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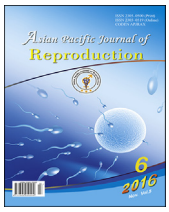

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Evaluation of infertile men: Mini-review

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ABSTRACT

Evaluation of infertile couple indicated because of failure of conception for one year of unprotected intercourse, and indicated for the infertile couple because of failure of conception for 6 months of unprotected intercourse if the female partner is above 35 years. Initial male partner evaluation includes: 1) thorough reproductive history, and at least one semen analysis. If the initial male partner evaluation showed any abnormality, complete assessment needed. Initial assessment of the infertile male include; thorough reproductive history, and at least one semen examination. Endocrine assessment indicated for males with abnormal semen analysis. Post-ejaculatory urine analysis performed in males having <1 mL ejaculation volume, except in congenital bilateral absent vasa deferentia (CBAVD), and hypogonadism. Genetic testing for cystic fibrosis transmembrane conductance regulator (CFTR) mutations offered to male with CBAVD before IVF. Males with severe oligozoospermia and/or non-obstructive azoospermia are at risk of genetic abnormality, and must offered karyotype and Y-chromosome testing before IVF.

1. Introduction

A previously fertility male, may acquire a secondary disease causing secondary infertility. Initial male partner evaluation include; thorough reproductive history and at least one semen analysis. If the initial male evaluation showed any abnormality, complete male assessment needed [1,2].

Methods of complete male evaluation include; 1) complete history, examination, and semen analysis by a male reproduction specialist; 2) endocrine evaluation; 3) post-ejaculatory urine analysis; 4) ultrasound; 5) specific semen and sperm tests; 6) genetic testing [1,2].

History and examination of the male partner include; 1) coital frequency; 2) duration of infertility; 3) medical disorders (upper respiratory diseases, diabetes mellitus); 4) previous surgery, and drug allergies; 5) previous sexually transmitted infections; 6) exposures to environmental or chemical gonadal-toxins.

2. Semen analysis

Semen analysis is a basic step in infertile male assessment, and the physician should provide the male partner with the proper instructions for semen collection such as pre-examination abstinence interval [3].

Semen should collected at the laboratory or at home by intercourse or by masturbation using special condoms not containing toxic sperm materials. If the semen sample collected at home, the sample should transferred to the laboratory for examination within 1 h, and kept at body temperature during transfer [4].

Semen examination report should provides information about the volume of the semen sample, the concentration of the sperm, viability, motility, and the morphology of the sperms in the sample.

According to world health organization definitions, lower limit of normal semen sample should contains: 1.5 mL volume, 15×10^6 spermatozoa/mL (total sperm number 39×10^6 spermatozoa/ejaculate), 40% of the sperms of the sample motile (32% forward progressive motility), 4% of the sperms of the sample with normal morphology with absent of agglutination in the sample [5].

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Detailed sperm morphology is not needed except after failed *in-vitro*-fertilization (IVF) and before *intra*-cytoplasmic injection (ICSI) [6].

Sperm concentration ≥48 million/mL, motility ≥63%, and morphology ≥12% usually seen in normal fertile male. Sperm concentration <13.5 million/mL, motility<32%, and morphology <9% normal usually seen in sub-fertile male [7].

3. Complete assessment of the infertile male

If the initial assessment of the male partner showed abnormality in the semen sample a complete male assessment needed. The complete assessment of the male partner includes; 1) Thorough reproductive history and thorough examination performed by male reproduction specialist; 2) endocrine evaluation; 3) post-ejaculatory urine analysis; 4) ultrasound; 5) specific semen and sperm tests; and 6) genetic testing.

3.1. Thorough reproductive history and thorough examination performed by male reproduction specialist

Thorough history should includes; 1) Thorough evaluation of the whole body systems; 2) family history of infertility; 3) use of anabolic steroids.

General physical examination includes; 1) Thorough genital examination; penis, testes, epididymides, and both vasa; 2) the reproduction specialist examining an infertile male should comment on presence or absence secondary sexual character and/or varicocele and perform per rectal examination if needed.

The reproduction specialist can diagnose the congenital bilateral absent vasa deferentia (CBAVD) by general and scrotal examinations.

3.2. Endocrine evaluation

Endocrine disorders are uncommon in males with normal semen analysis. Endocrine evaluation is needed for male with; 1) <10 million/mL sperm concentration; 2) sexual dysfunction; 3) history or examination findings suggestive of endocrinopathy.

The initial hormonal evaluation includes: serum follicle stimulating hormone, and total serum testosterone (T). If the total serum T level is < 300 ng/mL, more evaluation is needed, and includes morning total serum testosterone and free serum testosterone, prolactin, and luteinizing hormone, to identify the source of abnormal total testosterone level [8]. Carter *et al*., suggests that the serum inhibin B level are lower in infertile male, and related with the sperm parameters better than the follicle stimulating hormone [9].

3.3. Post-ejaculatory urine analysis

Low volume or absence of the semen in the sample suggests incomplete collection, obstruction of the ejaculatory duct, retrograde ejaculation, or CBAVD. In order to exclude the possibility of retrograde ejaculation; a post-ejaculatory urine analysis performed in males having <1 mL ejaculation volume, except in CBAVD and hypogonadism.

3.4. Ultrasound

The male genital tract can easily and accurately imaged using ultrasound. Ultrasound can detect male genital tract abnormalities that may cause infertility. Trans-rectal ultrasound can diagnose seminal vesicles, prostatic and ejaculatory ducts abnormalities. Scrotal ultrasound can diagnose varicocele, absent vasa and testicular lesions [10].

3.5. Specific semen and sperm tests

Specific semen and sperm tests include: 1) Identification of leukocytes in the semen sample; increased white blood cells (WBCs) count in semen associated with decreased motility, and function of the sperms. The immature germ cells and WBCs appear as round cells under microscopic wet-mount examination. WBCs cells can differentiated from the immature germ cells by the immuno-histo-chemical staining [11].

2) Antisperm antibodies (ASA); Infertile couple due to ASA typically treated with ICSI. ASA suspected when there is isolated asthenospermia with normal semen parameters, and normal sperm concentration. ASA developed after break in blood-testis barrier as after trauma, testicular biopsy or vasectomy. ASA in the serum or in the seminal fluid detected using indirect antibody agglutination test. ASA bound to the sperms detected using immuno-bead test [12,13].

3). Sperm viability. Assessed by mixing semen with eosin dye (eosin dye test). Viable sperm remain colorless after mixing with eosin dye, while non-viable sperm will take up the eosin stain [14,15].

4). Sperm DNA fragmentation; The term "DNA fragmentation" means no repairable damage of the DNA of the sperm. This damage of the sperm DNA detected by 1) Direct tests, including single-cell electrophoresis (Comet), and terminal deoxy-nucleotide transferase–mediated dUTP nick-end labeling (TUNEL) [16–18]. 2) Indirect tests, including sperm chromatin structure, to identify the abnormal structure of the chromatin, and increased liability of DNA of the sperms to denaturation.

DNA damage of the sperms is common in infertile males, and males with decreased reproductive ability. ICSI with retrieved sperms through testicular aspiration or testicular biopsy is the best treatment for males with abnormal ejaculated sperm DNA integrity [19,20].

3.6. Genetic testing

Males with severe oligozoospermia and/or non-obstructive azoospermia are at risk of genetic abnormality, and must offered karyotype and *Y*-chromosome testing before IVF [21].

Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations seen in eighty percent (80%) of the males diagnosed as CBAVD. CFTR gene mutations increased among azoospermia males, CBAVD, and men with vasa agenesis.

Chromosomal abnormalities seen in 10%–15% of the azoospermic males. Sex chromosomal abnormalities (Klinefelter syndrome) constitute 2/3 of chromosomal abnormalities found in infertile males. Balanced chromosomal translocation is also high in infertile males [21].

Males with non-obstructive azoospermia, or severe oligozoospermia should have chromosomal study before using their sperm for IVF [22].

Y-chromosome micro-deletions seen in 16% of infertile males with azoospermia or severe oligospermia. *Y*-chromosome micro-deletion detected with PCR testing to visualize the whole *Y* chromosome length. Most deletions causing oligozoospermia or azoospermia occur in the *Y*-chromosome long arm known as

the azoospermia factor; identified as proximal, central and distal. Sixteen percent (16%) of men with *Y*-chromosome micro-deletion had short-stature-homeo-box abnormalities. Short-stature-homeo-box abnormalities mean short stature males with arm and wrist deformities, and mental retardation. *Y*-chromosome micro-deletions rarely found in male who has children [23–25].

Sperm chromosome aneuploidy can found in infertile males with sperm morphology, and karyotypic abnormalities. Six percent (6%) of infertile males with normal chromosomal study had a tendency of meiotic abnormalities in their sperms [26–29].

4. Conclusion

Initial assessment of the infertile male include; thorough reproductive history, and at least one semen examination. Endocrine assessment indicated for males with abnormal semen analysis. Post-ejaculatory urine analysis performed in males having <1 mL ejaculation volume, except in CBAVD and hypogonadism. Genetic testing for CFTR mutations should offered to male with CBAVD before IVF. Males with severe oligozoospermia and/or non-obstructive azoospermia are at risk of genetic abnormality, and must offered karyotype and Y-chromosome testing before IVF.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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