Facts and fiction in the management of male infertility

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Diagnosis of male factor infertility
Diagnostic tests

The evaluation of diagnostic techniques is less advanced than that of treatments. Unlike with drugs, there are generally no formal requirements for adoption of diagnostic tests in routine care.
In spite of important contributions, the methodology of diagnostic research is poorly defined compared with study designs on treatment effectiveness, or on etiology, so it is not surprising that methodological flaws are common in diagnostic studies.

(Grol, 1997; Geijer et al, 1999; Zaat et al, 1992)
Several factors may be responsible for the increasing use of investigations:

- increasing demand for care.
- Availability.
- The urge to make use of new technology.
Conventional semen analysis is the gold standard investigation for the male.
WHO new reference values for Human semen (2009)

• Based on semen samples from:
  – 4500 men
  – 14 countries
  – 4 continents
  – Samples taken from fertile men, normozoospermic men and men of unknown fertility
WHO new reference values for Human semen (2009)

• Lower limits of normal semen (with 95% CI)
  – Volume 1.5 ml (1.4 – 1.7)
  – Sperm concentration 15 millions per ml (12 – 16).
  – Total sperm count 39 millions per ejaculate (33 – 46)
  – Vitality: 58% live (55 – 63).
  – Progressive motility: 32% (31 – 34)
  – Total motile sperms 40% (38 – 42)
  – Normal morphology 4% (3 – 4)
Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system (Hamilton et al., 2015)

• In a large study of male subfertility patients waiting for spontaneous pregnancy, total motile sperms count was a better indicator than WHO classification.

• Severity of male factor was assessed by three prognostic groups, TMSC less than 5 millions, between 5 – 20 millions, and over 20 millions.
Computer-assisted semen analysis systems (CASA):
Comparison with routine evaluation and prognostic value in male fertility and assisted reproduction showed that CASA is of limited value as compared to conventional semen analysis in optimising the evaluation of male infertility.

(Krause 1995)
A prospective double blind cohort study comparing conception in antisperm antibody-positive and antibody-negative couples showed similar prognosis for conception.

(Collins et al., 1993)
Sperm function tests

- Sperm motion analysis.
- Induced acrosome reaction.
- Sperm penetration assay.
- Sperm zona pellucida binding.

Validity and clinical application of these tests are not confirmed and they need standardization and more future research.

Oehninger et al., 2000
Microdeletion and male factor

• Microdeletion occurs in about 1:4000 men in the general population
• In severe male factor and azoospermia, it could reach 2-10% (Krousz et al., 2013)
Microdeletion of Y Chromosome
The diagnosis of complete deletion AZFa region implies the virtual impossibility to retrieve testicular spermatozoa for ICSI (Vogt et al., 1996)
Complete deletion of AZFb and AZFbc are characterized by histological picture Sertoli cell only syndrome with no testicular sperm present. (Krausz et al., 2000)
Deletion of AZFc region are associated with variable clinical and histological phenotype (Reijo et al., 1996). There is residual spermatogenesis in these patients and in 50% of them sperm could be retrieved.
Treatment of male factor infertility
Optimal treatment should be:

• Effective
• Safe
• At the lowest cost
Evidence-based treatment

- Several established lines of treatment are based on pilot or retrospective studies and certain treatment modalities were proven to be not effective in the era of evidence-based medicine.
Evidence based medicine has been established as an essential tool for the practice of medicine, however, we should remember that what is statistically significant might not always be clinically relevant.
Until recently, it was acceptable to look for \( P \) values in the results and the difference is considered significant if \( P < 0.5 \).

The magnitude of the effect of the intervention is of utmost clinical importance to evaluate the implications of this significance.
Evidence based Medicine is not a static science. It undergoes a process of continuous evaluation with the publication of new data.
Grade A Evidence (RCOB) for Treatment of Male Infertility

Drug treatment for idiopathic male infertility has to be considered experimental and should take place only in the context of controlled trials.
On-label and off-label drugs used in the treatment of male infertility (Chehab et al., 2015)

- While the role of hormone therapy for men with an identified abnormality is well defined, the literature remains inconclusive and controversial regarding hormone manipulation using empirical (off-label) medical therapies for men with idiopathic infertility.
Infection of the male genital tract should be treated if present, but there is no evidence that this will improve fertility (Grade A).
Pregnancy rate after IUI for treatment of male factor is low, and only slightly increased compared to no treatment and considerably less than ICSI. (RCOG)
IUI versus timed intercourse in natural cycles in couples with subfertile male factor – a meta analysis of 6 randomized studies, (Cohlen 2005)

<table>
<thead>
<tr>
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<th>IUI</th>
<th>Intercourse</th>
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<tbody>
<tr>
<td>Cycles</td>
<td>608</td>
<td>561</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
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OR 3.1, 95% CI 1.5-6.3
Meta-analysis of COH + IUI versus COH + timed intercourse in male subfertility (Cohlen 2005)

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<tr>
<th></th>
<th>COH+ IUI</th>
<th>COH + timed Intercourse</th>
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<tbody>
<tr>
<td>Cycles</td>
<td>438</td>
<td>432</td>
</tr>
<tr>
<td>Pregnancies</td>
<td>46 (10.5%)</td>
<td>22 (5%)</td>
</tr>
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OR 2.1, 95% CI 1.3-3.5
Surgery for varicocele in subfertile men: (A Cochrane review) (Evers et al., 2009)

• Eight randomized studies comparing the outcome for varicocelectomy versus no surgery
• Showed: OR 95%, CI 0.73 – 1.68 indicating no benefit for varicocelectomy.
Surgery of varicocele in subfertile men Kroese 2012

- Ten studies, 894 men, no studies reported live birth.
- OR 95% CI 1.05-2.05
- There is evidence that varicocelectomy may improve couples’ chance of pregnancy, however, the evidence is low.
Future of varicocelectomy

- All andrologists feel a prospective study on varicocelectomy is important (Trussell et al., 2014)
- Most results are retrospective and poor quality.
- Randomized trials are conflicting and methodologically poor.
Varicocelectomy
Trussell et al., 2014

• A planned randomized study of microgurgical varicocelectomy versus no treatment of male factor was planned to start in 5 US major centers.

• All 5 centers failed to recruit adequate number of patients because:
  – Lack of interest of urologists.
  – Previous medical treatment for the male.
  – Lack of interest of placebo arm.
The royal College book on Evidence-Based Fertility Care states that “there is insufficient evidence for improvement of the pregnancy chances after varicocele surgery, although there seems to be a small increase in sperm counts”.
Close attention to female age and the duration of subfertility helps to avoid lost opportunity through delays in treatment when IVF with ICSI is indicated. Future trials of male fertility treatments should focus on pregnancy as the primary outcome, rather than less important surrogates such as sperm quality. (Hughes et al., 2015)
Future prospects for treatment of male infertility
The urge to have one’s own biological child supersedes any desire in life
Evidence on the use of stem cells in treatment of male infertility
Stem cells for regeneration of spermatogenesis

- Adult tissue stem cells SSCs are located in basement membrane of seminiferous tubules.
- They are self-renewing and differentiating divisions to maintain continuous sperm production after several mitotic division and two meiotic divisions to produce sperm (Valli et al., 2014).
SSC culture

- In rodents cells can be greatly expanded and maintain competence to generate spermatogenesis and retrieve fertility (Kanatsu-shinohara 2003)
Tarford et al. (1999) in Manchester performed autologous transplantantation in the human.

- 12 patients with non hodgkin lymphoma had a cryopreserved cell before starting chemotherapy.
- 7 patients had their cells injected in the testis.
- No outcome results were published.
Culture of SSC cells of large animal species was successful (Izadyar 2003).

• A number of researches were able to culture human SSCs but they were not able to evaluate the full spermatogenesis potential of culture cells (Chen et al., 2009)
Several researchers cultured human SSC in vitro (WU 2009)

• The studies are promising but challenged by the inability to evaluate their full spermatogenesis potential.
Elhija et al. (2011) cultured testicular cells from a 7 days old mice and produced morphologically normal sperm. Studies are needed to confirm that these sperms are capable of fertilization.
Sato et al., (2013) demonstrated that haploid germ cells from mice could be generated in testicular tissue organ culture. The produced sperm which was capable of fertilizing oocytes and they resulted in normal offspring)
Hayashi et al., (2011) used pluripotent stem cells. These cells can be induced to primordial germ cells which, if transplanted in infertile mice and generate spermatogenesis and fertilize, gave rise to offspring. We should wait for replication of the study.
Clinics worldwide are preserving testicular tissue which does not have sperms with hope of a future successful procedure (Vali et al., 2014)
Problems of transplantation in the human

• Few SSCs cells can be obtained for the human
• Very few cells are present in the prepubertal testis.
• In cancer there is a risk of reintroducing the malignant cells.
Herman et al. (2014) was able to obtain functional sperm after autologous SSC transplantation in non-human primates. They were able to produce blastocystcs after IVF.
Currently via stem cells

There are tens of serious publications in *Nature* and in *Science* on how to develop eggs and sperms in experimental animals. Still we are far from developing this for the human.
Conclusion 1

- Conventional semen analysis is the gold standard test of male infertility.
- Medical and hormonal treatment have no value in the treatment of male factor.
- IUI has a very small chance to improve pregnancy rate.
- Varicocelectomy may improve the pregnancy rate in male infertility, however its value is very small.
Conclusion 2

- ICSI gives excellent results particularly if the wife is young.
- Sperm donation is effective but it is not allowed in many countries.
- So far there is no evidence that the use of stem cells in the human in total absence of sperms is of any value.