

Advanced treatment regimes and application of regenerative medicine for human male infertility treatment

A.S Vickram¹, G.V. Sree Charan², M. Kusuma², P. Venkatasaikumar², P.N.
Ramya Bhargavi², G. Gulothungan², R. Nanmaran², S. Thanigaivel²,
P. Jeyanthi^{3*}

^{*1}-Department of Biotechnology, Saveetha School of Engineering, Saveetha Institute of
Medical and Technical Sciences, Chennai

²-Department of Bioomedical Engineering, Saveetha School of Engineering, Saveetha
Institute of Medical and Technical Sciences, Chennai

³-Department of Biotechnology, Vel Tech Rangarajan Dr. Sagunthala R&D Institute of
Science and Technology, Chennai

Corresponding:

Dr. P. Jeyanthi
Assistant Professor,
Department of Biotechnology,
Vel Tech Rangarajan Dr. Sagunthala R&D Institute of Science and Technology,
Chennai

Abstract: Male reproductive organ and other assessory sex glands plays an massive role in sperm production process, sperm maturation process, maintaining the entry of sperm cells in the female reproductive tract and until child birth. Many events could happen properly from semen ejaculation until it reaches the oocyte for proper fertilization. Any problem during the process of semen reaching female reproductive tract could men responsible. Overall 20 to 35 % of men contribute to the infertility. Clinical evidence suggests that tissue engineering and regenerative medicine could help men achieve the fertility status. Congenital abnormalities, iatrogenic injuries, trauma and other chronic conditions could be treated by regenerative medicine. Recently stem cell therapy has been emerging in the file of male infertility treatment regimes. In case of trauma, penile reconstruction, testes reconstruction available as most advanced treatment regime. Here we summarized the

important findings and functions of testes, penile and scrotum reconstruction techniques, organ based regeneration for various male infertile disorders. Non-obstructive azoospermia conditions will be very tough to diagnose and this review comprises the important treatment regimes available for non-obstructive azoospermia. Antioxidants therapy, trace elements therapy, oral administration of carnitines and its potential applications were carefully elucidated for idiopathic conditions. We also summarized the role of prebiotics and probiotics as treatment regime for male infertility. All advanced treatments methods available were in general summarized in this review.

Key Words: *Antioxidants, Corticosteroids, Carnitines, Human male infertility, Penile reconstruction, Probiotics, Prebiotics, Regenerative Medicine, Semen, Seminal Plasma, Testicular Disorder, Trace Elements, Stem cell therapy.*

I. INTRODUCTION:

Worldwide male infertility range lies between 3 to 12% [1]. On an average 30 to 35 million men found to be infertile worldwide. Highest rate of infertility arises from Africa and Europe, and estimated around 6% were infertile in case of North America [2]. In general, 10% of men exhibit the inability of child birth in America. Only men contribute around 20 to 30% of overall infertility worldwide [3]. The management of male infertility patients involved with a complex integrity of analyzing potential health problems related to reproductive potential [4]. Infertility could cause sociocultural and financial problems for the patients [5]. Infertility term not only affects the individual, it could affect the couple as a whole if at all the problem lies with any one of the partner [6]. Infertility assessment could provide information on the diagnosis path as well as efficient therapy for male infertility after diagnosis [7]. Recently many surgical methods and ART methods available for male infertility, but the success by these methods remains silent in some cases. In case of idiopathic type and subfertility, the only choice remains as assisted reproductive technology [8]. Emerging medical field like regenerative medicine, tissue engineering, reconstruction techniques, advanced therapies could help the male infertile men in an amended way [9].

Biomaterials, tissue engineering, assist devices, various biomedical technology, and stem cell therapy were the integral part under one wing called regenerative medicine [10]. This term “regenerative medicine” had emerged in early 90s and then onwards its applications in medicine especially in treatment regimes were limitless [10]. The basics of regenerative medicine are to alter the degrees of treatment protocols for the chronic diseases, regenerate the organs by stem cell therapy and tissue engineering. In general, regenerative medicine had the following procedures including isolation of cells, differentiation, cell proliferation and transplantation procedures [11]. Basically Sperm cells or first line germ cells has the capacity of self renewal and have the ability to pass the genetic information from one generation to next generation. So sperm cells could have the maximum chance of maintaining the fertility status of men in general [12]. Spermatogonia stem cells have the capacity of pluripotency so that it could be easily applicable or as a source for regenerative medicine. Many researchers proven and used the pluripotent property and able to produce a mature spermatozoa or sperm cells from the testicular tissue or testicular germ cells [13]. This type of mature spermatozoa production from the immature testicular and mature testicular tissue might be a boon for

young cancer survivors [14]. Cancer treatment for the per-pubertal patients may lead to loss of fertility status, thus these regenerative medicine could be the choice of preserving the mature testicular tissue [15]. Later whenever the need, after treatment, the young cancer survivor may prefer this regenerative technique to have the mature spermatozoa that could be taken for assisted reproductive technology like in vitro fertilization, intracytoplasmic sperm injection etc [15]. Many researchers proved the 2D agar base cell culture for helping the spermatogenesis process and thus in the production of mature spermatozoa with normal morphology [16].

Urogenital infections, many inflammatory conditions, genital tract infections are considered as a major cause of human male infertility. Genital tract infections influences 15% of men overall under male infertility conditions [17]. Surgical techniques, sperm integrity functions, treatment regimes, glucocorticosteroids, mast cell blockers and other advanced treatment were available for male infertility. Also for idiopathic conditions, antioxidants therapy, trace elements therapy, prebiotics and probiotics therapy, and other treatments could be possible.

In this review, major regenerative medicine techniques available for male infertility, major stem cell therapy, scrotal and testes reconstruction techniques, penile reconstruction techniques, other advanced therapies like antioxidant role, trace elements role, prebiotics and probiotics as treatment regime, and carnitines as treatment regimes as discussed exhaustively. This compiled review could help many clinicians and surgeons an updated knowledge about the male infertility treatment regime.

II. Azoospermia under regenerative medicine:

Azoospermia is the major drawback for deriving treatment regimes for male infertility. Approximately 0.7 to 1% of the population of men will be azoospermic in nature, under two categories like obstructive and non obstructive azoospermia [18]. Out off all male infertility cause, azoospermia leads the role in 15 to 20% of all infertile men. Population with obstructive azoospermia, the treatment regime will be very simple, diagnosis will be very simple and the men may go for surgery to remove the obstruction [19]. But treatment regime for the non-obstructive azoospermia (NOA) will be very difficult to treat [20]. Congenital abnormalities, any chemotherapy reagents, medications, gonadotoxins, varicocele and any other idiopathic causes were the conditions for NOA. For the last 3 decades, surgery and other therapy, including hormonal regimes were the hope to treat NOA [21]. But very recently regenerative medicine emerged and had its own treatment for NOA [21]. Somatic stem cells could be differentiated into mature cells that could help from recovery of damaged tissues, organs and also in rebuilding. In regenerative medicine, bone marrow stromal cells could be the easy choice for regeneration, as it has very effective proliferation and differentiation rate. Other than these, it also has low immunological rejection, so that naturally suitable for stem cell therapy. NOA with idiopathic conditions could be treated under this category with regenerative medicine. Bone marrow stromal cells not only be acting as a hypo-immunogenic, it could act as a immunosurveillance after the successful transplanatation [22]. For any type of alogenic transplanatation, bone marrow stromal cells could be the choice. As because of sertoli cells were found to have immune tolerant, there could be high chance for the survival of donor bone marrow cells into the host semineiferous tubules [23]. This is the reason behind the no high immune response or no inflammatory response occurs after the transplanatation. These types of works succeeded in the rat model and for human it is still under the clinical trial. But the rat model works given a best outline

and proper mechanism to treat non-obstructive azoospermia using the regenerative methods [24].

III. Reconstruction of testes and scrotum for male infertility treatment:

Andrologists and urologists working with wide conditions that affect the testes and scrotum. These conditions may often require surgical protocols [25]. The management may fall under simple hydrocelectomy and sometime complex scrotum reconstruction methods. Hydroceles affect generally 1 % of population of adult men, in that 0.7% found to be infertile conditions [26]. In infertile category, hydroceles causes could be idiopathic, the diagnosis method for hydroceles could be either a neat physical examination of the scrotum or by using ultrasonography. Either scrotal transillumination test to find the presence of hydrocele or solid testicular mass test could be used [27]. If not able to diagnose, the last method is by using ultrasonography to confirm the hydrocele or spermatocele presence, its volume and the level of complexity. With primary stage, injection with tetracycline or phenol will be injected into the hydrocele sac [28]. This technique said to be sclerosing or sclerotherapy and curing rate found around 60 to 95%. This could be the easy choice of removing hydrocele and plays a major role in male infertility management [29].

Skin grafting and scrotal reconstruction:

Skin grafting and tissue engineering could be the choice if when 60% or greater scrotal skin loss or damage. Several reconstruction and regenerative techniques available for infertility management under grafting [30]. Generally split thickness skin grafts will be the apt method to reconstruct the scrotum. Both beneficial as well as risk factors associated with this grafting technique [31]. The important factors need to be considered before the reconstitutions are the technique of choice, optimal timing, effects on sexual parameters. The choice of technique going to be adapted purely depends on the andrologists, urologists and surgeons and fertility goal will be given the first priority in case of infertility [32]. Most of the surgeons will prefer the STSG technique for reconstruction, as because of its high success rate and easy to follow up the procedures [33]. Majorly thigh tissues will be utilized from the donor for all these techniques involving scrotum and testes reconstruction [34]. Many researchers found that the most common reason or complication after the scrotum skin grafting will be the wound breakdown, which might be most common at graft edges [35]. In case of non-healing wounds exist for more than 1 month after grafting; the patient has to check in the clinic for regular updates or by sending the photos to the clinician regularly for physical clarity. In rare cases, there could be chance for the patient to undergo reoperation for the wound breakdown [36].

Functions of Testicular Prosthetics:

Traumatic experience could be experienced in both adults and children in case of testicular absence. Testicular prosthetics could be the choice of these cases [37]. This could be used in case of testicular torsion, cancer, and atrophy in both children and adults. Prosthetics done a major role in providing a male sexual image attainment, but not having any real functions for the treatment of male infertility [38]. Testes made up a fluid filled sac, in the same way the prosthetics have evolved over the years and now the testes prosthetics made up of silicone coated with saline filled sac. Coloplast Torosa is the only one FDA, USA approved testicular prosthetics, although many like exist in the market. Based on its silicone properties and components, many testicular prosthetics were not approved by FDA [39]. The FDA approved

Torosa comes in four different types like small, extra small, large and medium, each differs in the filled volume of saline, and the injection port [40]. There could be chance for the infection during the placement of prosthetics as maintaining aseptic conditions could be very critical. Testicular prostheses have some sort of issues to the patients like post infection, extrusion, hematoma and chronic pain [41]. Some common complaints from implanted testes were abnormal perceived size, and migration [42]. The common procedures that could be done to avoid infections during and after testicular prostheses were pubic hair shave, chlorhexidine shower, local antibiotics, betadine scrub for at least 10 minutes, water proof drapes [43]. After placement, general antibiotics towards gram positive and negative microbes should be given properly to avoid the spread of infections.

IV. Total Penile Reconstruction:

Total penile reconstruction was done in early 1930s itself, but had many difficulty and disadvantage in it. Bipedicled abdominal flap has been used a technique, but was unsuccessful due to poor aesthetic output [44]. Later in 1940s another research team had done with penile reconstruction with advent form first one [45]. This was done with “tube within tube” technology [46]. The increased in the scope of regenerative medicine, increases the technology later in penile reconstruction filed [47]. The microsurgery later gave the opportunity for phalloplasty technique [48]. These techniques include radial artery forearm flap, thigh flap and latissimus dorsi flap [49]. Prospective considerations for penile reconstruction patients includes the stoppage of tobacco, smoking cessation, testosterone or any related medications should be stopped very prior to the reconstruction day In prospective preparation, bowel preparation play a major role that includes 2 times saline enemas, this could be done before 1 day of the surgery [50].

Major surgical techniques for penile reconstruction:

In case of phalloplasty, radial forearm will be the most commonly used technique. Generally this technique could be used with three staged protocol [51]. First stage could be critical, harvest and insertion of the flap. The second stage could be easy choice, just creating and neoglans, here glans penis can be fashioned [52]. The third stage could be final insertion of prosthetics. Some clinicians could modify this protocol, probably using a portion of bone. By using this, the surgeon could have more advantage of reliability, with stiffness in reconstruction [53]. In a large population study, 11% from the total who done penile reconstruction reported with or in need of anastomotic revision, 1% showed with complete flap failure [54]. This could be the large population study so far did with the penile reconstructive studies. There are other forms of complication through this technique includes fistula, and strictures. In another study 80% of the patients reported with sensation, 99.1% of the patients were able to urinate from the tip, 98% population were satisfied for cosmesis, and proper interventions should be there for the better outcomes [55]. Most importantly 75% of the population could able to achieve orgasm [56]. 78% of the population could able to void during standing. These all parameters show the advantage of this technique for penile reconstruction. The second commonly used technique for penile reconstruction will be fibular osteocutaneous flap; this had some extra advantage when compared with radial, is that providing long time rigidity to the penis as that allows for normal sexual intercourse, because of bony component. Because of the stiffness, split thickness skin graft will be done before the reconstruction technique [57]. The second step is to insert the fibular flap in a correct position and the final stage could be urethral anastomosis. Researcher also suggests not to opted for fibula bone, in order to decrease the morbidity procedure [58]. The hospital stay could be the

disadvantage as long as 26 days as to be stay at hospital. Researchers confirmed the partial flap loss with 12 % of the total population who did reconstruction [59]. 9.6% of the patients reported with unmanageable fistula, 33% with manageable fistula [60].

Anterolateral thigh flap is the 3rd commonly used technique for the penile reconstruction procedure [61]. This technique has emerged because of alternative phalloplasty and it could eliminate the disadvantage of other 2 techniques previously disused, this could able to eliminate the conspicuous donor and might need for the microsurgery [62]. The stages involved were, first one the flap could be raised up, use of femoral cutaneous nerves. The second step is tunnelling the flap; last stage is to do neurorrhaphy and anastomosis. Urethral strictures could be the chance after reconstruction. Wound problem may also be the disadvantage for this technique [63]. Outcomes could be very good for this technique as 100% will achieve the sensation [63].

Management after reconstruction:

Standard microsurgery care should be given for the patients who done the penile reconstruction [64]. After surgery, the patients should be kept in a ward to monitor the hourly flap checks for minimum of first 24 hours. The risk for arterial and venous insufficiency could be greatest during these hours [65]. After these hours, the flap could be monitored for hematoma and seroma formation if any [66]. Flap monitoring could be gradually decreased day by day and before discharge. Broad spectrum antibiotics for 10 to 14 days or as per the course could be completed after the reconstruction; this could avoid maximum of infection and the spread of infection [67]. A catheter could be placed to allow some urinary diversion for proper healing. These catheters could be removed after 1 or 2 week as per the surgeon's recommendations [68].

V. Treatment for male infertility with inflammation in genital tract:

Treatment of any inflammation in the genital tract is an important parameter for proper diagnosis and prognosis for human male infertility [69]. Complete elimination of pathogenic bacteria in human ejaculate is an important treatment regime for male genital tract inflammation. Through this normalization of inflammatory parameters in genital tract, way for improvising abnormal sperm parameters could be possible. Clinicians have to be very clear in distinguishing the infections related to inflammation and non-inflammatory conditions [70]. Broad spectrum antibiotics should be given for the most acute prostatitis, urethritis and or epididymitis and these are very well established by the researchers and clinicians [71]. Also some patients found to be asymptomatic for the inflammation and have the abnormalities well [72].

Antibiotics will be the preferred method for asymptomatic genital tract infections or inflammation in infertile patients, the same method of approach as done for symptomatic patients [73]. Antimicrobial therapy could be the choice for all either symptomatic or asymptomatic patients, also there should be co-treatment mandatory for the partner of the patient if diagnosed with any STI (sexually transmitted infections) [74]. The treatment procedure will be strictly based on the microbiological recommendations and only if the bacterial count exists beyond the limit set by the world health organization in an ejaculate [75]. Antibiotics treatment course lies on the type of infection caused the spread capacity of the microbes and other major parameters [76]. Mostly 10 to 14 days of antibiotic course will be prescribed for genital tract infections or inflammation [77]. In case of the symptoms are too much, and then ad hoc treatment with fluoroquinolones will be the better choice as it

could penetrate easily and most effectively [78]. Conflicting results were produced in case of using antibiotics like doxycycline, sulfamethoxazole in asymptomatic leukocytospermia patients [79]. But some researchers suggest that efficiency of antibiotics and improvement in the semen quality especially in case of motility and morphology, and resolution or recovery from leukocytospermia [80]. All these data suggest that antibiotics under controlled use could help effectively to both abacterial and bacterial leukocytospermia.

Patients with acute and chronic conditions of epididymitis may have the increased risk associated with azoospermia conditions if not treated [81]. Azoospermia may contribute around 5 to 20% of overall human male infertility, but among these obstructive azoospermia will be more, obstructions could cause because of any infections or inflammation in the genital tract [82]. Major surgical techniques were available to get out off obstructions, many researches confirmed that obstructive azoospermia patients could have a chance of surgery and become fertile, but treatment to non-obstructive azoospermia could be very tough as the diagnosis is itself a big job because of idiopathic reasons [83]. Fertilizing surgical procedures were the choice for obstructive azoospermia, but the only option for non-obstructive azoospermia patients were go for testicular sperm extraction. This sperm could be used for further assisted reproductive techniques like in vitro fertilization, intra cytoplasmic sperm injection and other techniques [84]. There are no alternative techniques for permanent recovery from infertility for non-obstructive azoospermia [85].

Glucocorticosteroids treatment also evolving now towards male infertility as allied treatment for some kind of testicular inflammatory lesions [86]. More beneficial effects of corticosteroids could be seen including improvising sperm parameters when the admitted levels of glucocorticosteroids were administrated orally [87]. Oligospermia patients were given with prednisone under prescribed amount as a anti inflammatory treatment, this could be monitored by using ultrasound images [88]. A daily dose of prednisone 25 mg for continuous one month improved the semen parameters like sperm concentration, sperm motility, sperm morphology in oligospermia patients [89].

VII. Mast cell blockers as treatment regimes:

Cytokines, histamine and other mediators will be released when the inflammation happens or any infections could possibly occur in genital tract [90]. Researchers believe that mast cells have both adaptive and innate immunity that could involve in the inflammatory diseases associated with genital tract [91]. Increase in the number of mast cell directly correlates with the poor spermatogenesis and poor sperm parameters [92]. Very few studies suggests to provide with optimal mast cell stabilisers could be the choice for clinicians and found improved sperm parameters at the end of the study [93]. The drug ketotifen, found to be mast cells stabilizer or blocker, prescribed 1mg dose for 12 weeks, the patients later found with reduce number of white blood cells in the semen and increased in the semen parameters including sperm concentration, sperm motility and sperm morphology [94]. Few researchers worked on the ketotifen ability in pregnancy, and found that there is a cumulative increase in the pregnancy rate when compared to the non treatment group [95]. There are very fair chances for the increased amount of mast cells in case of varicocele patients, idiopathic male infertility, azoospermia conditions and asthenozoospermia [96].

VI. Antioxidants as treatment regime:

Men with genital infection and inflammation, there could be chance for the imbalance between antioxidants role and the ROS encounter, the infection in genital tract lead to increased amount of ROS in the semen, which in turn reduces the sperm parameters including sperm concentration, motility and morphology [97]. This could increase the oxidative stress in the seminal plasma reduces the antioxidant capacity; this could cause the damage in spermatozoa by means of lipid peroxidation [98]. In the diseased conditions, the sperm functions like acrosome reactions, integrity in DNA were also affected [99]. Oral supplementation of antioxidants could be the better choice for treatment of oxidative stress mediated male infertility [100].

Researchers also confirmed the role of oral supplementation of antioxidants those who undergoing ART (any methods), with improvising live birth rates via ART methods [101]. Also few researchers confirmed the essential role of antioxidant supplementation resulted in increased pregnancy rate [102]. Both partners should be given with antioxidants supplementation for normal conception as well as by ART methods [103]. A variety of standard antioxidants including zinc, coenzyme Q10, selenium, Vitamins C, E, D, and folic acid were given generally for the oxidative stress treatment or general male infertility treatment regime for any idiopathic conditions [104]. But few studies suggest that there were no significant improvement in the pregnancy rate and live child birth rate after prolonged antioxidants treatment [105]. Medication with antioxidative properties in idiopathic men shows increased rate in pregnancy, but could not have success in case of live birth rate [106].

VIII. Prebiotics and Probiotics as male infertility treatment regimes:

Many researchers working with gut microbiota confirmed its physiological effects to human body [107]. The primary role of gut microbiota had many effects on intestinal function, but recently, its functions with immune system, tissue homeostasis, the bone mass and metabolic profile and its potential behaviour [108]. Gut microbiota able to regulate the estrogens concentration by secreting an enzyme for mediating the process [109]. In women, absence of gut microbiota leads to major problems including obesity, polycystic ovarian syndrome, cancer and even female infertility, but in men the gut microbiota study had not come to a good correlation [110]. Still, by influencing the estrogen level, microbiota could possibly interact and monitor the hypothalamic pituitary mechanisms. Surprisingly research found that treatment with pre and pro biotics for intestinal disorders, also found increase in sperm quality and quantity [111]. Researcher evaluated the role of pre and probiotics in treatment and placebo group, the population in treatment group had significant improvement in the sperm parameters and not in the case of placebo [112]. Even the volume of ejaculate also found to be increased in the treatment group. Probiotics also helps in maintaining the FSH, and LH levels and lead to spontaneous pregnancy. The researcher highlights the role of probiotics and prebiotics in a pilot study, which includes optimization of the free radical concentration in the semen, regulation of prostate microenvironment [113]. The major mechanism of action behind this is, it could influence the kisspeptin production, secretion of gonadotrophins in an optimal way [114]. Need more primary and basic research on prebiotics and probiotics and its influence on male fertility, if it could succeed, then very economic friendly treatment could be possible for idiopathic male infertility and sub fertility [115].

IX. Carnitines as treatment regime:

In humans, there exist two different forms of carnitine, one is L-carnitine and another one is L-acetylcarnitine. L-carnitine found to have more antiapoptotic effects and helps in recovery of male infertility [116]. Carnitine proved to be a marker for any epididymis related

infections or disorders, because more concentration of carnitine could present in the male reproductive tract. In fact decreased level of L-carnitine in the seminal fluid correlates with the epididymitis and other male infertility disorders [117]. Supplementation of oral carnitine for inflammation related issues could result in increased semen parameters. L-carnitine also play a major role in decrease the apoptosis rate [118]. Low levels of L-carnitine were reported in asthenospermia, azoospermia and other infertile groups, when compared with normospermia and other control group. Carnitine had functions in regulating the sperm maturation, and sperm motility [119]. In spite of many antioxidants exist and their role in male fertility, L-carnitine is the major antioxidant that could be prescribed by many clinicians for male infertility treatment [120]. Many research findings reported the role of both 2 forms of carnitine for the treatment of asthenospermia patients. Study suggests that 2 gram of L-carnitine and 1 gram of L-acetylcarnitine per day could help the patients for improvising sperm parameters. In another study, only 3 grams of L-carnitine alone gave good results as a male infertility treatment regime [121].

X. Trace elements role in male infertility treatment:

Zn found abundantly in the semen, mostly secreted by prostate gland [122-126]. Its functions towards fertility were found to be very high. More number of researchers were worked/working on the functional values of Zn on human male fertility status. Many researchers found that lower concentration of seminal Zn in infertile group when compared to the control group [123]. Zn acts as a cofactor for more than 250 enzymes that could have role in fertility status. Zn play a defensive role against oxidative stress [127]. Zn also play a unique role in DNA repair, cell replication and transcription process [128]. Selenium a trace element has its own role in testicular development, sperm functions including transportation of sperm into the female reproductive tract. Selenium is an essential component for selenoproteins to run its show against cell interventions, against oxidative stress and acts as anti-inflammatory agents during infection in the genital tract [129]. Lack of selenium in semen has been reported by researchers in various studies and correlates with low testes volume, seminiferous atrophy, sperm maturation and sperm normal morphology [130].

In a study conducted, 26 weeks oral supplementation of selenium was given to patients, in which 70% showed better results in semen parameters before and after treatment [131]. But in few studies, no improvement was observed in selenium oral administration, the results were contradictory and conflicting. Vitamin E, N-acetylcysteine and selenium had yielded good results and improved sperm parameters in the infertile group [132]. Average dose consideration will be around 90 to 120 microgram per day for oral administration. Zinc oral supplementation proved to be a better way for treatment of male infertility especially for asthenospermia and azoospermia patients, increased level of sperm count, motility were observed after oral administration of Zn one year [133]. Average amount may vary from 60 to 450 mg of Zinc per day other than food intake for infertile category.

XI. CONCLUSION:

In general, we confirm the advanced medical therapeutics available for human male infertility will be the regenerative medicine. Various treatment regimes available for the idiopathic male infertility were evaluated briefly. Spermatogonial stem cells treatment holds promising results and acts a goal keeper for providing a rehabilitated life for the infertile men. As per the recent literature, checking for infections and inflammation in male reproductive tract could be added in a routine andrology test for human male infertility. Physical examination of penile tissue, testes, and prostate could also be performed for proper diagnosis. Probiotics

and probiotics could be used as a economic friendly weapon against human male infertility. Regular dietary Zn intake could be the choice for men who undergoing ART techniques.

XII. FUTURE SCOPE:

Robotics treatment regimes for male infertility could be better understood with basic research in the area of gut microbiome and male fertility. It could be greatly helps the poor to combat the male infertility if it succeeds in a large population. Assisted reproductive technology treatment and success lies in the combination of antioxidants and carnitines therapy. Research in regenerative medicine on reconstruction techniques could be improvised as existing techniques not giving enough success rates for male infertility treatment. Further research needed in non-obstructive azoospermia diagnosis and prognosis.

Conflict of Interest: The authors declare no conflicts for this article

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