Male infertility - too often ignored & forgotten

A review of the guidelines

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The journey

1. The optimal evaluation of the men

The optimal evaluation

We got sperms, full stop.

Sperm + Egg = Embryo

The optimal evaluation

Surely it is enough?

_,000,000

“I only need 1”
The optimal evaluation

Tests:
KISS
“Keep it sophisticated and subspecialised”

Chromatin assays for DNA fragmentation evaluation
- Sperm chromatin structure assay (SCSA)
- TdT-mediated-dUTP nick end labeling (TUNEL)
- Sperm chromatin dispersion (SCD)
- Acridine orange staining technique (AOT)

Chromatin assays for DNA fragmentation evaluation

The optimal evaluation

DNA integrity

4.8 DNA fragmentation in spermatozoa
There is increased DNA damage in spermatozoa from men with oligospermia. This increase is associated with reduced chances of natural conception and, in a lesser extent, conception after IVF/ICSI, and with an increase in early pregnancy loss (25, 76). DNA damage may improve after varicocelectomy (77, 78).

European Association of Urology

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Chohan et al; J Androl; 27:53-59

Recommendation: Currently there is insufficient evidence in the literature to support the routine use of DNA integrity testing in the evaluation and management of the male partner of an infertile couple. Presently, there are no proven therapies to correct an abnormal DNA integrity test result.
Chromatin assays for DNA fragmentation evaluation

Tests:
- To know you I have to kill you
- Difficulty in finding threshold value

Sperm selection techniques
- HA sperm selection
- MACS
- IMSI

HA sperm selection
- Hyaluronic acid
- Bind to HA in vitro
- Completed plasma membrane remodelling, cytoplasmic extrusion and nuclear maturation
- Low chromosomal aneuploidies & DNA fragmentation, good nuclear morphology
- Only mature spermatozoa which have extruded their specific receptors to bind to & digest HA can reach the oocyte & fertilize it

HA sperm selection
  - HA-ICSI significantly improves embryo quality & implantation
  - Awaiting multi-center randomized studies (UK)

IMSI
- Morphologically selected sperm injection
- What is the best criteria for selection?
IMSI

- Conflicting results:
  - No difference in fertilization rate, early embryo cleavage rate or cleavage rate. Similar proportion of top quality embryos. (Mauri et al. Eur J Obstet Gynecol Reprod Biol. 2010 May; 150(1):42-6)
  - Based on motile sperm organelar morphology exam (MOSONE), individuals with best morphologically normal nucleus has significantly higher pregnancy & delivery rates. Also significantly lower miscarriage rates. (Bertovitz et al. Reprod Biomed Online. 2006 May; 12(5):634-8

MACS

- Magnetic-activated cell sorting
- Colloidal superparamagnetic microbeads conjugated with annexin V

MACS (meta- analysis)

Sperm selection techniques

- HA sperm selection
- MACS
- IMSI

TOO EARLY FOR INTERNATIONAL GUIDELINES
The optimal evaluation

Tests:
KISS

“Keep it sophisticated and subspecialised”

The optimal evaluation

Sperm + Egg = Embryo

Have you got the latest WHO manual?

The optimal evaluation

Sperm + Egg = Embryo

Why the difference?

The optimal evaluation

Sperm + Egg = Embryo

There is a significant difference on how the old and new reference ranges were derived. In the past, semen data from random population of men were analyzed and the results were plotted on a statistical distribution curve. The 5th percentile was considered to be the lower limit of normal (or reference), in other word, 95% of men tested would have sperm parameters higher than the reference ranges.

In WHO 2010, the new normal values are based on data from men with proven fertility, and who were shown to help their partners conceive in the previous 12 months. Following a comprehensive analysis of semen parameters from over 4000 men in 14 countries, a new set of 5th percentile parameters was recommended. Below are the comparisons of the old and new reference values:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO 1999</th>
<th>WHO 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>2 ml</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>Concentration</td>
<td>20 million/ml</td>
<td>15 million/ml</td>
</tr>
<tr>
<td>Progressive motility</td>
<td>50%</td>
<td>32%</td>
</tr>
<tr>
<td>Normal forms</td>
<td>14%</td>
<td>4%</td>
</tr>
</tbody>
</table>
The optimal evaluation

One step back - history and examination!!

The optimal evaluation

One step back - history and examination!!

<table>
<thead>
<tr>
<th>Male infertility associated factor</th>
<th>Distribution %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic male infertility</td>
<td>31</td>
</tr>
<tr>
<td>Maldescended testes</td>
<td>7.8</td>
</tr>
<tr>
<td>Urogenital infection</td>
<td>8.0</td>
</tr>
<tr>
<td>Disturbances of semen deposition and sexual factors</td>
<td>5.9</td>
</tr>
<tr>
<td>General and systemic disease</td>
<td>3.1</td>
</tr>
<tr>
<td>Varicocele</td>
<td>15.6</td>
</tr>
<tr>
<td>(Endocrine) hypogonadism</td>
<td>8.9</td>
</tr>
<tr>
<td>Immunological factors</td>
<td>4.5</td>
</tr>
<tr>
<td>Obstructions</td>
<td>1.7</td>
</tr>
<tr>
<td>Other abnormalities</td>
<td>5.5</td>
</tr>
</tbody>
</table>

The optimal evaluation

One step back - history and examination!!

**Box 22-4**

**Significant Medical Conditions Presenting as Male Infertility**

- Adult polycystic kidney
- Cystic fibrosis
- Diabetes
- Hemochromatosis
- Hypopituitarism
- Klinefelter syndrome
- Multiple sclerosis
- Pituitary adenoma
- Prostate cancer
- Retropertitoneal tumors
- Spinal cord tumors
- Testis cancer
- Thyroid disease
- Urinary tract infection

The optimal evaluation

One step back - history and examination!!

Prognostic factors for male infertility are:
- duration of infertility;
- primary or secondary infertility;
- results of semen analysis;
- age and fertility status of female partner.
The journey

1. The optimal evaluation of the men
2. Further investigations

Further investigations

Endocrine evaluation

Recommendation: An initial endocrine evaluation should include at least a serum testosterone and FSH. It should be performed if there is (1) an abnormally low sperm concentration, especially if less than 10 million/ml; (2) impaired sexual function; or (3) other clinical findings suggestive of a specific endocrinopathy.

Endocrine evaluation

<table>
<thead>
<tr>
<th>Condition</th>
<th>T</th>
<th>FSH</th>
<th>LH</th>
<th>PRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
</tr>
<tr>
<td>Primary testis failure</td>
<td>Low</td>
<td>High</td>
<td>NL, High</td>
<td>NL</td>
</tr>
<tr>
<td>Hypogonadotropic</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>NL</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Low</td>
<td>Low/NL</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Androgen resistance</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Further investigations

Genetic studies

Recommendation: Karyotyping and genetic counseling should be offered to all patients with nonobstructive azoospermia and severe oligospermia (<5 million sperm/ml).

Further investigations

Genetic studies

Recommendation: Men with congenital bilateral absence of the vasa deferentia should be offered genetic counseling and testing for cystic fibrosis transmembrane conductance regulator mutations. The female partner should also be offered cystic fibrosis transmembrane conductance regulator mutations testing before proceeding with treatments that utilize sperm from men with congenital bilateral absence of the vasa deferentia. Imaging for renal abnormalities should be offered to men with unilateral vasal agenesis or congenital bilateral absence of the vasa deferentia and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.
Further investigations
Genetic studies

Men with severely damaged spermatozoa (with < 1 million spermatozoa/ml) should be advised to undergo Y microdeletion testing for both diagnostic and prognostic purposes. Y microdeletion also has important implications for genetic counselling (see below).

Is there anything I can do to improve my sperms?

The journey
1. The optimal evaluation of the men
2. Further investigations
3. Strategy to improve sperm parameters

Strategy to improve sperms

Medical Surgical

Strategy to improve sperms

Medical Surgical

The insult can be permanent
Strategy to improve sperms

- Medical

**Options for improving natural fertility:** exist for a minority of infertile men, including those with pituitary hormonal deficiency or hyperprolactinemia, genitourinary infection, erectile and psychosexual problems, and through the withdrawal of drugs.

**NOTE:** NO MENTION OF MALE SUPPLEMENT!
Strategy to improve sperms

- Surgical
- Urology
- Varicocele

Evidence for varicocelectomy removal to improve fertility is lacking.

Varicocele repair

<table>
<thead>
<tr>
<th>Study</th>
<th>Control (a)</th>
<th>Treatment (a)</th>
<th>Control (%)</th>
<th>Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MShah et al.</td>
<td>10.9</td>
<td>13.9</td>
<td>16.9</td>
<td>24.9</td>
</tr>
<tr>
<td>M. Gudeman et al.</td>
<td>8.5</td>
<td>11.5</td>
<td>18.4</td>
<td>28.7</td>
</tr>
</tbody>
</table>

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Confused.com
Strategy to improve sperms

- Surgical
- Urology
- Varicocele

The insult can be permanent.

The journey

1. The optimal evaluation of the men
2. Further investigations
3. Strategy to improve sperm parameters
4. Surgical sperm retrieval

Surgical sperm retrieval

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free and low cost</td>
<td>Free sperm retrieval</td>
</tr>
<tr>
<td>No microsurgical operation required</td>
<td>Postoperative infection</td>
</tr>
<tr>
<td>No anesthesia and hospitalization</td>
<td>No sperm extraction</td>
</tr>
<tr>
<td>No surgical complications</td>
<td>Risk of hematoma/complications</td>
</tr>
<tr>
<td>Longitudinal follow-up</td>
<td></td>
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<tr>
<td>Relevant clinical outcome</td>
<td></td>
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<tr>
<td>Testicular volume preservation</td>
<td></td>
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<tr>
<td>Reimbursement possible</td>
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</table>

Recommendation

In azoospermia caused by epididymal obstruction, a surgical exploration with microsurgical epididymal sperm aspiration and cryopreservation of the spermatozoa should be offered, together with microsurgical reconstruction (MSE).

Summary

- Semen analysis
- History & examination
- Referral for further evaluation & treatment
- If <10 million/ml
  - FSH, LH, prolactin, testosterone, TFT
  - Karyotyping
  - Y-chromosome deletion
  - Cystic fibrosis if absent vas deferens
- Surgical sperm retrieval for azoospermia, or severe oligosperma when appropriate
Quiz

- How about eggs...
  - How many is enough in a fresh cycle?

Thank you

Sunkara et al., Hum Reprod, 2011