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Infertility in the Male: A Review and Update

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Abstract

Infertility in a couple may be solely due to female factor infertility, a solely male factor infertility, or both female and male factor infertility. If a couple have undergone regular unprotected coital activities for 12 months without any conception, then the couple would need to be assessed to ascertain in the infertility is a sole female factor, a sole male factor or joint female and male factor infertility. The through assessment of an infertile man should include history taking, clinical examination, routine haematology and biochemistry investigations, endocrine assessment, and analyses of semen. Radiology investigations and genetic testing may be required in selected cases. Many lifestyle and environmental factors could negatively impact upon fertility which the general public may not be aware of and for this reason all clinicians who assess the infertile couple need to educate the infertile couple during their assessments about the lifestyle and environmental factors that affect fertility. Male infertility may be attributable to:

[1] Semen and sperm abnormalities some of which include low sperm count (oligospermia); no sperm at all on semen analysis (azoospermia); sperm motility problems; abnormality of the spermatozoa; a large number of cases of abnormal semen cannot be explained. Increased temperature of the scrotum due to various reasons including varicocele and being a long-time firefighter had been stated to be responsible for reduction in sperm quality.

[2] Testicular factors some of which include: Infections of the testes including specific and non-specific acute and chronic epididymo-orchitis; Malignancies of the testis; Testicular surgical operations; Congenital testicular problems; Undescended testes / cryptorchidism; Testicular injury through direct or indirect injury or torsion.

[3] Sterilisation from previous vasectomy

[4] Ejaculatory disorders

[5] Hypogonadism which at times is due to medicament taking, Klinefelter syndrome, or tumour.

[6] Medicaments and drugs which include: Sulfasalazine: Anabolic steroids; Chemotherapy; Herbal remedies including root extracts of Tripterygium can affect the production of sperm or reduce the size of the testis; marijuana and cocaine can affect semen quality

[7] Unexplained infertility.

There are situations where assessment of both the male and female partners with infertility does not reveal any cause for the infertility and such couples can be treated by means of invitro fertilization. In the United Kingdom about 25% of infertile couples are said to have unexplained infertility.

Various management options are utilized depending upon the cause of the male infertility including: Lifestyle medication, cessation of infertility causative medicaments, taking of medicaments to improve sperm count and quality, surgical operations to relieve obstructive causes of infertility, and assisted conception. Many men with infertility problems have been helped to have their own children out of their own spermatozoa but others have had children by means of donor

assisted conception. There is ongoing research globally to find more ways to help the infertile couple. Men who have infertility problems should be encouraged to seek medical attention.

Key Words: Infertility; male; oligospermia; azoospermia; ejaculation; follicle stimulating hormone, luteinizing hormone, gonadotrophin; aspermia, asthenozoospermia

Introduction:

Infertility had traditionally been considered a problem of women and not a problem of men and married women had been blamed for not being able to continue the family lineage and for this reason new wives were arranged for the infertile man as an attempt to bring new children into the family to continue the family lineage. The diagnosis of male infertility could pose one of the most enormous challenges a man could face especially in some of the developing countries. If a male dignitary including a chief or a king is unable to father a child that tends to pose tremendous headache to the individual, his immediate and extended family. A male factor does contribute to the inability to infertility in about 40% to 50% of all cases of couples who are not able to achieve conception, and this tends to be ensued by tremendous psychological marital stress to the couple, their immediate and extended families. Developments in medical science has enabled clinicians to thoroughly assess couples who have infertility problems, investigate them thoroughly to establish the cause of the infertility in order to address the underlying cause and or provide suitable treatment options that would help the infertile couple have children. Through the development of medical science many men with male factor infertility have been helped to have children but up to date it has not been possible for many other men to have their own biological children. If a couple despite having regular unprotected coital activities for 12 months are unable to achieve pregnancy, a screening assessment of both partners becomes mandatory or essential to address the problem, but this concept has not yet been embraced globally. For the assessment of male factor infertility, this would include careful history taking, thorough clinical examination, endocrine assessment, and analyses of semen. Many lifestyle and environmental factors could negatively impact upon fertility which the general public may not be aware of and for this reason all clinicians who assess the infertile couple need to educate the infertile couple during their assessments about the lifestyle and environmental factors that affect fertility. The ensuing article on male infertility is divided into two parts: (A) Overview, and (B) miscellaneous narrations and discussions from some reported cases, case series, and studies.

Aim:

To review the literature related to male infertility.

Method:

Internet data bases were searched including Google, Google scholar, Yahoo and PUBMED. The search words that were used included: Male infertility, male factor infertility, and infertile man. Eighty-five references were identified that were used to write the review which has been divided into two parts: (A) Overview and (B) Miscellaneous narrations and discussions from case reports, case series, reviews and studies on male infertility.

Result/Literature Review:

(A) Overview

Definition and General Comments.

Infertility in the male refers to the inability of a male to cause conception in a fertile female. It has been stated that in human being's male infertility does account for 40% to 50% of all cases of infertility. [1] [2] [3] It has also been documented that infertility in the male does affect about 7% of the male population [1] [5] and that infertility in the male has commonly been a sequel of deficiencies in semen and that the quality of semen is utilized as a surrogate measure of male fecundity. [1] [6]. Infertility in the male does cause a lot of anxiety to the infertile male as well as his partner as well as the extended families of the couple.

Causes of male infertility:

The causes of infertility had been summated as follows: [1] [7]

- Immune infertility.
  - It has been stated that anti-sperm antibodies (ASAs) had been considered as a cause of infertility among 7% to 10% of infertile couples and that production of ASAs tend to be directed at surface antigens of spermatozoa which could interfere with the motility of spermatozoa as well as transport of spermatozoa via the female reproductive system which do inhibit capacitation and reaction of acrosome, impair fertilisation, influence upon the process of implantation, and impairment of growth as well as the development of the embryo. Documented risk factors for immune infertility in men due to formation of anti-sperm antibodies (ASAs) include:
    - The breakdown of the blood-testis barrier.
    - Surgery and trauma.
    - Orchitis/epididymitis-orchitis.
    - Varicocele.
    - Infections.
    - Cancer of the testis.
    - Prostatitis.
    - Failure of immunosuppression.
    - Unprotected receptive anal or oral coitus with men. [1] [8] [9]
- Causes related to Testicular factors.
  - Testicular factors related to infertility in the male have been defined as conditions in which the testes produce spermatozoa of low quality and / or poor quality irrespective of adequate hormonal support and these testicular factors do include:
    - Varicocele.
      - ✓ It has been state that varicocele tends to be present in 15% of normal men who do not have any infertility problems and in 40% of men who have infertility problems. [1]
      - ✓ It has been documented that varicocele tends to be present in up to 35% of men who have primary infertility and in 69% to 81% of men who have secondary infertility. [1] [10]
    - Age
      - ✓ It has been stated that the genetic quality and volume of sperm as well as motility could decrease with age [1] [11] [12] which tends to lead to the population geneticist James F Crow to postulate that the greatest mutational health to the human genome is fertile older males. [13]
      - ✓ It has been documented that the paternal age was first implicitly promulgated by Weinberg in 1912 [14] and it was explicitly postulated by Penrose in 1955 [15] as well as DNA-based research had commenced more recently in 1998, within the context of paternity testing. [1]
    - Genetic defects on chromosome Y.

✓ It has been stated that Y chromosome microdeletions had

been documented in some cases of male infertility. [1]

- Abnormal set of chromosomes.
- ✓ It has been documented that Klinefelter syndrome has been associated with male infertility.
- Centriole. [16]
- ✓ Atypical centrioles have been documented in male infertility. [1] [16]
- Neoplasms.
- ✓ Malignancies including seminoma of the testis had been linked with male infertility. [1]
- Idiopathic testicular failure.
- ✓ Idiopathic testicular failure has been documented in association with male infertility. [1]
- Cryptorchidism.
- ✓ It has been stated that fertility is impaired pursuant to both unilateral and bilateral cryptorchidism. [17]
- ✓ The reported paternity rates with regard to adults are said to be about two-thirds for unilateral undescended testis and less than one-third for bilateral undescended testes. [17]
- ✓ The concepts of related to cryptorchidism have changed as knowledge related to its effects had accumulated from research undertaken globally. [17]
- ✓ The recommended age for undertaking orchidopexy had fallen progressively from adolescence to less than one year. [17]
- ✓ It has been stated that the realization that the infantile testes are not in a state of 'suspended animation' and the finding of the defect in the androgen dependent transformation of gonocytes into adult dark spermatogonia in cryptorchidism has been identified as the primary cause of sub-fertility in these individuals. This had opened the way for hormonal therapy as an attempt to simulate the 'post-natal gonadotrophin surge' or 'mini puberty'. [17]
- Trauma.
- Hydrocele.
- Mumps [18]
- Malaria.
- Defects in USP26 in some cases. [19]
- Acrosomial defects that affect penetration of egg.
- Idiopathic oligospermia

It has been documented that unexplained sperm deficiencies do account for 30% of infertility of the male sex. [20]

- Pre-testicular causes of male infertility.

Pre-testicular causes of infertility in the male allude to conditions which impede adequate support of the testes and they include scenarios of poor hormonal support as well as poor general health of the man. Some of these pre-testicular causes of infertility in men include the following:

- Hypo-gonadotrophic hypogonadism which doe result from various causes. It has been iterated that: [1] [21]
  - Obesity does increase the risk for the development of hypo-gonadotrophic hypogonadism. [1] [21]
  - Animal models had indicated that obesity does cause leptin insensitivity in the hypothalamus which does lead to decreased expression of Kiss 1, that in turn, does alter the release of gonadotrophin-releasing hormone (GnRH). [1] [21]
- Undiagnosed and un-treated coeliac disease (CD).
  - It has been stated that men who have coeliac disease could have reversible infertility; however, Coeliac disease could manifest with many non-gastrointestinal symptoms which could involve nearly any organ system, even with absence of gastrointestinal symptoms. Hence the diagnosis of coeliac disease could be missed which to lead to the risk of developing long-term complications. [1] [22]
  - It has been documented that with regard to men, coeliac disease could reduce semen quality which could then lead to the development of immature secondary sex characteristics, hypogonadism, and hyperprolactinaemia, which tends to be ensued by impotence and loss of libido. [1] [23]
  - It has been stipulated that the offering of gluten-free diet and the correction of deficient dietary elements could lead to the return of fertility. [1] [22] [23]
  - It had been suggested that there is the likelihood that an effective evaluation for infertility would best have included assessment for an underlying coeliac disease in the male as well as in the female. [24]
- Drugs and alcohol. [1] [25]

Emanuele and Emanuele [25] stated that the male reproductive system does consist of the hypothalamus, the anterior pituitary gland, and the testes and that alcohol can interfere upon the function of each of the components, the hypothallus, the anterior pituitary gland, and the testes, thereby inducing impotence, infertility, as well as reduced male secondary sexual characteristics. Within the testis, alcohol, could adversely affect the Leydig cells, that produce and secrete the hormone testosterone. Emanuele and Emanuele [25] further stated that studies had documented that the consumption of alcohol heavily does result in reduced testosterone levels in the blood. They also stated that alcohol does impair the function of the testicular Sertoli cells which play an important role with regard to maturation of sperm. Within the pituitary gland, alcohol could decrease the production, release, and / or activity of two hormones that have critical reproductive functions, namely, luteinizing hormone and follicle stimulating hormone. Alcohol could also interfere with the production of hormone in the hypothalamus. [25]

Marijuana and cocaine utilization have also been associated with some cases of infertility in the male.

- Strenuous riding (bicycle riding [26], and horse-back riding).
- Medicaments including (a) medications that affect spermatogenesis for examples, chemotherapy agents, anabolic steroids, cimetidine, spironolactone, (b) medications that decrease follicle stimulating hormone (FSH) levels, for example phenytoin, and (c) medications that decrease sperm motility for examples, sulfasalazine and nitrofurantoin. [1]
- Genetic abnormalities including Robertsonian translocation. [1]
- Tobacco smoking.
  - It has been iterated that the harmful products of tobacco smoking could damage the testes [27] as well as destroy the spermatozoa [28] [29]; however, it had also been documented that the effect of tobacco smoking on fertility has not been clarified. [30]
  - It has been documented [1] that: some governments have necessitated manufactures to put warnings on packets of tobacco/cigarettes. Smoking of tobacco does increase the intake of cadmium, in view of the fact that the tobacco plant does absorb the metal. Cadmium which is chemically similar to zinc, could replace zinc in the DNA polymerase, which does play a critical role in the production of sperm. It has been stated that when Zinc is replaced by Cadmium in DNA polymerase, it could particularly be damaging to the

testes. [1] [31]

- DNA damage.
  - It had been stated that common inherited variants within genes which encode enzymes that are employed in DNA mismatch repair tend to be associated with increased risk of damage to sperm DNA and infertility in the male. [32]
  - It had been stated that as men age or get older there tends to be a consistent decline in the quality of the semen, and this decline within the quality of semen, does appear to be due to damage of DNA. [1] [33]
  - Additionally, it has been iterated that the DNA damage is manifested by DNA fragmentation and by the increased susceptibility to denaturation when exposed to heat or acid, which are features that characterise apoptosis of somatic cells. [1] [34] It has been suggested that these findings would indicate that DNA damage is an important factor related to infertility in the male. [1]
- Epigenic
  - It has been stated that some authors had documented abnormal sperm DNA methylation in association with abnormal semen parameters and infertility in the male. [1] [35] [36]

- Post-testicular causes of infertility.

Post-testicular factors generally decrease fertility in the male as a result of conditions which affect the male genital tract following testicular sperm production and these include defects of the genital tract and ejaculatory problems as follows:

- Obstruction of vas deferens.
- Lack or absence of vas deferens (which quite commonly tends to be related to genetic markers for cystic fibrosis).
- Infection for example prostatitis.
- Retrograde ejaculation.
- Obstruction of ejaculatory duct.
- Hypospadias.
- Impotence.

Diagnosis:

Investigation for the cause of primary and secondary male infertility does entail a good history taking, clinical examination and various laboratory investigations apart from assessment the female partner of the male infertile patient to be sure that the female partner does not have any infertility related problem.

Medical history:

Some of the points pertinent to male infertility that must be asked for in the history include:

- Issues related to the testis and penis including: testicular torsion, cryptorchidism, testicular trauma, infections of the testis and epididymis whether acute or chronic (mumps orchitis and epididymitis as examples), environmental factors that may affect the testis, excessive heat, radiotherapy to the testicular area, medicaments that could affect the testes, the use of drugs including alcohol consumption, the use of anabolic steroids, and smoking [1]
- Sexual habits of the individual including the timing of coital activities, utilization of lubricants for coital activities and types of lubricants used, previous history of fertility experience of the patient and partner of patient,, exclusion of possible pituitary cause of infertility by asking for loss of libido, visual problems and headaches.
- Asking about whether the patient has ever had (a) thyroid and liver function problems that could induce abnormalities of spermatogenesis, (b) diabetic neuropathy which could be responsible for retrograde ejaculation, (c) radical pelvic or retroperitoneal surgery which could induce absent emission of semen due to injury to the sympathetic nerves, (d) previous herniotomy of hernia repair which could have led to obstruction of or damage to the vas deferens. [1]
- Asking for a family history of any genetic problems that could affect fertility.

Clinical examination:

A full general and systematic examination are carried out in the initial assessment. If there are any visual issues then a full visual acuity test is undertaken in the suspected case of possible pituitary tumour. The breasts would be thoroughly examined to exclude gynaecomastia. The penis would be carefully examined to exclude meatal stenosis and hypospadias. The testes would be thoroughly examined for size, position, consistency and the epididymis and cord would also be examined to exclude any abnormalities. Digital rectal examination would be undertaken to check for size, consistency, and tenderness of the prostate gland to ascertain whether or not there is any clinical evidence of any abnormality. Assess for presence or absence of varicocele needs to be documented together with the findings.

Laboratory investigations:

- Two separate semen analyses are generally undertaken to undertake a total count and differential semen analysis studies. In the semen analysis the following tend to be documented: the volume of the sample of semen submitted, the approximate total number of spermatozoa cells, the sperm motility/forward progression of spermatozoa, the percentage of spermatozoa that have normal morphology. Deficiencies in the seminal analysis tend to be documented as follows:
  - Oligospermia or oligozoospermia – which means decreased number of spermatozoa in the semen.
  - Aspermia. – which refers to complete absence or complete lack of spermatozoa.
  - Hypospermia – which refers to reduced volume of semen.
  - Azoospermia- which also refers to absence of sperm cells within the semen.
  - Teratospermia – which refers to increase in sperm with abnormal morphology.
  - Asthenozoospermia – which refers to reduced sperm motility.
  - Necrozoospermia – which refers to all spermatozoa within the ejaculate are dead.
  - Leucospermia – which refers to a high level of white blood cells in the semen.
  - Normozoospermia or normospermia – which refers to a result of semen analysis which shows normal values of all the parameters of the ejaculate by World Health Organization (WHO) standards, but still there are chances of being infertile and it has been stated that normozoospermia or normospermia is also called

unexplained infertility. [37]

- Full blood count and coagulation screen tend to form part of the general initial assessment of the patient but this would not establish the cause of infertility.
- Serum urea and electrolytes, blood glucose , liver function tests, serum testosterone, follicle stimulating hormone (FS), LH, and prolactin level tests are also undertaken as part of the initial investigation of the male who has infertility problems.
- Blood tests can be gone for genetic testing, and if Klinefelter's syndrome is suspected blood test can be done to ascertain whether or not the individual patient has this.

- Ultrasound scan.

It has been stated that ultra-sound scan of scrotum and testes has been useful in scenarios of suspicion of some intra-scrotal / testicular disease(s). [1] It had also been iterated that ultrasound scan of the scrotum could detect signs/features of testicular dysgenesis, which commonly tends to be related to an impaired spermatogenesis, as well as to a higher risk for the development of cancer of the testis. [5]. The usefulness of ultrasound scan in the investigation of infertility in the male has been summated as follows: [1] [5]

- Ultrasound scan of scrotum could also identify lesions of the testes that that would be suggestive of malignancy.
- Decreased vascularization of the testis would be characteristic of torsion of the testis; whereas, hyperaemia of testis is often seen in cases of epididymo-orchitis and in certain malignant conditions for examples, lymphoma and leukemia.
- Doppler ultrasonography tends to be useful with regard to the assessment of venous reflux in cases of varicocele, in the scenario when palpation of varicocele is unreliable, or with regard to the detection of recurrent varicocele pursuant to surgery (in the form of ligation of varicocele or embolization) of varicocele., even though the impact of detection of varicocele and surgical correction of the varicocele upon sperm parameters pursuant to the correction and overall fertility had remained debatable.
- Dilatation of the head of the epididymis or dilatation of the tail of the epididymis would suggest obstruction or inflammation of the male reproductive tract. Such abnormalities tend to be associated with abnormalities of sperm parameters, as well as with abnormalities of the texture of the epididymis.
- Ultrasound scan of the scrotum and trans-rectal ultrasound (TRUS) scan has been useful with regard to the detection of unilateral or bilateral congenital absence of the vas deferens (CBAVD), which could be associated with abnormalities or agenesis of the epididymis, seminal vesicles, or kidneys, and this could indicate necessitation of testicular sperm extraction.
- Trans-rectal ultrasound scan does play a vital role with regard to the assessment of azoospermia which has been caused by obstruction and to detecting distal CBAVD or anomalies that are related to ejaculatory duct obstruction, for examples, abnormalities within the ejaculatory duct itself, a median cyst of the prostate which would necessitate aspiration of the cyst which can also be performed under ultrasound scan guidance, or an impairment of the seminal vesicles to become enlarged or emptied.

Additionally, ultrasound-scan-guided cannulation of the vas deferens or epididymis can be undertaken for antegrade vasogram, retrograde vasogram with epididymogram to assess the area of obstruction within the vas deferens, epididymis and seminal vesicle. Ultrasound scan images of the contrast procedure can be taken or the procedures could also be undertaken under the guidance of radiology image intensifier screening and images stored, or under the guidance of computed tomography (CT) scan or magnetic resonance imaging (MRI) scan and the images stored but the initial cannulation of the vas deferens or ejaculatory duct can be done initially at the start of the procedure prior to injection of the contrast medium into the cannulated lumen which would then be followed by CT scanning or MRI scanning when the contrast medium is injected. When a unilateral vas deferens or bilateral vasa deferentia are obstructed by obstructed scar tissue from previous inguinal hernia operation or operations or as a result of inadvertent ligation of the vas deferens or transection, ultrasound-scan guided vasogram or vasogram with radiology image screening could be undertaken on the theatre table to establish the point and length of obstruction and at the end of the corrective procedure the vasogram could be repeated to establish the results of the vaso-vasostomy or epididymo-vasostomy to illustrate that patency of the epididymis and the vas deferens. Ultra-sound guidance can be utilized in cases of vas deferens obstructed azoospermia but with semen within the epididymis and sperm production in the testis to obtain sperm from the epididymis/testis for assisted conception whilst waiting for corrective surgery of vaso-vasostomy and the sperms could be stored in liquid nitrogen for future use. In situations when patients are diagnosed as having malignancies of the testis for which they are going to under radical orchidectomy and following histology examination of their specimens the would be considered for radiotherapy / chemotherapy, even though they may not have problems of infertility at that time, many patients do agree to have their semen obtained or self-produced before their surgical treatment to be utilized for sperm banking / storage.

Preventive measures to avoid infertility in the male.

A number of measures have been recommended various authors to prevent infertility in the male and these include: [1]

- Smoking of tobacco and tobacco products should be avoided [38] in view of the fact smoking damages spermatozoa DNA. [1]
- Heavy marijuana use as well as use of alcohol should be avoided. [39]
- Excessive heat to the testes should be avoided. [39]
- Optimal frequency of sexual activity should be maintained, because sperm counts could be decreased by means of daily coital activity, [39] as well as sperm motility could be depressed via coital activity which takes place infrequently for instance abstaining from coital activity for 10 days to 14 days or more than 14 days. [39]
- It has been recommended that a protective cup and jockstrap should be worn to protect the testes before undertaking a number of sporting activities including: baseball, football, cricket, lacrosse, hockey, softball, paintball, rodeo, motor-cross, wrestling, soccer, karate, other martial arts, or before any sporting activity where a ball, foot, arm, knee, or bat, could come into contact with the groin. [1]

- The adoption of healthy dietary habits, for example consumption of Mediterranean diets, which are rich in nutrients such as omega-3 fatty acids, some antioxidants, and vitamins, and which are also low in in saturated fatty acids (SFAs) and trans-fatty acids (TFAs) have been inversely associated with low semen quality parameters. With regard to groups of food, fish, shellfish, as well as seafood, poultry, cereals, vegetables, and fruits, as well as low-fat dairy products had been documented to be positively related to good sperm quality. Nevertheless, diets that are rich in processed meat, soy foods, potatoes, full-fat dairy products, coffee, alcohol, as well as sugar-sweetened beverages and sweets that had been inversely associated with the quality of semen as reported in some studies. The few studies that had related male nutrient or food intake and fecundability had also had indicated that diets that are rich in red meat, processed meat, tea and caffeine, have been associated with fecundability. However, it has been stated that this association has been controversial with regard to consumption of alcohol. It has been stated that the potential biological mechanisms that link diet with sperm function and fertility largely had remained unknown and unclarified and this would need to be further studied in the future. [1] [newww 40 34]

Treatment of male infertility:

It has been stated that the treatment of male infertility does vary depending upon the underlying cause or disease responsible for the infertility as well as upon the degree of male fertility impairment.[1] It has also been recommended that in every infertility situation, the fertility of the female would need to be taken into consideration as well. [1] Both the male and the female should be investigated in cases of infertility.

It has been iterated that with regard to pre-testicular conditions causing male infertility could often be managed and addressed by interventions or medical means. [1]

With regard to testicular-based causes of infertility in the male, the infertility does tend to be resistant to medicaments. The usual approaches to this group of patients does include assisted conception by means of: [1] utilization of the spermatozoa for (a) intra-uterine insemination (IUI), (b) invitro fertilization, (IVF), or (c) invitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI). It has been documented that with regards to utilization of IVF plus ICSI, with utilization of a few spermatozoa pregnancies can be achieved. [1]

It has been documented that obstructive causes of post-testicular male infertility could be overcome with utilization of surgery of to relieve the obstruction or IVF-ICSI. [Wikipedia 1]. With regards to ejaculatory failure as a cause of male infertility, it has been documented that they could be treated by utilization of (a) medicaments, or by (b) intra-uterine insemination (IUI), or (c) by invitro fertilization (IVF). [1].

Further iterations that had been made relating to the treatment of male infertility include: [1] Utilization of vitamin E does help counter oxidative stress, [41] which tends to be associated with DNA damage of spermatozoa and reduced motility of spermatozoa [42]. It had been stated that utilization of a hormone-antioxidant combination therapy could help improve sperm count and sperm motility. [43] Nevertheless, it has been stated that only some low quality evidence from few small studies that oral antioxidants that are given to males among couples who had been undergoing invitro fertilization for male factor infertility or unexplained sub-fertility had resulted in higher live birth rate. [1] [44] Additionally it had been stated that it is not clear if there are any adverse effects associated with utilization of antioxidants in males that male factor infertility. [1] [44]

Hormonal treatment:

It has been iterated that the administration of hormonal treatment by means of (a) luteinizing hormone (LH) or (b) human chorionic gonadotrophin (HCG), and follicle stimulating hormone (FSH) has proven to be very effective with regard to the treatment of male infertility that is caused by hypo-gonadotrophic hypogonadism. [45], [46] off-label clomiphene citrate, which is an anti-oestrogen, could also be effective in the treatment of male infertility due to hypo-gonadotrophic hypogonadism by the elevation of gonadotrophin levels. [45]

It has been documented that even though androgens are said to be essential for the process of spermatogenesis and therefore fertility in the male, it had been observed that, exogenous testosterone treatment has not been effective with regard to benefiting men who have low sperm count. [1] [47] This finding has been explained by the belief that very high local levels of testosterone within the testes in which the concentrations within the seminiferous tubules have been documented to be 20-fnewold to 100-fold greater than the circulating levels of testosterone [48] tend to be required to mediate spermatogenesis, and exogenous testosterone treatment that is administered systemically, is not capable of achieving these local high concentrations of testosterone. [1] [47] It had also been stated that exogenous androgen treatment could actually impair, or abolish fertility in the male by the suppression of gonadotrophin secretion from the pituitary glands, as had been observed in users of androgens/anabolic steroids who had experienced partial or complete suppression of sperm production. [1] [45] [47] It has been explained that this observation has been because suppression of gonadotrophin levels do result in decreased production of testicular androgen [1] [45] [47] as well as follicle stimulating hormone (FSH) is said to be independently critical with regard to spermatogenesis. [1] [49] [50] Furthermore, it has been stated that in contrast to follicle stimulating hormone (FSH), luteinizing hormone (LH) does play little role with regard to male fertility outside of induction of gonadal testosterone production. [1] [51].

It has been stated that oestrogen, at some concentration, had been observed to be essential with regard to male fertility / spermatogenesis. [1] [52] [53] Nevertheless, it had also been stated that oestrogen levels which are too high could impair fertility in the male by the suppression of secretion of gonadotrophin and thus diminishing androgen levels within the testis. [1] [47] It had been documented that clomiphene citrate, which is an anti-oestrogen, as well as aromatase inhibitors such as testolactone or anastrozole had depicted effectiveness with regard to benefitting spermatogenesis. [1] [47]

It has been documented that utilization of a combination of low-dose oestrogen and testosterone treatment could improve sperm count and motility in some men, [54] with the inclusion of men who had severe oligospermia. [1] [55]

Results of research and potential future utilization of results of the researches.

It has been iterated that Abu Elhija et al. [56] at Münster

University have developed in vitro culture conditions with utilization of a three-dimensional agar-culture system that induces mouse testicular germ cells to reach the final stages of spermatogenesis, which has included generation of spermatozoa. [1] Some authors had indicated that if the results of the study of Abu Elhija rt al. [56] are reproduced in human beings, the results could potentially enable infertile men to father children with utilization of their own spermatozoa. [1] [57] [58] Furthermore, it has been documented that researchers from Montana State University had developed precursors of spermatozoa from the skins of infertile men. [1] [59] [60] [61]

(B) Miscellaneous narrations and discussions from case reports, case series and studies:

Samplaski et al. [62] undertook a retrospective review to ascertain the magnitude of improvement in semen parameters following varicocelectomy and the fraction that have improvements such that couples who need invitro fertilization (IVF) and intrauterine insemination (IUI) are upgraded to needing less invasive assisted reproductive technology (ART). This study had included men who had presented for fertility evaluation who had a clinical diagnosis of varicocele. These patients had undergone repair of varicocele either by means of surgical ligation of varicocele or embolization of varicocele. The main outcome of the study had included: total motile sperm count (TMSC), before and after repair of varicocele; and the proportion of the men who were considered candidates for: natural pregnancy (NP) > 9 million, or for invitro fertilization (IVF) < 5 million sperm count. Samplaski et al. [62] summarized the results as follows:

- A total of 373 men had undergone varicocele repair.
- The TMSC had increased from 18.22 +/- 38.32 to 46.72 +/- 210.92 (P =.007).
- The most pronounced increase had been with baseline TMCS < 5 million, from 2.32 +/- 1.50 to 15.97 +/- 32.92 (P = .0000002). 58.8% of men had been upgraded from IVF candidacy to IUI or NP.
- With regard to baseline TMSC 5 million to 9 million, the mean TMSC had increased from 6.96 +/- 1.16 to 24.29 +/- 37.17 (P = .0004) which had allowed 64.9% of the men to become candidates for natural pregnancy (NP).
- With regard to baseline TMSC of greater than 9 million, TMSC had increased from 36.26 +/- 52.08 to 81.80 +/- 310.83 (P = .05).

Samplaski et al. [62] made following conclusions:

- Repair of varicocele has an important role with regard to the treatment of infertility.
- Even for low TMSCs, a varicocelectomy could reduce the need for IVF.
- Varicocele repair by means of embolization or microsurgery does potentially reduce the need for IVF and IUI.

Binhazzaar et al. [63] reported a consecutive series of 76 patients who had clinical varicocele, alteration of semen parameters, as well as infertility, and who had undergone either microsurgical varicocelectomy with regard to 49 patients and embolization or embolization of varicocele with regard to 27 patients, who had been prospectively analysed pre-operatively and post-operatively at 1 month, 3 months, 6 months, 9 months, and 12 months. The outcome measures that were analysed included: semen parameters, pregnancies, pain, side effects, recovery time, and overall satisfaction. The patients in January 2015 had been subsequently contacted by means of telephone with a median delay of 4 years pursuant to the procedure in order to ascertain the subsequent reproductive events. Binhaazzar et al. [63] summated the results as follows:

- Pre-operatively, both groups of patients had been identical with regard to clinical as well as biological items.
- Binhaazzar et al. [63] did observe an improvement of sperm concentration, at 3 months, 6 months, 9 months, and 12 months, (P < 0.001, < 0.001, <0.012, < 0.018, respectively), and sperm motility at 6 months (P = 0.002). The sperm concentration was found to be higher at 6 months with regard to the post-embolization of varicocele patients in comparison with the post microsurgical varicocelectomy patients (P = 0.043).
- With a median follow-up of 4 years pursuant to the varicocele treatment procedure, 27 pregnancies had occurred with a spontaneous pregnancy rate of 32%.
- No difference was noticed between the two procedures with regard to sperm quality, pregnancy rate, and satisfaction. However, the patients who had undergone per-cutaneous embolization of varicocele, did report a faster recovery time (P = 0.002), as well as less post-operative pain, (P = 0.007).

Binhaazar et al. [63] concluded that:

Both procedures of microsurgical varicocelectomy and per-cutaneous embolization of varicocele, had given equivalent results with regard to sperm quality, pregnancy rate, as well as satisfaction; although, recovery seemed to be faster and post-operative pain seemed to be lower pursuant to the per-cutaneous embolization of varicocele procedure.

D'Andrea et al. [64] undertook a prospective study in infertile men who had been affected by non-obstructive azoospermia (NOA) and left sided varicocele to ascertain whether or not the appearance of ejaculated spermatozoa following varicocele repair is predicted by baseline measures. With regard to methods, D'Andrea et al. [64] submitted patients who had non-obstructive azoospermia (NOA) and grade II or grade III left sided varicocele to hormone analysis and colour Doppler ultrasound (CDU) scanning of scrotum and testes. Azoospermia had been confirmed with regard to 23 patients who were aged between 25 years and 47 years, who had then undergone left side varicocele repair by means of retrograde left internal spermatic vein embolization. The patients were re-evaluated at their 6-months follow-up. D'Andrea et al. [64] summarized the results as follows:

- Six months following varicocele repair, 12 patients that amounted to 52.2% of patients had still remained azoospermic and they were assigned to group 1.
- Eleven (11) patients who had amounted to 47.8% of patients had reported ejaculated spermatozoa, who were assigned to group 2, whose sperm count had been reported to be 1.3 x 10^6 per m; – 0.5 x 10^6 per mL – 1.6 x 10^6 per mL (median, 25^{th} - and 75^{th} – centiles),
- The serum baseline follicle stimulating hormone (FSH) level was lower in group 2 in comparison with group 1 (P = 0.012). On the other hand, no differences had been noticed between the groups with regard to all other

clinical and laboratory parameters. Receiver operating characteristic (ROC) analysis had shown that base line FSH level had predicted the appearance of ejaculated spermatozoa following treatment ([AUC = 0/811; 95% Confidence interval (CI) 0.6 – 0.9; P = 0.0029]). A cut-off level of FSH <10.06 MIU/mL had identified 82% of cases that had ejaculated spermatozoa with a specificity of 81.8% and sensitivity of 83.3%.

D'Andrea et al. [64] concluded that:

- Selected patients who have non-obstructed azoospermia (NOA) could show ejaculated spermatozoa pursuant to a non-invasive repair of left sided varicocele and so avoiding testicular sperm extraction.
- Baseline serum FSH level was a valuable predictor of ejaculated spermatozoa following treatment.

Kovac et al. [65] developed a Markov-decision analysis model to estimate costs and pregnancy rates. Within the model the recurrences ensuing microsurgical varicocele repair (MV) and a non-microsurgical approach (NMV), were retreated by means of per-cutaneous embolization (PE) and recurrences following PE were treated with repeat PE, MV, or NMV. Pregnancy and recurrence rates were based upon the literature, while costs had been obtained from institutional and Government supplied data. Univariate and probabilistic sensitivity analyses were undertaken to ascertain the effects of the various parameters upon model outcomes. Kovac et al. [65] summated the results as follows:

- Primary treatment by means of microsurgical varicocele repair (MV) was the most cost-effective strategy at 5402 Canadian dollars per pregnancy.
- Primary treatment with non-microsurgical approach (NMV) was the least costly approach; however, it also did yield the fewest pregnancies.
- Primary treatment with percutaneous embolization of varicocele (PE) was the least cost-effective strategy which did cost approximately 7,300 Canadian dollars per pregnancy.
- Probabilistic sensitivity analysis did reinforce MV as the cost-effective strategy at a willingness-to-pay threshold of greater than 4,100 Canadian dollars per pregnancy.

Kovac et al. [65] made the following conclusions:

- MV did yield the most pregnancies at acceptable levels of incremental costs. As such MV is the preferred primary treatment strategy for varicocele-associated infertility.
- Treatment with PE was found to be the least cost-effective approach, and, for this reason, PE should be best utilized only in cases of surgical failure.

In 1983, Klosterhalfen et al. [66] reported that 326 epididymo-vasostomy had been undertaken in their establishment. They stated that a follow-up was possible for 241 patients. Klosterhalfen et al. [66] summarized their results as follows:

- Bilateral anastomosis had resulted in a 47% permeability.
- Following unilateral recanalization, a patency rate of 32% was achieved.
- Vaso-vasostomy following vaso-resection was undertaken in 56 men.
- Following a splinted one-layer anastomosis, which they had abandoned in the mean-time, patency was obtained in 64% of the patients.
- Current techniques with utilization of one or two layers without a splint had resulted in 88% permeability.
- The double-layer anastomosis does not offer any advantage over the one-layer anastomosis method.

Schoysman [67] stated that following ultimately successful microsurgery for male infertility, the delay with regard to the appearance of spermatozoa in the ejaculate of the patients is not uniformly immediate and that for the older latero-lateral epididymo-vasostomy it could take many months. Schoysman [67] also stated that when the actual microsurgical techniques are utilized, the appearance of spermatozoa within the ejaculate could be shorter. Occasionally, nevertheless, even in the latter group, very long delays had been observed with regard to the appearance of spermatozoa in the ejaculate. Schoysman [67] stated that there is no definite answer for this delay of observing spermatozoa in the ejaculate. Schoysman [67] conjectured that the most likely explanation would relate to a combination of reinforced peristalsis within the previously pathologically dilated epididymal tubules and the secondary breakthrough of a plug of epithelial sloughs and fibrin at the site of the microsurgical anastomosis.

Wagenknecht [68] reported that over a 15-year-ieriod, epididymo-vasostomy had been performed in 642 men for inflammatory (51%), inborn (44%), or acquired (5%) obstruction of the epididymis. Wagenknecht [68] stated the following: With regard to 327 selected cases, the permeability had ranged between 11% to 76% based upon the location of the anastomosis, and fertility had followed in 0% to 52% of cases. Vaso-vasostomy had been undertaken in 724 men. Depending upon the time following the sterilization, or herniotomy obstruction, permeability had ranged between 52% and 92%, fertility had ranged between 38% and 74%. Double-layered anastomosis with sealing of the anastomosis with utilization of fibrin glue did improve the results. Several operations for mobilisation of the vas deferens and elevation of the testis which avoided tension on the anastomosis were undertaken. With regard to four men who had had long obstructions of the vas deferens, transposition of the testicle into the inguinal area was undertaken and 3 out of the 4 patients did have a positive post-operative spermiogram, and two of them had fathered a child. With increasing duration of obstruction, the quality of the post-operative spermiograms had decreased. Sperm auto antibodies had significantly been elevated with regard to only 3% of 531 men, and in majority of cases normal values were observed following relief of the obstruction. The reasons for the seminal anastomoses being associated with problems were defective technique, sperm leak, traction upon the anastomosis, infection, and epididymal damage. The frequency with which the operation was performed by a surgeon constituted the main determinant of the competence of the surgeon and the chances of success.

Willets et al. [69] evaluated the efficacy and safety of utilization of clomiphene citrate in the treatment of male patients who had infertility. They undertook a literature search which had included a MEDLINE search between 1966 and June 2012 as well as EMBASE search between 1980 and June 2012 by utilization of the medical term's clomiphene and male infertility. Willets et al. [69] did identify 9 clinical studies, out of which 1 study had detected a statistically significant benefit on the pregnancy rate in the clomiphene group; nevertheless, most of the studies had demonstrated a statistically significant increase in sperm

concentrations. At doses that are utilized to treat infertility in the male, clomiphene had been well tolerated without any identified serious adverse effects. Willets et al. [69] did indicate that based upon the studies they had reviewed there was insufficient evidence to indicate that clomiphene is effective for the treatment of male infertility.

Ghanem et al. [70] assessed the effect of treatment with a combination of clomiphene citrate as an antioestrogen and vitamin E as an antioxidant upon the incidence of pregnancy and sperm variables in men who had idiopathic oligozoospermia and infertility. This study was a prospective, randomized, placebo-controlled trial that included sixty infertile men who had idiopathic oligoasthenozoospermia. The patients were randomly assigned into two therapeutic groups that included (a) a group that received the combination of clomiphene citrate 25 mg per day and vitamin E 400 mg per day of which there were 30 patients and (b) a placebo group of 30 patients. The treatment was continued for 6 months. The main outcomes that were measured were pregnancy incidence and variations in semen parameters. Ghanem et al. [69] summarized the results as follows:

- A significant higher pregnancy rate was observed among the clomiphene citrate and vitamin E combination group of patients in comparison with the control group. The odds ratio was 3.76 and the 95% confidence interval was 1.03 – 13.64, with a 36.7% pregnancy rate that represented 11 pregnancies out of 30 in the combination treatment group in comparison with pregnancies in 4 spouses out of the 30 spouses in the placebo group.
- The trial did show a significantly higher increase with regard to sperm count and progressive sperm motility with nonsignificant changes in total sperm motility, percentage of abnormal forms and volume of semen in the combination group in comparison with the control group.

Santi et al. [71] evaluated whether follicle stimulating hormone (FSH) administration to the male partner of infertile couples does improve pregnancy rate, spontaneously and / or following assisted reproductive techniques (ART). Santi et al. [71] undertook meta-analysis of controlled clinical trials in which FSH had been administered for male idiopathic infertility in comparison with placebo or no treatment. They did not consider randomization as inclusion criterion. Santi et al. [71] summated the results as follows:

- They had found 15 controlled clinical studies that included 614 men who had been treated by means of FSH and 661 men who had been treated with placebo or were not treated. With regard to the type of FSH, eight studies had utilized recombinant FSH, on the other hand seven studies had utilized purified FSH.
- Nine studies had evaluated spontaneous pregnancy rate which had resulted in an overall odds ratio (OR) of about 4.5; confidence interval (CI): 2.17 – 9.33.
- Eight studies had had evaluated pregnancy following ART, which did show a significant overall odds ratio (OR) of 1.60, confidence interval (CI): 1.08 – 2.37.
- With regard to sub-dividing the studies based upon the FSH preparations (purified/recombinant) that were utilized, the pregnancy rate improvement did remain significant for each preparation.
- Eleven studies had considered sperm quality following FSH treatment which found a significant improvement of sperm concentration (2.66 x 10^6 per mL, confidence interval (CI): 0.47 – 4.84; nevertheless, not of concentration of sperm that had progressive motility (1.22 x 10^6 per mL, confidence interval (CI): 0.07 to 2.52.
- Three trials had evaluated testicular volume which had shown a non-significant increase in men who had been treated (1.35 ml, confidence interval (CI): 0.44 to 3.14.

Santi et al. [71] made the ensuing conclusions and recommendation:

- The results of controlled clinical trials in the literature had indicated an improvement of pregnancy rate following FSH administration to the male partner of infertile couples, both spontaneously and following ART.
- Nevertheless, the heterogeneity of the studies, the high risk of bias, and the lack of precise criteria to guide FSH administration had limited the strength of these results.
- Future studies should be designed to identify the markers of FSH response which would be helpful with regard to the decision-making process. Meanwhile, the utilization of FSH in the treatment of male infertility must be cautious.

It would be argued that despite the limitations related to the studies evaluated by Santi et al. [71] there is sufficient information that indicates the usefulness of FSH treatment in idiopathic male infertility.

Hu et al. [72] investigated whether the trigger effect of human menopausal gonadotrophins (HMG) and human chorionic gonadotrophins (HCG) attributes to the treatment of unexplained non-obstructive azoospermia (NOA). Hu et al. [72] retrospectively analysed the clinical data of about 282 cases of unexplained NOA who had been treated between January 2010 and May 2017. All of the patients had undergone trigger treatment by intramuscular injection of HMG at 75 IU 3 times per week for 2 weeks, which was followed by HCG at 2,000 IU 2 times per week for another 2 weeks, and they meanwhile took vitamin E, Levocarnitine and Tamoxifen as adjunctive treatment. The treatment did last for 3 months to 12 months. Hu et al. [72] reported that 58 of the 255 patients who had completed the treatment were found to have spermatozoa in their semen following treatment, and all of them did have severe oligoasthenospermia. Forty-seven of the 58 patients had received assisted reproductive technology (ART), and out of them, 18 men had achieved clinical pregnancy. Semen centrifugation did not reveal any sperm in any of the other cases, of which 6 were found to have epididymal spermatozoa at epididymal and testicular biopsy following treatment and 3 of them did achieve clinical pregnancy following ART. Spermatozoa was found within the semen, or at epididymal or testicular biopsy in 64 of the patients pursuant to their treatment with an effectiveness of 25.1%. Hu et al. [72] concluded that trigger treatment with the injection of HMG and HCG which have been combined with adjunctive oral medicament does have a certain effect upon unexplainable NOA.

Liu et al. [73] reported a 30-year-old oligoasthenospermia man, who was found to have unbalance mosaic translocation between chromosome 22 and four other chromosomes that had included chromosomes 5; 6; 13; and 15; during investigations for his and his spouses of 3 years duration. Liu et al. [73] undertook classical cytogenetics analysis by means of fluoresce in situ hybridization (FISH), and chromosome microarray analyses (CMA) on peripheral blood lymphocytes, and copy number variation sequencing (CNV-seq) analysis was undertaken on sperm DNA.

Liu et al. [73] summarized the results as follows: Classical cytogenetics analysis had shown presence of six cell lines on peripheral blood lymphocytes which had included: 45, XY, der(13)t(13;22), -22[10]/46, XY, t(13;22)[6]/45, XY, der(15)t(15;22), -22[4]/46, XY, t(13;22)[1]/45, XY, der(5)t(5;22), -22[1]/45, XY, der(6)t(6;22)[1]. FISH and CMA which was undertaken on peripheral blood cells had shown presence of a 6.9 Mb mosaic 22q11 deletion (which was about 50% of cells); it was unexpected that the phenotypes of the man had been merely oligoasthenozoospermia, mild bradycardia, and mild tricuspid regurgitation. CNV-Seq analysis which was undertaken on sperm DNA did reveal the rate of 22q11 deletion cells had been obviously lower in comparison with peripheral blood cells. Furthermore, the frequency of gametes exhibiting a normal or balance chromosomal equipment had been higher than 80% in samples of spermatozoa. Liu et al. [73] iterated that to the best of their knowledge, their case report, was the first cases of a de novo gonosomal mosaic of chromosome 22q11 deletion that was just associated with infertility.

Flannigan and Schlegel [74] stated that about 15% of couples tend to be infertile and male factors do contribute to infertility in more than 50% of cases, as well as furthermore, identifiable genetic abnormalities do contribute between 15% to 20% of the most severe forms of male infertility, azoospermia. Flannigan and Schlegel et al. [74] documented that known genetic causes of infertility in the male include: Klinefelter syndrome, XYY men, Kallman syndrome, y microdeletions, Robertsonian translocations, autosomal inversions, mixed gonadal dysgenesis, x-linked- and autosomal gene mutations, as well as cystic fibrosis trans-membrane conductance regulator abnormalities.

Katz et al. [75] stated that infertility in the male could result from anatomical, or genetic abnormalities, systemic or neurological diseases, infections, trauma, iatrogenic injury, gonadotoxins, as well as development of sperm antibodies. Katz et al. [75] recommended that when a couple fail to achieve pregnancy after 12 months of regular, unprotected sexual intercourse, a screening examination of both partners would require to be undertaken. Katz et al. [75] stated that for the male partner, the screening examination should include a history taking, physical examination, endocrine assessment, and semen analysis. Katz et al [75] additionally iterated that lifestyle and environmental factors could have a negative impact upon male fertility, and in view of this the General Medical Practitioner has a pivotal role with regard to educating patients about modifiable factors related to male infertility.

Barnabas et al. [76] undertook a study to identify the cause of azoospermia in a 38-year-old infertile man. Cytogenetic evaluation was undertaken by G-banding, C-banding, and FISH with utilization of centromeric probes for chromosomes X and Y and this did show presence of a monocentric isochromosome Y that had a complex, mosaic karyotype 45,X/46,X,i(Y)(q10)/46,XX/47,XX,i(Y)(q10). Multiplex PCR for the commonly deleted genes within the AZFa, AZFb, and AZFc, regions of the Y chromosome were undertaken which did indicate presence of all 3 regions. Further, PCR amplification ensued by DNA sequencing of the SRY gene was undertaken, which had excluded mutations in that gene. In order to find the position of the SRY gene, FISH utilizing a locus-specific probe was employed and this did show that the gene had been translocated to chromosome 3. Sub-telomere FISH for 3q and Yp did provide evidence that the sub-telomere region of the Y chromosome was identified on the terminal region of 3q. Barnabas et al. [76] stated that the symptoms of the patient could be attributed to this abnormal genotype and that the importance of genetic testing with regard to infertile patients as well as the need for genetic counselling in order to prevent the transmission of the defect needed to be emphasized.

Hassan et al. [77] examined the relationship among vitamin D3, anti-Müllerian hormone (AMH), FT3, FT4, and thyroid stimulating hormone (TSH), in addition to the serum levels of reproductive hormones follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, as well as free testosterone, in oligoasthenoteratozoospermia and azoospermia patients within a cohort of infertile men from Egypt in order to ascertain marker/cause-effect relationship. The study was undertaken on 301 men that had included 105 males who had oligoasthenoteratozoospermia, and 96 males who had azoospermia, in addition to 100 male controls. Hassan et al. [77] undertook measurements of serum vitamin D3, AMH, FT3, FT4, and TSH levels, as well as reproductive hormone assays were undertaken on all subjects that had been included in the study, with utilization of ELISA kits. Hassan et al. [77] summarized the results as follows:

- On the whole, the results did show significant lower serum levels of vitamin D3 among infertile men in comparison with controls, with a greater decrease found in men who had azoospermia in comparison with those men who had oligoasthenoterazoospermia, ($P < .05$ for all for all).
- Significantly higher serum TSH, and FSH, levels, and significantly lower serum free testosterone levels were found in males who had azoospermia in comparison with males who had oligoasthenoteratozoospermia and the controls ($P < .05$ for both).
- There had not been any significant differences between the studied groups with regard to AMH, FT3, or FT4 levels.
- LH levels had been negatively correlated with TSH levels and had been positively with AMH levels with regard to men who had oligoasthenoteratozoospermia, but with regard to men who had azoospermia, LH levels had been positively correlated with vitamin D3 levels ($P <.05$ for all).

Hassan et al. [77] made the following conclusions:

Decreased levels of vitamin D3 could play in infertility of the male as well as abnormal thyroid function which would require further investigation. Based upon the findings of Hassan et al. [77] it would argued that there is enough information for clinicians who are investigating men who have infertility to ensure that they ensure all their patients have thyroid function tests and vitamin D3 levels and those who are found to have low levels of vitamin D3 should prescribed vitamin D and they should be encouraged to take vitamin D and have their vitamin D Levels checked during their follow-up assessments.

Zhang et al. [78] utilized meta-analysis to analyse the relationship between cadmium (cd) content in the semen and infertility in the male and they then objectively evaluated the effect of cd upon sperm quality. Zhang et al. [78] obtained 11 articles in the database up to April 2018. Zhang et al. [78] gathered the mean and variance of the infertility group and the control to compare the cd content in the two groups. Zhang et al. [78] reported that on the whole, the 11 studies had included 1707 males, of which 1093 were in the infertility group, and 614 males were in the control group. Zhang et al. [78] stated that information from their

meta-analyses revealed: SMD = 0.50 (95% CI 0.39 – 0.61), Z = 8.92, P < 0.05; the funnel plot of the meta-analysis did show incomplete symmetry, which could have the publication bias. Based upon their findings, Zhang et al. [78] concluded that the high content of cd in semen is a causative factor of in infertility and that the cd content within semen could be utilized as an indicator of sperm quality.

Ma et al. [79] reported two infertile brothers who had a uniquely prevalent sperm phenotype with completely amorphous sperm heads. In order to investigate the mechanism of familial teratozoospermia with amorphous sperm heads, Ma et al. [79] assessed chromatin condensation by aniline blue staining, western blot, sperm chromatin structure assay, and atomic force microscopy in the two brothers as well as in 40 control fertile donors. Ma et al. [79] reported that their results showed an abnormal condensation of chromatin with amorphous headed sperm. Ma et al. [79] had suggested that abnormal chromatin condensation which was induced by disturbances within the process histone-protamine replacement could be a possible cause of familial teratozoospermia with amorphous head, and the elasticity of sperm nuclei could represent a new index to assess the quality of sperm. Ma et al. [79] also stated that for the first time their study had provided a new biomechanics strategy for the evaluation of pathological sperm contributes to their understanding of teratozoospermia.

Petersen et al. [80] examined infertility among male firefighters in Denmark. Petersen et al. [80] established a cohort of 4,710 past, and present, male Danish firefighters. They did link information on vital status and infertility to cohort members from 1984 to 2017 from the Danish Civil Registration System, the In Vitro Fertilization Register and the National Patient Register. Hazard ratios (HRs) with corresponding confidence intervals (Cis) had been estimated for male factor and overall infertility via cox regression analyses that compared the firefighters to two reference groups which included a sample of employees and military men. Among the full time firefighters, male factor infertility had been found to have increased in comparison with the sample of employees (In Vitro Fertilisation model HR 1.46, 95% CI 1.10 – 1.94, and National Patient Register model HR 1.53, 95% CI 1.18 – 1.98). However, Petersen et al. [80] stated that the results had been less consistent with utilization of the military as reference. Additionally, the increase in infertility appeared restricted to the time they were employed as firefighters. Furthermore, no increase in risk of either male factor or overall infertility had been observed among part-time/volunteer firefighters. Petersen et al. [80] adduced that fulltime firefighting was associated with an increased risk of being diagnosed with male factor infertility in their cohort.

Feodorova et al. [81] investigated whether The novel Swedish variant of Chlamydia trachomatis (nvCT) could be a possible cause of infertility in a couple who were undergoing in vitro fertilisation (IVF). They analysed before and after antibiotic therapy, clinical specimens from both genital (urethra, and cervix) and extra-genital sites (pharynx, conjunctiva, and blood) of a couple who had unsuccessful attempts at pregnancy through natural fertilization and IVF procedures. Both partners did not have either somatic or endocrine abnormality or any clinically apparent genital manifestations of Chlamydia or other sexually transmitted diseases. Feodorova et al. [81] reported their results as follows:

- Prior to antibiotic therapy all the samples of the female partner (FP) did contain DNA of only nvCT.
- Pursuant to antibiotic therapy, additionally, DNA of wild type of Chlamydia trachomatis (wtCT) of genovars E and D had been detected in specimens from the woman's conjunctiva and oropharynx.
- All samples of the male partner (MP) had revealed co-infection of nvCT and wtCT
- Identical SNP in the variable region 4 ((VD4) of the ompA gene did confirm the identity of the wtCT strains that were found in both partners.
- The Female Partner (FP) did have a positive anti-Chlamydial igG titre.
- The sperm characteristics of the male partner (MP) revealed (a) motility (immotile spermatozoa had been 51.1% versus 21.6%; (b) vitality (had been 46% versus 68%), declined progressively, and the male partner (MP) anti-Chlamydial igG titre had been negative.

Feodorova et al. [81] made the following conclusions:

- Infertility in the couple could have been caused by chronic asymptomatic and persistent nvCT-associated infection which had been complicated by re-infection later with wtCT.
- Their study had illustrated the importance of including detection methods for nvCT strains in the investigation of cases of infertility.

Based upon lessons learnt from this case report it would be recommended that in the investigation of all cases of male infertility both the male and female partners should be screened for sexually transmitted diseases including Chlamydia whether they have symptoms or do not have symptoms of sexually transmitted disease.

Shuling et al. [82] undertook a prospective study of men who had idiopathic severe oligozoospermia with sperm count less than 5 million per millilitre between February 2015 and March 2017. The study was aimed at assessing if semen-analysis parameters would improve pursuant to treatment with letrozole. The secondary aims of the study were to monitor the safety of letrozole in men, and to measure the alterations in serum follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, and testosterone levels. Shuling et al. [82] summarized the results as follows:

- Fifteen men who had normal testosterone-oestradiol ratio (> 10) had undergone treatment with letrozole 2.5 mg orally daily for 4 months which did produce a 5,5-fold increase in sperm concentration (P = 0.0068).
- All of the men did have increased total serum testosterone and suppressed oestradiol levels pursuant to treatment, which did raise the over-all testosterone-oestradiol ratio (P > 0.0001).
- Adverse effects from letrozole had been relatively minor and had included loss of libido in 54% of patients, headaches in 25% of patients, fatigue in 21% of patients, weakness in 13% of patients, loss of hair in 8% of patients, and dryness of mouth in 8% of patients.

Shuling et al. [82] made the ensuing concluding iterations:

- Letrozole does improve sperm concentration and does increase testosterone-oestradiol ratio for men with oligozoospermia who do have normal testosterone-oestradiol ratio.
- The role of letrozole with regard to the treatment of infertility in the male could be extended to this group of patients.

- Additionally, letrozole is a relatively well-tolerated drug which does not have any serious side effects.

Steiner et al. [83] undertook a study to ascertain whether utilization of antioxidants does improve upon male factor infertility, as measured by means of parameters of semen and DNA fragmentation at 3 months and the achieving of pregnancy that has resulted in live birth after up to 6 months of undergoing treatment, among couples who have male factor infertility. The study was designed as a multi-centre, double-blind, placebo-controlled trial associated with an internal pilot study. The study was undertaken in the United States of America over a period of 3 years from December 2015 to December 2018 within nine fertility centres in the country. One hundred and seventy four (174) men who had sperm concentration that was equal to or less than 15 million per millilitre, sperm motility of 40% or less than 40%, presence of normal sperm morphology of 4% or less than 4%, or DNA fragments greater than 25%, as well as a female partners who were ovulating and were either 40 years old or less than 40 years of age and who had been assessed and documented to have patent fallopian tubes. The males had been randomly assigned to receive (a) antioxidant formulation with regard to 85 men who receive 500 mg of vitamin c, 400 mg of vitamin E, 0,20 mg of selenium, 1,000 mg of L-carnitine, 20 mg of zinc, 1.000 µg of folic acid, 10 mg of lycopene daily, or (b) they received placebo which had included 86 men. The treatment did last for a minimum period of 3 months and a maximum time of 6 months, and all the couples did attempt to conceive by natural means during the first 3 months and following which they attempted to conceive with utilization of clomiphene citrate with intrauterine insemination of the female partner from month 4 through to month 6. With regard to the outcome of the study, the primary outcome was the birth of a child who is alive, and the secondary outcomes did include conception (pregnancy) within 6 months of undergoing treatment. With regard to the internal pilot, the primary outcomes of the study included semen parameters, and sperm DNA fragmentation index following 3 months of undergoing treatment. With regard to the result(s), in the men, Antioxidants, and Infertility (MOXI) study, it was found that after 3 months of the therapy, the change within sperm concentration did differ between the antioxidant group (median -4.0 [interquartile range -12.0, 5.7] million per millilitre) and placebo group (+2.4 [-9.0, 15.5] million per millilitre). Nevertheless, no statistically significant differences were found between the two groups for changes in sperm morphology, sperm motility, or DNA fragmentation. Among the 66 men who had oligospermia at randomization, the sperm concentration was found not to differ at 3 months between the antioxidant treatment group (a) and the control group (b) 8.5 (4.8, 15.0) million per millilitre versus 15.0 (6.0, 24.0) million per millilitre. Out of the 75 men who had asthenospermia, the motility was not different at 3 months that was documents as: 34% +/- 16.3% versus 36.4% +/- 15.8%. Out of the 44 men who had high DNA fragmentation, the DNA fragmentation at 3 months was not different which were 29.5%, (21.6%, 36.5%) versus 28.0% (20.6%, 36.4%). Within the entire cohort of participants in the study, the cumulative live birth had not differed at 6 months between the antioxidant treatment group and the placebo group that were 15% versus 24%. Steiner et al. [83] made the ensuing conclusions:

- Utilization of antioxidants do not improve the parameters of semen, or DNA integrity among men who have male factor infertility.
- Even though the outcomes of the study have been limited by the size of the sample, the findings of the study had suggested that utilization of antioxidant treatment of the male partner of the infertile couple does not improve in vivo pregnancy or in live-birth rates.

Based upon the findings of the study, it would be argued that it is time to stop the recommendation of antioxidant treatment of the infertile couple. Considering also the fact that the number of participants enrolled in the study is small, it would also be argued that a similar study should be undertaken with the recruitment of a large number of participants through a global multi-centre study and if the results of Steiner et al. [83] are confirmed then clinicians globally would confidently be advised to stop recommending utilization of antioxidant treatment for the infertile couples as an attempt to help them achieve pregnancies and live births.

Jamil et al. [84] iterated that Non-somatic factors do play a significant role in erectile dysfunction. They assessed the effect upon men who are suffering from male factor infertility by employing the validated Self-Esteem and Relationship questionnaire (SEAR) and they compared the scores with controls. They asked men who have primary infertility to fill SEAR questionnaire. Normal fertile men who visited their clinic for unrelated problem or normal male accompanying infertile patients did constitute the control group. They compared the Transformed score of each domain and total score of SEAR questionnaire and means. They analysed their Data by R version 5.2. They undertook Univariate and multivariate analyses to ascertain factors that predict self-esteem and total relationship score. There were 45 men each in the study group and in the control group. They found that the mean transformed self-esteem score and total score of infertile men were significantly lower in comparison with the control group (74.44 versus 95.83) and (73.54 versus 95.86) *p*-value of <.0001. They also found that longer duration of infertility, advanced age, diabetes and higher education were factors that significantly lowered the scores on univariate analysis, and on multivariate analysis, diabetes was the only significant predictor of total SEAR score in infertile men. They additionally found that infertility does lead to lower self-esteem, sexual performance and confidence among infertile men in comparison with the controls. Furthermore, they found that the relationship score does worsen with increasing duration of infertility.

Del Giudice et al. [85] stated that ongoing evidence had indicated the role of male factor infertility as a potential predictor of mortality and general health status. They undertook a systematic review of the literature in order to update the current knowledge base regarding the association between male factor infertility and general health. They undertook a systematic review of the literature out from inception to November 2019 in order to assess significant associations between male infertility and adverse health outcomes such as cardiovascular, oncologic, metabolic and autoimmune diseases as well as overall mortality. With regard to the results, Del Giudice et al. [85] made the ensuing summations: In all, 27 studies had met their inclusion criteria, and these were critically examined. Five studies had examined male infertility and cardiovascular disease risk, 11 studies had examined oncological risk including the overall cancer risk, testis cancer and prostate cancer, 8 studies had examined aggregate chronic medical diseases and 5 studies had examined infertility related to

the incidence of mortality, for a total of 599,807 men who were diagnosed with as having male factor infertility which had covered a period from 1916 to 2016. Del Giudice et al. [85] based upon the analysis of their review of the literature findings made the following conclusions:

- A man's fertility and overall health did appear to be interconnected.
- Based upon their findings a diagnosis of male infertility could allow a window into future comorbidity and/or mortality which may help guide clinical decisions and counselling.
- Many possible aetiologies including genetic, epigenetic, developmental, and lifestyle-based factors need to be further evaluated in order to establish the underlying mechanisms between male infertility and health.

Conclusions:

Male infertility is a common global problem that requires a careful and thorough investigation to establish the cause of the problem. Various management options are utilized depending upon the cause of the male infertility including: Lifestyle medication, cessation of infertility causative medicaments, taking of medicaments to improve sperm count and quality, surgical operations to relieve obstructive causes of infertility, and assisted conception. Many men with infertility problems have been helped to have their own children out of their own spermatozoa but others have had children by means of donor assisted conception. There is ongoing research globally to find more ways to help the infertile couple. Men who have infertility problems should be encouraged to seek medical attention.

Conflict of interest - None

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