Updates on office based, cost-effective evaluation of male infertility

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Male Reproductive Medicine

One of the fastest growing subspecialties in Urology

- Microsurgeries
- Robotic Telesurgery
- Genetic evaluation
- Sperm DNA evaluation
- Sperm retrieval techniques
ICSI: Intra-Cytoplasmic Sperm Injection

Danger in bypassing male fertility evaluation

- Couples may be counseled for unnecessary assisted reproductive treatments when there are male factor infertility that can be treated to improve their fertility status.

- Male infertility can be associated with severe underlying illnesses
  - Malignancies (testicular cancer, hematological malignancies, etc)
  - Osteoporosis/osteopenia
  - Hormonal disorders (Kallmann syndrome, thyroid disorder, hyperprolactinemia)
  - Genetic disorders (e.g. Klinefelter, Y-Chrom microdeletion, Cystic fibrosis, Kartagener syndrome)

Chan PTK, Schlegel PN. AUA; June 2-7, 2001; Anaheim, CA. Abstract 1435.
Yang et al., Int J Androl 2012
Reasons for Evaluation of Male Fertility

- Should be done before female evaluations
- Evaluating men is easier than evaluating women

Scrotum and testes are more assessable than female reproductive organs for evaluations!

HOW TO EVALUATE MALE FERTILITY?

- History & Physical Exam
- Semen analyses
- Blood tests

1. Find out any reversible causes of infertility
2. Find out any serious underlying diseases
3. Azoospermia:
   - Is there an obstruction?
   - Is it testicular failure?
HISTORY – WHAT QUESTIONS TO ASK

- Duration of infertility and previous history of fecundity
- Previous fertility treatments
- Developmental history and childhood illnesses
- Coital frequency/timing? history of STI’s? Erectile dysfunction?

(Chan, Rosenwaks and Goldstein, In: "Reproductive Medicine Secrets", 2004.)

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HISTORY – WHAT QUESTIONS TO ASK

- Duration of infertility and previous history of fecundity
- Previous fertility treatments
- Developmental history and childhood illnesses
- Coital frequency/timing? history of STI's? Erectile dysfunction?
- Systemic medical illnesses and surgical history
- Family history of fertility and systemic illnesses
- Life style and psychosocial stress factors
- Exposure to gonadotoxins and heat.

(Chan, Rosenwaks and Goldstein, In: "Reproductive Medicine Secrets", 2004.)

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PHYSICAL EXAMINATION

- General physique, secondary sexual characteristics
- Stigmata of genetic anomalies
- Penis anatomy, urethral opening location
- Testes size and texture
- Presence of varicoceles
- Excurrent ductal system (vasa, epididymides)

(Chan, Rosenwaks and Goldstein, In: "Reproductive Medicine Secrets", 2004.)

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HORMONAL EVALUATION

- NOT all men need hormonal evaluation upfront
- [sperm] < 10 million/ml
  Sexual dysfunction
  Other symptoms or signs suggesting endocrinopathies
- Morning total T and FSH
  LH, bio-available T, estradiol prolactin if hypogonadal
  TSH if clinical thyroid dysfunction

FSH should be 1-6 IU/ml even though “normal” reference range is 2-13 IU/ml

- FSH < 1 with ↓↓[sperm] suggest hypogonadotropism
  FSH > 8 with ↓↓[sperm] suggest testicular dysfunction
- Inhibin B not for routine use due to high cost and impracticality
MALE FERTILITY EVALUATION

- History & Physical Exam

- Semen analyses
  - WHO criteria – sperm concentration, motility, morphology
  - pH, volume, fructose
  - Anti-sperm antibodies – unexplained infertility, poor motility
  - Vitality test – poor motility (live sperm or dead sperm?)
  - WBC stain
  - Semen culture

SEMEN ANALYSES

- Most commonly used investigation for male fertility evaluation

- Main parameters: sperm concentration, motility, morphology.
SEMEN ANALYSIS

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SEMEN ANALYSIS

SEMEN DETEC+OR

1. Connecting
Connect device to your smartphone via Bluetooth.

2. Operating
Follow the instructions on the app to complete the sampling process.

3. Feedback
After review of big data and doctors inspection, the result will be sent back to your phone app.

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WHO REFERENCE VALUES

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<tbody>
<tr>
<td>Volume (ml)</td>
<td>ND</td>
<td>≥ 2</td>
<td>≥ 2</td>
<td>≥ 2</td>
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<td>Sperm concentration (10⁶/ml)</td>
<td>20-200</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>≥ 20</td>
<td>≤ 15</td>
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<tr>
<td>Total sperm count (10⁹/ml)</td>
<td>ND</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 40</td>
<td>≥ 30</td>
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<tr>
<td>% Total motility</td>
<td>≥60</td>
<td>≥50</td>
<td>≥50</td>
<td>≥50</td>
<td>≥40</td>
</tr>
<tr>
<td>% Progressive motility †</td>
<td>≥ 60</td>
<td>≥ 25</td>
<td>≥ 25 (a)</td>
<td>≥ 25 (a)</td>
<td>≥ 32 (a+b)</td>
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<tr>
<td>% Normal Morphology §</td>
<td>80.5</td>
<td>≥ 50</td>
<td>≥ 30</td>
<td>≥ 14</td>
<td>≥ 4</td>
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</tbody>
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WHO, World Health Organization; ND, not defined.
* Lower reference limit obtained from lower 5th centile value.
† Grade a, rapid progressive motility (25 m/s); grade b, slow/sluggish progressive motility (≤ 25 m/s); normal, 50% motility (grade a) or 25% progressive motility (grade a); within 60 min of ejaculation.
‡ Forward progression (scale 0-3).
¶ Value not defined, but strict criterion suggested.
§ Strict (Tygerberg) criterion.

References values were derived from "young, fertile" men (n=1953):
- ≤12 months time-to-pregnancy
- Mean age 31±5 yrs (only 10 men > 45 yrs)
- 5 studies in 7 countries on 3 continents

Data were used to determine the one-sided lower (5th-centile) reference limits
- Lower "normal" limits
- One-sided because no one cares if sperm parameters are super high

[Graph: sperm ≥ 15 x 10⁶/ml, % progressive motility ≥ 32%, % normal/morphology ≥ 4%]
**WHO REFERENCE VALUES**

What is the significance of the WHO “reference” values??

- The averages of the population parameters? NO!
- The minimum to be considered fertile? NO!
- Above them means you are fertile? NO!
- Below them means you are infertile? NO!

**CORRECT WAYS TO USE THE WHO REFERENCE VALUES**

- The 50th percentile is [sperm] ≥ 73 x 10^6/ml
  % progressive motility ≥ 61%
  % normal morphology ≥ 15%

- Men in a couple with a history of infertility having parameters meeting the WHO reference values may still have male factor infertility that needs evaluations and treatments.
GENETIC EVALUATIONS

- CFTR (cystic fibrosis transmembrane conductance regulator) on Chrom 7
- Azoospermia with CBAVD or CF, low semen volume, Idiopathic obstruction of the excurrent ductal system.
- CUAVD, family history of CF or CBAVD
- Women with a male partner with CFTR mutation
- High success for surgical sperm retrieval for ICSI

GENETIC EVALUATIONS

- Prevalence depends on races
- The phenotypes depends on the mutations (Class 1-5)
- More than 1700 mutations in human CFTR gene
- Not all mutations are tested. Test panels usually cover >90% of clinically significant mutations of the population
- “Normal” test does not 100% rule out rare mutations
- Genetic counseling indicated
GENETIC EVALUATIONS

- Karyotype and Y-chromosome microdeletion
- Indicated in severe idiopathic spermatogenesis impairment
- ↓[sperm] (< 5 million/ml) with high FSH
- Klinefelter’s syndrome (47XXY) most commonly diagnosed Karyotypic disorder in infertility
- Deletion of AZFa, AZFb, AZFc regions of Y-chromosome
- Genetic counseling indicated

GENETIC EVALUATIONS

- CFTR, Karyotype and Y-chromosome microdeletion
- Do not order all three for every men with ↓[sperm]
HOW DO WE ASSESS SPERM?

Sperm Genetic Integrity

- TUNEL Assay
- Comet Assay
- Multi-color FISH
- In-situ nick translation assay
- Acridine orange test
- Sperm Chromatin Structure Assay®

Sperm DNA integrity – clinical significance

Some assays can predict failure of ART

- High DNA fragmentation > 27% correlates with lower success of pregnancy with IVF/ICSI (Larson-Cook et al., 2003)
- High sperm DNA fragmentation correlates with risks of pregnancy loss (Benchaïb et al., 2003; Bungum et al., 2004)
INDICATIONS OF TESTICULAR SONOGRAM IN MALE FERTILITY EVALUATION

Not all infertile men need a testis sonogram!

Testis sonogram cannot substitute a thorough physical examination

- R/O varicoceles when a thorough physical examination cannot be performed
  - Size of patient
  - Tight scrotum
  - Sensitive/ticklish scrotum
  - Unequivocal right-sided varicoceles
  - Objective documentation of varicoceles prior to therapy

- Assessment of complications after surgical sperm retrieval/vasectomy
  - Hematoma
  - Infection
  - Ischemia

- Reevaluation of varicoceles after initial management
  - Recurrent varicoceles
  - Persistent varicoceles
WHY SHOULD UROLOGISTS PERFORM SONOGRAMS FOR THEIR OWN PATIENTS?

- Radiologists experienced in scrotal ultrasound are great resources
- Urologists are in good position to develop their own experience
  - Urologists examine their own patients
  - Better patient satisfaction: no referral, no time lost, quick results
  - Non-invasive, low cost examination
  - Urologists are ultimately responsible for the findings, whether they choose observation, surgery or other forms of management
  - Cut the middle person to avoid unequivocal interpretations

BEWARE OF THE FOLLOWING ISSUES

- Continuing Medical Education
- Learning curve – even after proper training
- Licensure issues – verify with your local authorities
- Medicolegal responsibilities
  - SOPM – Standard Operating Procedure Manuel
- Cost of machine
SUMMARY

- A thorough and cost-effective male fertility evaluation remains an important part of the management of an infertile couple.
- A detailed history, properly conducted physical examinations along with semen analyses are the first steps in the initial assessment.
- Urologists should be up to date on the latest guidelines on the indications and interpretations of the results of latest diagnostic modalities.

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