - Fertilization
  - Post fertilization embryo development
- Use of sperm function testing in conjunction with the semen analysis contributes to a more efficient and cost-effective treatment plan for the subfertile couple.
Semen Analysis: it’s not time for an upgrade?

Allan Pacey, MBE, PhD, FRCOG
Professor of Andrology
University of Sheffield
United Kingdom

DISCLOSURE

- No relationships or conflicts to disclose

A European UK perspective ...
Arguments in support of semen analysis

- It has a long history
- It’s easy to perform (even in low resource countries)
- It’s relatively inexpensive
- It has global reach (courtesy of WHO)
- It is easy to interpret
- It can identify major problems (e.g. azoosperma, asthenozoosperma, globozoosperma, necrozoosperma)
- In the days of ICSI for almost everyone, why do anything more?
- We could probably get away with less!

Semen analysis has a long history ...

“What I investigate is only what, without sinfully defiling myself, remains as a residue after conjugal coitus. And if your Lordship should consider that these observations may disgust or scandalise the learned, I earnestly beg your Lordship to regard them as private and to publish or destroy them as your Lordship sees fit.”

(Leeuwenhoek 1678)

Semen analysis is not perfect ...

Semen analysis is not perfect ...

Lack of compliance by UK andrology laboratories with World Health Organization recommendations for sperm morphology assessment

Diederik Riddell, Alvin Pang and Kate Whitington

Institute of Reproduction and Development, University of Cambridge, Cambridge, UK

To whom correspondence should be addressed. Email: k.w@whitington.co.uk

INTRODUCTION: Sperm morphology has become a cornerstone of male infertility assessment. Aspermia and oligospermia are associated with a reduced probability of pregnancy. This study aimed to assess the accuracy of sperm morphology assessment and to determine the causes of non-compliance with the World Health Organization (WHO) recommendations. The diagnosis of male infertility in the WHO guidelines is based on a combination of clinical and laboratory parameters. The study was approved by the Ethics Committee of the University of Cambridge. All participants were asked to consent to the use of information for research purposes. The data were analyzed using SPSS software. The results were presented as mean ± standard deviation. The differences between groups were analyzed using the Student t-test. The level of significance was set at p < 0.05.

The AG-7 Antigravity Space Pen

Semen analysis is relatively inexpensive ...

- A person
- A laboratory
- A microscope
- Some consumables
- Some training
- Quality Control
- IT
- Safety / waste disposal
- Regulation
- Building and services

Which all equates to:
- £60 (UK)
- €70 (Euros)
- $80 (US dollars)

Courtesy of Dr Matt Tomlinson, University of Nottingham, UK
But semen analysis has global reach ...

|---------------|----------------|---------------|----------------|--------------|

World Health Organisation

Semen analysis normogram
(Fathers with TTP <12 months)

<table>
<thead>
<tr>
<th>Centiles</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>90</th>
<th>95</th>
<th>97.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centiles</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
<td>25</td>
<td>50</td>
<td>75</td>
<td>90</td>
<td>95</td>
<td>97.5</td>
</tr>
<tr>
<td>Semen volume (ml)</td>
<td>1.2</td>
<td>1.5</td>
<td>2.7</td>
<td>3.7</td>
<td>3.7</td>
<td>4.8</td>
<td>6.0</td>
<td>6.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Sperm Concentration (10^6/ml)</td>
<td>9</td>
<td>15</td>
<td>22</td>
<td>41</td>
<td>73</td>
<td>116</td>
<td>169</td>
<td>213</td>
<td>259</td>
</tr>
<tr>
<td>Total number (10^6 ejaculate)</td>
<td>23</td>
<td>39</td>
<td>69</td>
<td>142</td>
<td>255</td>
<td>422</td>
<td>647</td>
<td>802</td>
<td>928</td>
</tr>
<tr>
<td>Total Motility (%)</td>
<td>34</td>
<td>40</td>
<td>45</td>
<td>53</td>
<td>61</td>
<td>69</td>
<td>75</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>Progressive Motility (%)</td>
<td>28</td>
<td>32</td>
<td>39</td>
<td>47</td>
<td>55</td>
<td>62</td>
<td>69</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Normal forms (%)</td>
<td>3.0</td>
<td>4.0</td>
<td>5.5</td>
<td>9.0</td>
<td>15.0</td>
<td>24.5</td>
<td>36.0</td>
<td>44.0</td>
<td>48.0</td>
</tr>
<tr>
<td>Vitality (%)</td>
<td>53</td>
<td>56</td>
<td>64</td>
<td>72</td>
<td>79</td>
<td>84</td>
<td>88</td>
<td>91</td>
<td>92</td>
</tr>
</tbody>
</table>


Potential Impact of uncertainty ...
(765 = no pregnancy in 12 months; 696 = paternity within 2 years)

Guzick et al., (2001) NEJM 345: 1388-1393
Multiple semen parameters are better than one

Table B: Odds Ratios for Infertility for Combinations of Sperm Measurements.

<table>
<thead>
<tr>
<th>Sperm Measurement</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>2 (1.2 - 3.2)</td>
</tr>
<tr>
<td>Motility</td>
<td>2 (1.1 - 3.6)</td>
</tr>
<tr>
<td>Morphology</td>
<td>2 (1.5 - 10.5)</td>
</tr>
</tbody>
</table>

Tomlinson et al. (2013) Human Fertility 16: 175-193

National Institute for Health & Care Excellence (NICE)

1.3.1 Semen analysis

1.3.1.1 The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization reference values.

1.3.1.2 Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility.

1.3.1.3 If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered.

1.3.1.4 Repeat confirmatory tests should ideally be undertaken 3 months after the initial analysis to allow time for the cycle of spermatogenesis to be completed. However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected, the repeat test should be undertaken as soon as possible.

https://www.nice.org.uk/guidance/cg156

British Fertility Society Guidelines

- The concentration of progressively motile sperm has consistently been the most predictive factor with regards to outcome;
- 64% of studies suggest there is a reasonable chance of success with IUI requires 5x10^6 million motile sperm;
- Regarding sperm morphology, the expert group concluded that a lack of standardisation across centres, the adoption of ever-stricter scoring criteria, and changing reference values meant no conclusion could be drawn;
- It proposed that there was insufficient evidence to justify the use of ICSI in cases of isolated teratozoospermia.
British Fertility Society Guidelines

<table>
<thead>
<tr>
<th>Expectant Management</th>
<th>IUI</th>
<th>IVF</th>
<th>ICSI</th>
<th>Donor Sperm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


The increasing use of ICSI (USA Data)


So perhaps semen analysis should just become?

Pacey (2019) being provocative
Sperm function tests today

Attributes
- Motion
- Shape
- Survival proteins
- Capacitative proteins
- Binding/penetration proteins
- Zona-lysing enzymes
- Properly packaged and stable DNA

Tests
- Motility – manual/CASA
- Strict criteria
- N/A
- Cap-Score™
- Hyaluronan Binding Assay (HBA®)
- Cap-Score™ - indirect
- SCSA®, COMET, TUNEL, Halosperm™

ART add ons in the UK

- 38 add on interventions offered by UK fertility clinics
- NICE offers clear advice on only 13 (34%)
- Poor quality evidence to support:
  - Sperm DNA testing
  - IMSI
  - Sperm slow
- No others are mentioned


ART add ons in the UK

Signatories include:
- Association of Biomedical Andrologists
- Association of Clinical Embryologists
- British Andrology Society
- British Fertility Society
- British Infertility Counselling Association
- European Society of Human Reproduction and Embryology
- Fertility Network UK
- Human Fertilisation and Embryology Authority
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Senior Infertility Nurses Group

Arguments against anything else

- There has been a long history of fancy sperm-function tests which have come and gone
- There is no evidence that fancy sperm-function tests improve patient outcome
- There is evidence that fancy sperm-function tests increase the financial cost to patients
- In the days of ICSI for almost everyone, what do they add?
- Therefore semen analysis should remain the test of choice!

Semen Analysis: *it is time* for an upgrade?

Christopher De Jonge, Ph.D., HCLD

Rebuttal
Results of the American Association of Bioanalysts national proficiency testing programme in andrology

Keel et al, 2000

Lack of standardization in performance of the semen analysis among laboratories in the US

Keel et al, 2002
ESHRE basic semen analysis courses 1995-1999

Semen analysis workshops in India and Africa; the vital role of training and external quality control programmes

15yrs Belgian experience with external quality assessment of semen analysis
15yrs Belgian experience with external quality assessment of semen analysis

Punjabi et al 2016

Consequences of ICSI in non-male factor cases: wider implications

- Use of non-evidence based treatments undermines public trust, particularly if there are financial motivations behind ICSI use
- Mechanisms of male infertility remain poorly understood
- Guidelines on ICSI use such as ASRM (2012) are available
- Will ICSI use in future respond to these recommendations?


Independence from semen analysis – the benefit of an adjunct test

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Concentration (mL/mL)</th>
<th>Motility (%)</th>
<th>Cap Score</th>
<th>PHC%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>28</td>
<td>45</td>
<td>32.7</td>
<td>43.9</td>
</tr>
<tr>
<td>A2</td>
<td>30</td>
<td>80</td>
<td>16.7</td>
<td>17.3</td>
</tr>
<tr>
<td>B1</td>
<td>31</td>
<td>45</td>
<td>19.3</td>
<td>20.3</td>
</tr>
<tr>
<td>B2</td>
<td>35</td>
<td>46</td>
<td>48.0</td>
<td>56.0</td>
</tr>
<tr>
<td>C1</td>
<td>85</td>
<td>80</td>
<td>32.0</td>
<td>40.6</td>
</tr>
<tr>
<td>C2</td>
<td>91</td>
<td>97</td>
<td>18.7</td>
<td>19.6</td>
</tr>
<tr>
<td>D1</td>
<td>94</td>
<td>96</td>
<td>16.7</td>
<td>17.3</td>
</tr>
<tr>
<td>D2</td>
<td>96</td>
<td>58</td>
<td>34.0</td>
<td>44.0</td>
</tr>
<tr>
<td>E1</td>
<td>98</td>
<td>80</td>
<td>32.7</td>
<td>43.9</td>
</tr>
<tr>
<td>E2</td>
<td>102</td>
<td>84</td>
<td>22.7</td>
<td>24.9</td>
</tr>
<tr>
<td>F1</td>
<td>112</td>
<td>45</td>
<td>16.7</td>
<td>17.3</td>
</tr>
<tr>
<td>F2</td>
<td>113</td>
<td>54</td>
<td>10.0</td>
<td>16.9</td>
</tr>
</tbody>
</table>
Conclusions

- Compliance with standardized semen analysis is still a work in progress.
- Persistent monitoring of test and personal quality will assure providers and patients of high-quality test results.
- Greater acceptance and implementation of standard processes for semen analysis will enhance comparability and amalgamation of results.
- Mining of databases from larger and diverse populations of fertile and subfertile patients will create opportunities for generation of expanded reference values for general and specific populations.
- Sperm parameters should be cross-matched (3X3) to enhance predictive value of semen analysis.
- Greater basic understanding of ejaculate and sperm biology is needed.

Semen Analysis: it's not time for an upgrade?

Allan Pacey, MBE, PhD, FRCOG

Rebuttal

Quality control and regulation
Quality control and regulation

HFEA Traffic lights

- Assisted hatching
- Artificial egg activation (ionophore)
- Elective freeze all
- Embryo glue
- Endometrial scratching
- Intratubal culture
- Preimplantation genetic screening
- Reproductive immunology
- Time lapse imaging
- Intracytoplasmic Morphologic Sperm Injection (IMSI)
- Physiological Intracytoplasmic Sperm Injection (PICSI)

https://www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons/

Sperm DNA Damage and professional guidance

ASRM (2013) Fertility and Sterility 99: 673-677
Destruction and correlation


Hyaluronic acid binding

Huszar et al., (2007) RBM Online 14: 655-663

Hyaluronic acid binding


<table>
<thead>
<tr>
<th>Table 1: Determination of sperm DNA fragmentation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study:</strong> Determination of sperm DNA fragmentation.</td>
</tr>
<tr>
<td><strong>Group 1:</strong> Initial semen sperm</td>
</tr>
<tr>
<td>Spermatozoa</td>
</tr>
<tr>
<td>Total no. of spermatozoa analyzed</td>
</tr>
<tr>
<td>DNA fragmentation rate</td>
</tr>
</tbody>
</table>

Note: HA = hyaluronic acid; PVP = polyvinylpyrrolidone.
<sup>α</sup> P<sub>.01</sub> versus groups 2, 3, and 4.
<sup>β</sup> P<sub>.05</sub> versus groups 3.
<sup>γ</sup> P<sub>.05</sub> versus group 4.
<sup>δ</sup> P<sub>.05</sub> versus group 4.

Paradigm: Sperm selection with hyaluronic acid; Final 3/6/09.
Hyaluronic acid binding


Findings: Between Feb 1, 2014, and Aug 31, 2016, 2772 couples were randomly assigned to receive PICSI (n=1387) or ICSI (n=1385), of whom 2752 (51.0%) in the PICSI group and 1771 in the ICSI group were included in the primary analysis. The term birth rate did not differ significantly between PICSI (27.4% [179/650]) and ICSI (25.3% [174/687]) groups (odds ratio 1.12, 95% CI 0.89-1.39; p=0.54). There were 16 serious adverse events in total, including 31 in the PICSI group and 23 in the ICSI group; most were congenital abnormalities and none were attributed to treatment.

Interpretation: Compared with ICSI, PICSI does not significantly improve term birth rates. The wider use of PICSI, therefore, is not recommended at present.

Non-invasive approaches in medicine

Pacey (2019) personal thoughts
Sperm radar


Conclusions

● Regulation and healthcare systems can improve the quality of semen analysis but also regulate the premature introduction of new tests.
● Large multi-centre randomised controlled trials are needed to examine the effectiveness of new sperm-function tests with pregnancy / live birth as the primary end point.
● New tests should focus on non-destructive methods to assess sperm quality.
● In the meantime, semen analysis remains the test of choice to guide patient management.
Thank you ....