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Effectiveness of hCG and Aromatase Inhibitors Before Micro TESE in Men with Non-Obstructive Azoospermia

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ABSTRACT

Diabetes mellitus, particularly type 2 diabetes, is a growing global health issue, often exacerbated by insulin resistance, metabolic disturbances, and inflammatory responses. Emodin, a natural anthraquinone derivative, has been widely recognized for its

Keywords: *PCOS, metformin, immunomodulation, mTOR, TGFβ1, IL6.*

1. INTRODUCTION

Azoospermia can arise from pre-testicular or testicular causes affecting spermatogenesis or from post-testicular obstructions with complete spermatogenesis present in histopathology (Jow et al., 1993). Pre-testicular causes involve defects in the hypothalamus or pituitary gland leading to impaired FSH and/or LH production, resulting in secondary testicular spermatogenic failure. Primary spermatogenic failure, which is not due to hypothalamic-pituitary issues, presents as severe azoospermia with various underlying causes. Testicular causes of azoospermia, termed non-obstructive azoospermia, include these primary spermatogenic failures (Jarow et al., 1989).

2. ETIOLOGY

Table (1) Causes of non-obstructive azoospermia (Fahmy, 2010)

- **Congenital causes**
  - **Genetic disorder**
    - **Klinefelter's syndrome**
    - **Y chromosome microdeletions**
    - **Myotonic dystrophy**
    - **Kennedy's syndrome**
    - **Androgen insensitivity syndromes**
    - **Noonan's syndrome**
    - **Sex reversal syndrome (XX male)**

- **Other disorders**
  - **Maldescended testes**
  - **Bilateral anorchia (Vanishing Testis Syndrome)**
  - **Gonadal dysgenesis**
  - **Varicocele**
- **Acquired Causes**
- **Trauma**
- **Testicular tumors**
- **Testicular torsion**
- **Medications**
  - **Cytotoxic drugs**
  - **Hormones (androgens, antiandrogens, estrogens, progestogens, anabolic)**
  - **Hormonally active drugs (cimetidine, spironolactone, digoxin, ketoconazole)**
  - **Psychotropic drugs, certain antiepileptics, antiemetics,**
  - **Anthelminthics (niridazole)**
  - **Salazosulphapyridine**
- **Radiotherapy**
- **Surgeries that can cause devascularization of the testes**
- **Infections**
  - **Viral infections (Mumps orchitis, influenza)**
  - **Bacterial (brucellosis, typhoid fever)**
  - **Specific granulomas (Syphilis, Leprosy)**
- **Environmental factors (toxins, irradiation, heat)**
- **Systemic diseases (liver cirrhosis, renal failure)**
- **Idiopathic**

3. CONGENITAL CAUSES OF NON-OBSTRUCTIVE AZOOSPERMIA

Klinefelter's Syndrome

Among congenital malformations, Klinefelter's syndrome is the most prevalent, affecting 1 in 500 male infants. With an additional X chromosome, around 11% of azoospermic men and 0.7% of oligozoospermic men have a 47XXY karyotype. Classic karyotypes are 47XXY, whereas mosaic karyotypes are 46XY/47XXY (Ahmed et al., 2025).

The presence of extra X chromosomes during gametogenesis, which can originate from either the mother's (44%) or father's (53%) genes, causes this disorder (Smyth et al., 1998). Clinical presentations vary: prepubertal cases show cryptorchidism and developmental disorders, puberty cases present with small testes, developmental disorders, and gynecomastia, while adults typically report infertility, small testes, reduced libido, and erectile dysfunction. Laboratory findings include azoospermia in 89.3% and oligozoospermia in 10.7%, with elevated FSH, normal to low testosterone, and increased estradiol (Pacenza et al., 2012).

Y Chromosome Microdeletions

Microdeletions on the Y chromosome, affecting 3-15% of cases, lead to severe spermatogenic impairment. These deletions affect regions AZFa, AZFb, and AZFc on Yq11.23. AZFa causes complete germ cell absence, AZFb leads to spermatogenic arrest, and AZFc may cause azoospermia or severe oligozoospermia (Chan and Schlegel, 2000). These deletions are often de novo and rarely transmitted through pregnancy.

Sex Reversal Syndrome (XX Male)

Sex reversal syndrome presents similarly to Klinefelter's syndrome but with shorter stature, hypospadias, and fewer mental deficiencies. Patients have a 46XX chromosome complement due to translocation of the SRY gene from the Y to the X

chromosome during paternal meiosis, leading to testicular development but infertility due to loss of other essential spermatogenesis genes (Fechner et al., 1993).

Noonan Syndrome

Noonan syndrome, with a prevalence of 1 in 1,000–5,000, is characterized by short stature, delayed puberty, and fertility issues. Affected individuals often have typical facial features, delayed bone age, and cardiac defects, such as pulmonary valve stenosis and ventricular septum hypertrophy, found in 80% of patients (Elsawi et al., 1994). This syndrome should not be confused with "male Turner syndrome" (Nieschlag, 2010).

Other Chromosomal Disorders

Rare autosomal or X-linked disorders, like myotonia atrophica and Kennedy's syndrome, can lead to primary spermatogenic failure. Incomplete androgen resistance (Refenstein syndrome) results in variable androgen deficiency and impaired spermatogenesis (Wieacker and Nieschlag, 2010).

Maldescended Testes

Cryptorchidism affects 0.8% of adult males and is linked to infertility. About 10% of azoospermic men have a history of cryptorchidism. Undescended testes usually become morphologically abnormal after age two, with bilateral cases leading to poorer semen quality. Treatment by six months is recommended to improve fertility (Grasso et al., 1991; Aynsley-Green et al., 1976; Kolon et al., 2004). Orchidopexy should be followed by testicular biopsy to assess the need for LHRH treatment, which can improve fertility chances (Chung and Brock, 2011).

Bilateral Anorchia (Vanishing Testis Syndrome)

One in twenty thousand men suffer with bilateral anorchia, a disorder that causes sexual immaturity since the testes cannot be felt. Despite a typical karyotype, this patient has dangerously low testosterone levels, high blood levels of luteinizing hormone and follicle-stimulating hormone and is otherwise in good health (Saad et al., 2025).

Trauma, vascular damage, infection, or testicular torsion are among potential causes. The hCG stimulation test fails to increase testosterone levels, unlike in other cases with non-palpable testes (Lobaccaro et al., 1993). Diagnosis is confirmed with undetectable AMH and inhibin B levels, and elevated FSH. Treatment with low-dose testosterone during puberty can lead to normal adult height (Brauner et al., 2011).

Gonadal Dysgenesis

In hereditary diseases of gonadal differentiation, known as gonadal dysgenesis or "streak gonads," stromal tissue replaces germ cells and Sertoli/granulosa cells. There are three variations of this condition: straight gonadal dysgenesis (Turner syndrome) characterized by a 45,X karyotype, mixed gonadal dysgenesis (one streak gonad and one differentiated testis), and pure gonadal dysgenesis (two streak gonads). Mutations in genes such as WT1, SF1, SRY, SOX9, and DHH may cause XY gonadal dysgenesis (Hughes, 2008). Surgical excision of streak gonads is necessary in cases where frequent monitoring is not possible due to the high risk of neoplastic transformation. Nieschlag et al. (2010) states that no treatment is currently available for infertility.

Varicocele

A prominent cause of male infertility is varicocele, which is the dilatation of the pampiniform plexus veins. This condition occurs when the spermatic vein valves are not functioning properly, allowing blood to backflow (Pryor and Howards, 1987). It impacts 4.4%-22.6% of the general population, 21%-41% of males experiencing original infertility, and 75%-81% experiencing secondary infertility. It is not known how varicocele affects azoospermia, but it is present in 5% of NOA males (Esteves and Glina, 2005). Weedin et al. (2010) found that out of 233 men who had varicocele surgery and NOA, 39% had sperm that could be motile, and 26% of those guys were able to conceive. A good indicator of success is histopathology; sperm production is more probable in cases of hypospermatogenesis and maturation arrest than in cases with Sertoli cell-only syndrome. According to Miyaoka and Esteves (2012), the only time a subclinical varicocele should be treated is if it is accompanied by a clinical one. Sperm retrieval with micro-TESE is estimated to be 60% successful after varicocele repair (Schlegel, 2009). Inci et al. (2009), found a 2.6-fold improvement in the likelihood of successful sperm retrieval for in vitro fertilization (IVF) after varicocele surgery.

4. ACQUIRED CAUSES OF NON-OBSTRUCTIVE AZOOSPERMIA

Testicular Trauma

Testicular trauma, the third most common cause of acute scrotal pain (Ragheb and Higgins, 2002), can lead to testicular atrophy, affecting 50% of patients with scrotal trauma.

Testicular Torsion

Testicular torsion occurs in 1 in 4,000 males under 25 years (Barada et al., 1989). Key complications include testis loss due

to delayed medical attention (58%), incorrect initial diagnosis (29%), and referral delays (13%) (Jones et al., 1986).

Testicular Tumors

Testicular cancer is associated with reduced fertility compared to age-matched controls and cancer incidence in infertile men is 20 times higher than in fertile men (Raman et al., 2005). Carcinoma in situ is common in biopsies of sub-fertile men Azoospermia or severe oligozoospermia is often observed at diagnosis, but fertility recovery is possible post-treatment (Olesen et al., 2007).

Chemotherapy and Irradiation

Chemotherapy, particularly with alkylating agents (e.g., procarbazine, cyclophosphamide), and cisplatin can lead to long-term azoospermia, with recovery possible within 1-3 years at lower doses (Pryzant et al., 1993). Anthracyclines and microtubule inhibitors have less impact unless combined with more toxic agents. Testicular irradiation with doses as low as 20 rads can cause azoospermia, with recovery time proportional to dose (Meistrich et al., 1989). Effective shielding can mitigate damage, though scatter doses may still exceed safe levels (Meistrich, 1990).

Mumps Orchitis

Post-vaccination, mumps orchitis affects 20%-30% of post-pubertal men, with 10%-30% having bilateral involvement. Affected testicles may experience atrophy, leading to transient oligospermia or azoospermia, and fertility impairment occurs in about 13% of cases (Bartak, 1973).

Renal Failure

Advanced chronic kidney disease impairs spermatogenesis and causes testicular damage, evidenced by reduced ejaculate volume, oligozoospermia, or azoospermia, and decreased motile sperm. Uremia and materials in dialysis tubing may contribute, with reduced testosterone levels observed (Toorians et al., 1997).

Liver Disease

Acute liver disease increases SHBG levels, leading to elevated gonadotropin and sex steroid secretion. Chronic liver failure results in hypogonadism, including infertility, impaired spermatogenesis, and testicular atrophy (Nieschlag et al., 2010).

5. DIAGNOSIS OF NON-OBSTRUCTIVE AZOOSPERMIA

Clinical Evaluation

The initial diagnosis of azoospermia involves a thorough clinical evaluation. This includes inspecting semen sediment from centrifuged specimens, requiring confirmation of sperm absence in two samples. Cases with minimal sperm are termed cryptozoospermia and should be managed similarly, except testis biopsy might be avoided if motile sperm are found (Gamal Eldin et al., 2025).

A comprehensive medical history should address factors affecting spermatogenesis, and a detailed physical examination is necessary to assess secondary sexual characteristics and testicular condition. Using an orchidometer improves testicular size estimation. Epididymal distension or nodularity, as well as the presence of the vas deferens, must be assessed. Other abnormalities, such as varicocele, should be excluded, and co-existent conditions like androgen deficiency or testicular neoplasia should be managed (Jarow et al., 1989).

Laboratory Investigations

Hormonal profiling, including FSH, LH, prolactin (PRL), and testosterone, is crucial. Low levels of FSH, LH, and testosterone indicate hypogonadotropic hypogonadism, often associated with delayed puberty and previous hormonal therapy. Hyperprolactinemia may be due to medication, medical conditions, stress, or pituitary tumors; MRI with gadolinium is used for diagnosis (Abdelzahera et al., 2025).

Effective treatments are available for this condition (Chan and Schlegel, 2000). FSH levels reflect spermatogenesis but are not always accurate for predicting spermatogenesis status, particularly with normal FSH levels. Elevated FSH with small testes typically requires no biopsy to avoid hindering future sperm retrieval (Martin-du-Pan and Bischof, 1995; Fahmy, 2010).

Testicular Biopsy Evaluation

Testicular biopsy reveals histopathological patterns including normal spermatogenesis, hypospermatogenesis, spermatogenic arrest, Sertoli cell only syndrome (SCOS), and tubular hyalinization. These patterns are consistent across various etiologies (Cooperberg et al., 2005; Fahmy, 2010).

6. TREATMENT OF NON-OBSTRUCTIVE AZOOSPERMIA

Diagnosis and Differentiation

The diagnosis of azoospermia is based on the absence of spermatozoa in centrifuged specimens from two separate semen tests taken three weeks apart. For samples with a volume of less than 1.5 mL, it is important to look for signs of retrograde ejaculation or collection mistakes. Once azoospermia has been confirmed, the next important step is to rule out any obstructive factors. Endocrine and exocrine dysfunction, low testosterone symptoms, and risk factors should all be part of a comprehensive physical examination and medical history (Amin et al., 2025).

Gynecomastia, decreased virilization, and other genetic abnormalities or endocrinopathy symptoms should be considered during the routine physical examination. While a digital rectal exam can pick up on blocking cysts or full seminal vesicles, a scrotal exam should show any varicocele or surgical scars. Sera levels of testosterone and follicular stimulating hormone (FSH) are the first to be measured in a laboratory. A non-obstructive azoospermia diagnosis can be made when the FSH level is over 7.6 mIU/mL (Esteves et al., 2011). According to Silber, (2000), genetic testing that includes a karyotype and a Y chromosome microdeletion should be done for all suspected instances.

Role of Interventions

Following genetic testing, medical and/or surgical interventions may be considered before sperm retrieval. Nearly 50% of men with non-obstructive azoospermia may face unsuccessful sperm retrieval despite treatments. Empirical medical treatments are often ineffective in high plasma gonadotropin levels, but they may still benefit men with low endogenous gonadotropins. Gonadotropin secretion issues and low endogenous testosterone (<300 ng/dL) may affect spermatogenesis and Sertoli cell stimulation (Esteves et al., 2010).

Medical therapy

Table (2): Summary review of empirical medical therapy for infertile men with NOA (SC Esteves)

Study	*Design*	*Study group*	*Control group*	*Medication*	*Main findings*
Pavlovich *et al.*[77]	Prospective cohort	43 men with T/E ratio<10	N/A	Testolactone, 50–100 mg twice daily for a mean of 5 months	None of the 12 men who completed 3 months of treatment had sperm in ejaculate; T/E ratios were restored to normal range (>10) in all treated men
Hussein *et al.*[78]	Prospective cohort	42 men with favorable histology (hypospermatogenesis or maturation arrest)	N/A	CC, 50 mg every other day for a mean of 5 months; dose titrated by 25 mg increments until target T levels between 600 and 800 ng dl^{-1} were achieved	64.3% of the men had sperm in posttreatment semen analysis (mean density of 3.8×10^6 ml^{-1}, and motility of 20.8%); all of the men (n=15) who remained azoospermic had success at SR
Selman *et al.*[79]	Prospective cohort	49 men with normal endocrine and genetic profile in whom diagnostic testis biopsy showed maturation arrest and no sperm on wet examination	N/A	rec-hFSH, 75 IU SC on alternate days for 2 months, then dose increased to 150 IU and hCG (2000 IU SC twice weekly) added for another 4 months	None of the patients had return of sperm in ejaculate; posttreatment SRR were 21.4%
Ramasamy *et al.*[80]	Retrospective cohort	56 men with nonmosaic Klinefelter's syndrome and T levels lower than 300 ng dl^{-1}	N/A	Testolactone (50–100 mg) or anastrozole (1 mg) were used orally, alone or combined with SC hCG (up to 2500 IU three times a week) for at least 3 months	SRR were 1.4-fold higher (77% *vs* 55%; P=0.03) in men who responded to treatment with a resultant T level of 250 ng dl^{-1} or higher compared with those men in whom posttreatment T was less than 250 ng dl^{-1}
Reifsnyder *et al.*[29]	Retrospective cohort	307 men with T levels lower than 300 ng dl^{-1}	41 men with T levels lower than 300 ng dl^{-1}; 388 men with T levels higher than 300 ng dl^{-1}	AI (50–100 mg testolactone orally twice daily or 1 mg anastrozole daily), hCG (at a dose of 1500–2000 IU SC twice or three times a week) and CC were used, alone or combined, for at least 2–3 months before surgery	None of the patients had return of sperm in ejaculate; SRR were not different in treated (51%; n=307) and untreated (61% ; n=41) men with baseline low T levels; SRR were not different between treated males with T levels lower than 300 ng dl^{-1} (51%; n=307) and untreated ones with T levels>300 ng dl^{-1} (51%; n=388)
Shiraishi *et al.*[81]	Prospective cohort	28 men with idiopathic* NOA who had negative SR	20 men with idiopathic* NOA who had negative SR	At least 6 months after the first SR attempt, patients received hCG (5000 IU SC three times a week) for 3 months. When FSH levels decreased after hCG (<3 mIU ml^{-1}) recombinant FSH (rec-hFSH, 150 IU SC three times a week) was added for 2 months	Sperm was obtained at the second SR attempt in 6 (21%) of the 28 treated men, but in none of the untreated men (P<0.05)
Hussein *et al.*[82]	Prospective cohort	612 unselected men	116 unselected men	CC (50 mg every other day) alone or combined with hCG (5000 IU SC twice a week) and hMG (75IU SC once weekly) were administered for an average of 5.4 months	Sperm were found in ejaculates of 10.9% of the treated males; in the patients who remained azoospermic, SRR were higher in those who received medical therapy compared with controls (57.0 *vs* 33.6%, P<0.001)

AI: aromatase inhibitor; CC: clomiphene citrate; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; hMG: human menopausal gonadotropin; IU: International Units; NOA: nonobstructive azoospermia; rec-hFSH: recombinant human FSH; SC: subcutaneous; SR: sperm retrieval; SRR: sperm retrieval rates; T: total testosterone; T/E: testosterone to estradiol ratio; N/A: not applicable. *Exclusion criteria were men with Klinefelter syndrome, testis volume<4 ml, T levels<200 ng dl^{-1}, varicocele and cryptorchidism

Clomiphene Citrate and Gonadotropins

Clomiphene citrate (CC), a selective estrogen receptor modulator, competes with estrogen at hypothalamic and pituitary receptors, resulting in increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Elevated LH stimulates androgen production in Leydig cells, increasing testosterone (T) levels. Gonadotropins, such as human chorionic gonadotropin (hCG), also enhance androgen production by binding to LH receptors at Leydig cells, with hCG exhibiting

higher receptor affinity and longer half-life (Kumar et al., 2013).

Aromatase Inhibitors

Aromatase inhibitors (AIs) block the aromatase enzyme, which converts T and other androgens to estradiol. This treatment can correct the T/estradiol (T/E) imbalance often seen in obese men (Hammoud et al., 2010).

Effectiveness and Results

Empirical treatments have shown varying success in sperm production, though all increase endogenous T levels even with hypergonadotropic conditions (Reifsnyder et al., 2012). Notably, hCG-based therapy increased intratesticular testosterone (ITT) by 5-fold (post: 1348.1 ± 505.4 ng/mL; pre: 273.6 ± 134.4 ng/mL; $P < 0.0001$). Additionally, hCG treatment can suppress endogenous FSH levels, potentially benefiting Sertoli cell function, which is crucial for germ cell development (Shinjo et al., 2013).

Mechanisms and Clinical Insights

The exact mechanisms behind these interventions remain unclear, but increased ITT levels may stimulate spermatogonia DNA synthesis and spermiogenesis in patients with residual spermatogenic activity (O'Shaughnessy et al., 2010). Current evidence supports that these medications enhance endogenous T production, but definitive conclusions on sperm production await further well-designed trials. Routine evaluation of T and estradiol levels is recommended for men with non-obstructive azoospermia, with treatment strategies outlined in Figure 1.

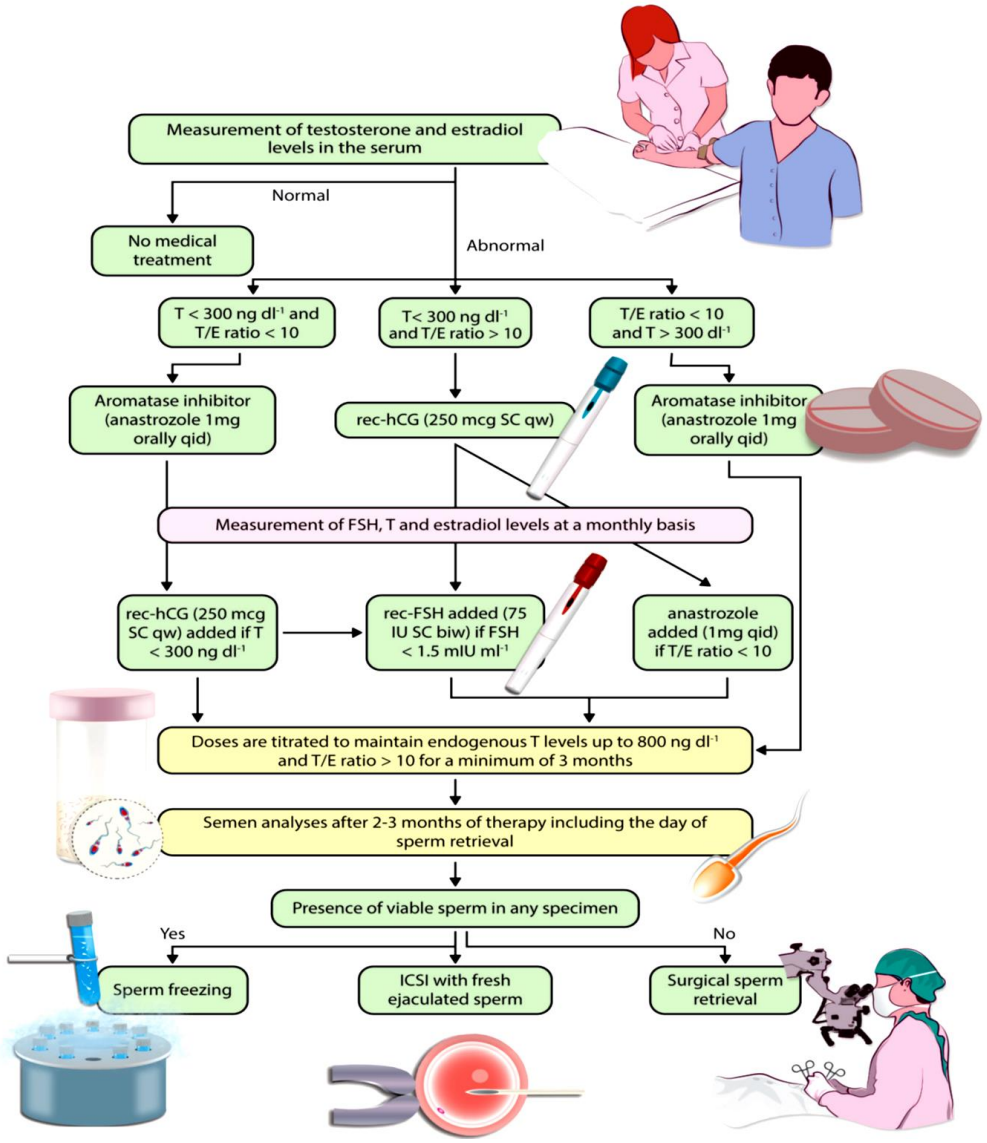

Fig. 1: Algorithm for the medical management of infertile men with non-obstructive azoospermia (Esteves et al, 2010)

7. VARICOCELE REPAIR

Prevalence and Treatment Goals

Varicocele affects around 5% of men with non-obstructive azoospermia (NOA) and is targeted for intervention to improve sperm production (Miyaoka and Esteves, 2012). The goal of varicocele repair is either to detect sperm in the ejaculate, potentially avoiding sperm retrieval (SR), or to increase SR success.

Effectiveness of Varicocelectomy

Varicocelectomy improves sperm production in up to 33% of NOA men, but many remain azoospermic and still need SR. Studies show variable outcomes: Schlegel, (2009) found a 60% SR rate regardless of prior varicocele treatment, while Inci et al. (2009) reported a higher SR success in treated men (53% vs 30%, OR: 2.63, 95% CI: 1.05–6.60; $P = 0.03$). Turunc et al. (2010) observed a 61% SR success in treated men versus 38% in untreated ($P < 0.01$). Microsurgical repair in young men with large bilateral varicoceles could improve SR outcomes, but more controlled trials are needed to validate these findings.

8. CHOICE OF SPERM RETRIEVAL METHOD

Predictors of Sperm Retrieval

Intracytoplasmic sperm injection (ICSI) has expanded options for severe spermatogenesis impairment. Studies on predictors of sperm retrieval in NOA cases, such as testicular volume, FSH levels, testicular blood flow, and histopathology, show mixed results.

- **Testicular Volume**: Research is inconclusive; some studies (Turunc et al., 2010; Ghalayini et al., 2011) suggest a positive correlation between sperm retrieval and testicular volume, particularly if >12 cm^3, while others (Hibi et al., 2005; Seo & Ko, 2001) find no correlation.
- **FSH Levels**: No consistent correlation between FSH and sperm retrieval is found in some studies (Seo & Ko, 2001). Conversely, Colpi et al. (2009) and Ghalayini et al. (2011) report a negative correlation.
- **Testicular Blood Flow**: Doppler ultrasound studies do not reliably predict sperm retrieval success, and further research is needed to explore its potential in identifying isolated spermatogenic foci (Har-Toov et al., 2001).

9. METHODS OF SPERM RETRIEVAL IN AZOOSPERMIA

Major Advances

Two significant advancements in male infertility have been the development of intracytoplasmic sperm injection (ICSI) for men with extremely abnormal sperm (Palermo et al., 1994) and its expansion to men with an absence of sperm (azoospermic men), showing that sperm from either the testis or the epididymis can result in normal fertilization and pregnancy (Silber et al., 1994; Devroey et al., 1995). Azoospermia, in which sperm are not present in the ejaculate, impacts around 1% of males and 10–20% of men who are unable to conceive (Jarow et al., 1989). Sperm generation in the testes is observed in many males despite azoospermia (Esteves et al., 2011).

Percutaneous Sperm Retrieval Methods

- **Percutaneous Epididymal Sperm Aspiration (PESA)**: Described by Craft et al., (1993), PESA involves retrieving sperm from the epididymis without scrotal exploration. Advantages include low cost, repeatability, minimal discomfort, and suitability for obstructive azoospermia. However, it requires a clear diagnosis of obstruction (Esteves et al., 2011).
- **Microsurgical Epididymal Sperm Aspiration (MESA)**: Temple-Smith et al. (1985), introduced MESA, which involves a scrotal incision to retrieve sperm with minimal damage to the epididymis, preserving future reconstructive options and enabling sperm cryopreservation. MESA is invasive and expensive, requiring microsurgical skills (Tournaye et al., 1997).

Sperm Retrieval in Non-Obstructive Azoospermia

- **Testicular Sperm Extraction (TESE)**: TESE involves extracting sperm from the testis, effective for non-obstructive azoospermia (Hauser, 1995). TESE is performed using an open surgical biopsy technique without optical magnification, typically under local or epidural anesthesia (Devroey et al., 1994). It is effective for obstructive azoospermia and ejaculatory disorders.
- **Testicular Sperm Aspiration (TESA)**: TESA uses a fine needle to aspirate sperm from the testicular parenchyma. Turek et al. (1997) developed FNA mapping to locate sperm production sites. TESA is less invasive and costs less compared to TESE but has a lower sperm retrieval rate (SRR) of 10-30% in non-obstructive cases (Friedler et al., 1997; Ezeh et al., 1998; Donoso et al., 2007; Carpi et al., 2009). In cases of previously successful TESA or hypospermatogenesis, SRR may reach 100% (Esteves et al., 2011).

Comparison and Complications

- **TESE vs. TESA**: TESE generally has a higher SRR than TESA, especially in cases of Sertoli cell-only syndrome and maturation arrest. TESE yields an SRR of 49.5% for non-obstructive azoospermia (Donoso et al., 2007).
- **Complications**: Common complications include persistent pain, swelling, infection, hydrocele, and hematoma. TESE, particularly with multiple biopsies, may lead to intra-testicular hematomas and potentially decreased testosterone levels due to testicular damage (Carpi et al., 2005; Ramasamy et al., 2009; Schiff et al., 2005; Turunc et al., 2010).

Microsurgical Testicular Sperm Extraction

Microsurgical Testicular Sperm Extraction (TESE) uses magnification to identify active spermatogenic tubules, seen at 25X magnification, distinguishing them from non-sperm-producing tubules. This technique removes less testicular parenchyma compared to conventional TESE, preserving testicular androgen production in men with non-obstructive azoospermia (NOA) (Esteves, 2011). The sperm retrieval rate (SRR) for microsurgical TESE ranges from 42.9% to 63% (Ramasamy, 2005; Colpi, 2009; Turunc, 2010; Ghalayini, 2011).

Disadvantages

Microsurgical TESE requires surgical exploration, is more costly, time-consuming, and demands specialized microsurgical instruments and expertise, which can lead to increased postoperative discomfort (Esteves et al., 2011).

Sperm Retrieval Rate by Histopathology

Sperm retrieval rates (SRR) vary widely based on histopathological diagnosis of NOA. For Sertoli cell-only syndrome (SOCS), SRR ranges from 15% to 60%, reflecting both differences in surgical and laboratory techniques and possible inconsistencies in interpreting testicular histopathology (Cooperberg et al., 2005).

Table (3) Represent the review of sperm retrieval rate (SRR) as regard the histopathological diagnosis. (Tournaye et al., 1997; Amer et al., 1999, and Donoso et al., 2007)

Histopathology	SRR	Remarks
Hypospermatogenesis	79-100%	The definition is not constant in most studies.
Spermatogenic arrest	25-85%	Early and complete forms have lower SRR.
Sertoli cell only syndrome	16-86%	Complete forms have lower SRR.
Hyalinization	10-42%	Includes patients with KF.

The most frequently reported complications post testicular sperm retrieval were haematoma, fibrosis and testicular atrophy.

Hematoma

Intra-testicular haematoma develops in up to 80% of patients after TESE, with detection based on ultrasounds performed 3 months post-surgery (Schlegel and Su, 1997). Microsurgical TESE shows a lower incidence of hemorrhagic complications compared to conventional TESE, with hypoechoic areas observed in 51% of conventional TESE cases versus 12% in microsurgical TESE cases 1 month after surgery (Okada et al., 2002). Despite its advantages, microsurgical TESE requires specialized skills and equipment, making it less accessible (Friedler et al., 1997).

Fibrosis

Ultrasonographic studies reveal scar tissue formation after TESE. Fibrosis incidence at 6 months is 30% for conventional TESE versus 3.3% for microsurgical TESE (Amer et al., 2000). Additionally, focal echogenic lesions were found in 23% of conventional TESE patients versus none in microsurgical TESE patients (Okada et al., 2002). Microsurgical TESE has been linked to segmental DE vascularization in four patients (Ramasamy et al., 2005).

Testicular Atrophy

Severely oligospermic men's blood testosterone levels are lower and their levels of LH and estradiol are greater, as a result of reduced Leydig cell activity. Osteoporosis, insulin resistance, and depression are all made more likely after a testicular biopsy, which further lowers testosterone levels. Androgen deficit and hypogonadism following TESS are common in men with NOA. According to Okada et al. (2002), these risks may be mitigated with microsurgical TESE compared to traditional TESE since it removes less testicular tissue. Nevertheless, both Ramasamy et al. (2005), that microsurgical TESE does not eliminate the significant drop in testosterone levels. Neither the proportion of patients whose testosterone levels returned to their pre-surgery levels after microsurgical TESE (95% vs. 85%) nor the amounts of testosterone in the blood after traditional

TESE (85% vs. 95%) (Ramasamy et al., 2004; Komori et al., 2004).

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