(IJESIR) International Journal of Science and Innovative Research
e-ISSN: 2724-3338
2021, 02(01)
https://www.ijesir.org
Paper id: 0100016IJESIR

A Review and Update on Male Infertility Problems Based on Present Status

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ARTICLE INFO

Received: 26.12.2020

Accepted: 15.01.2021

Final Version: 25.01.2021

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ABSTRACT

Healthy semen quality plays an important role in maintaining the healthy fertilizing ability to spermatozoa. Male infertility is a global problem with increasing male semen quality in men living in Asia, Europe, Africa, and North America. The sperm acquire proactive mechanisms during spermatogenesis and their maturations; they still remain viable for toxic insult. The healthy semen quality is a major contributor to infertility. Studies prove that different factors such as exposure to pesticides, heavy metals, obesity, tobacco, smoking, industrial chemicals, alcoholism, sedentary lifestyle, poor nutrient intake oxidative stress, physiological and genetic factors can decrease male fertility. Routine semen analysis and assays for sperm chromatin integrity are the most widely utilized and best studies adjunctive diagnostics in male infertility. Now, scientists have found many different options for male infertility problems. This review article summarizes protective mechanisms of spermatogenesis, causes, diagnosis, and both traditional and modern treatment approaches of male infertility. This review article highlights present issues and directions for further exploration of the male infertility problems.

Keywords: Male infertility, proactive mechanisms, causes, diagnosis, treatment, future

Introduction

Infertility is a global significant health affecting around 15% of couple. Most infertility is due to the male components of fertilization [1] infertility is mainly due to male factors. Infertility is described as the inability to get pregnant during unprotected intercourse [2] by transmitting paternal genes to the egg; the sperm and its nucleus act as "Genome bridge" from parents to baby [3]. Any sperm chromatin may have serious consequence for either fertilization or the risk of development disorder in embryo. During spermatogenesis and epididymal maturation, the sperm nucleus is a uniquely condensed structure which has protect to haploid genome as it is carried to the oocyte [4]. Retrospective evaluations of laboratory semen records are plentiful and have indicated a decrease in semen quality as reported from Belgium [5], Finland [6], France, Scotland [7], United Kingdom [8], Canada and united states [9:10]. In variations have been reported from regions such as Denmark [8], Australia [9], Israel [10]. But the data reporting on variation in semen quality is still unconvincing considering the global trends. For example, it was recently confirmed that the Asian male population followed the same global trends over the periods of past 50 years [13].

Protective mechanisms of the sperm

Spermatogenesis: The production and formation of sperm occur in the seminiferous tubules in the testis. Seminiferous tubules contain germ cell at various stages of development as well as somatic cell. Somatic cells are also known as Sertoli cells. Main function of Sertoli cells is the formation of the "Blood – testis barrier" or the BTB. BTB formed when adjacent Sertoli cells come into contact with each other and form a series of a tight junction thus regulating the passage of macromolecules to the systemic circulation to the developing of germ cells.

During meiosis germ cells may have chromatin decondensed for long days, particularly they are susceptible to nuclear damage. Presence of barrier may help to prevent noxious factors from reaching them. As germ call undergo mitotic and meiotic divisions and several major types of cell can be distinguished in mammalian. These are the spermatogonia. Germ cells after the first and second meiotic divisions developing haploid germ calls and testicular sperm [16].

Spermatogonia will undergo a series of mitotic divisions and it turn into divide meiotically into primary spermatocyte when it enters the spermatogenesis cycle. Main characteristic features of male germ cells are that cytoplasm does not separate upon nuclear divisions [17]. when spermatocytes enter into the leptotene stage they move away from the basement membrane toward the lumen of the seminiferous tubule. Then there are separated from the basement membrane by the BTB. Since chromatin replication has already been occurring. Spermatocytes contain tetraploid(4n) amount of DNA. When homologous chromosomes one from each parent will come together and nucleoli become more visible. At

this stage primary spermatocytes are known as zygotene spermatocytes. After the next stage crossing over of chromosomes occurs. This process is highly susceptible to chemical damage. After this process the chromosomes become more condensed. Preleptotene spermatocytes are high in DNA synthesis and pachytene spermatocytes are high in RNA synthesis. The chromosomes will segregate from one another at final stage of meiosis. After the divisions tetraploid converted into secondary spermatocytes. After the complete of secondary phase of meiotic phase each one of the secondary spermatocytes give 2 haploid spermatids. During mitosis of each spermatogonia DNA synthesized. At the inter phase of each cell cycle in nucleus histones are produced basic proteins surrounded the DNA and they are incorporated into newly synthesized DNA [18].

Spermiogenesis: Spermiogenesis process involved in physiological and biochemical changes. Shaping of the nucleus, nuclear condensation, acrosome formation, elimination of cytoplasm, flagellum development and mitochondria arrangement into middle of the sperm piece.

At the starting of the spermiogenesis, nucleus contain decondensed chromatin and there is to be active transcription. But after stage of spermiogenesis with a series of basic protein nucleus replaces lysine and histone. At beginning they are transitional proteins and ultimately arginine and cystine basic protamines. Spermatid becomes highly condensed. Nuclear histone replaced by protamines. During spermiogenesis a transition protein mediated a series of interaction which is involved in nuclear condensation. TP1 and TP2 are two major classes of transition proteins [19].

After this arrangement, nuclear DNA of mammalian sperm becomes 6- fold more condensed than somatic cells DNA. At the beginning of the process the anterior end of the nucleus and toward the tail. This process makes nuclear DNA of sperm and make most highly condensed eukaryotic DNA [20]. Duringepididymal transit the main important changes are the formation of disulfide cross links in nucleus. Protamine which are rich in cystine which are contain sulfhydryl groups they are participate in formation of covalent bonds [21]. Between highly stable keratinous nature provided by protamine molecule. Production of disulfide cross links assures a stable condensation of the nuclear protein complex and makes the sperm nucleus uniquely resistant to sonication and strong detergents. These disulfide bonds are prominent only in the sperm of eutherian mammals and are particularly confined to the anterior region of the sperm nucleus [22].

Limited amount of unoxidized protamine and cystine are present in human nuclear protein. Arginine contain free amino groups and cysteine contain free thiol groups are chelated by reversible group of zin ion, and further nucleus of sperm condensing. The zinc in the sperm nucleus hinders premature thiol disulfide exchange and during transfer to ovum decreases the vulnerability of sperm chromatin by chemical attack [23]. In the cauda of the epididymis storage of fully matured sperm takes places primarily until ejaculation. In the epididymis sperm can remain viable 4 to 6 weeks. Sperm can expose to toxicants during this time. If such chemicals subvert the normal condensation mechanism to protect the nucleus, they may have a detrimental effect on sperm nuclear integrity and function [26].

Causes of male infertility

There are so many factors may contribute to this decline of male fertility. Environmental, occupational and lifestyle factors are including in male infertility. Lifestyle factors include alcohol intake, smoking cigarettes, obesity, psychological stress, advanced paternal age, diet and coffee consumption, testicular heat stress, lack of sleep and exposure to electromagnetic waves from mobile phones [27].

Environmental Chemicals and Other Factors in Impaired Spermatogenesis

The male reproductive tract is a potential site of toxic insult [28:29] to increasing pollutants and chemicals in environmental. Increase in disease burden and costs in treating infertility disorders are cause to raise pollutants in environmental [30].

Taxological studies show that testicular and spermatogenesis are vulnerable because of continuously large number of cell divisions with call differentiation and its maturation process in animals. These include not only environmental pollutants but it also includes heavy metals, industrial chemicals, insecticides or scrotal heat exposure. In the interstitum Capillaries and leydig cells are targets for cadmium and ethanol. In the seminiferous tubule's targets are the Sertoli cells, spermatocytes, spermatogonia and spermatids. Sperm epididymal maturation and sperm motility are directly affected.

Organophosphorus Pesticide

In laboratory rats showed significant reduction in testicular and epididymal weights when they exposed to very low doses of chlorpyrifos for 30 consecutive days [31]. When animal treated with 5mg/kg and 10mg/kg chlorpyrifos which reduction in epididymal sperm count and sperm motility. After both doses were observed that increased sperm abnormalities. It increased DNA damages when animal exposed very low dose of chlorpyrifos (2.5mg/kg). chlorpyrifos affect sperm parameters and it reduced serum follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone which decreased fertility. Similar results were obtained with human spermatozoa indicating detrimental effects of organophosphorus pesticides to human spermatozoa [32:33].

Industrial chemicals

Dinitrobenzene and methoxy acetic acid are plasticizer which are industrial chemical can impair sperm fertilizing ability and sperm motility at acute and chronic dose level. Exposure to industrial chemicals not only degrades male infertility but also can result in DNA fragmentation [37].

Inorganic Pollutants

Metals toxicity depends on several factors, including their ability to bind to thiol groups of enzymes and proteins, thus altering their structure and function. Genotoxic elements may damage DNA structure directly through the production of oxygen free radicals or indirectly the alteration of enzymes responsible for DNA repair [38].

Lifestyle factor

For DNA damage and formation of reactive oxygen species tobacco smoking is responsible. A study on male partners of couples facing primarily infertility found that abnormal morphology present in 63% and 72% males who drank alcohol heavy (>80g/d) and moderately (40-80g/d). None of the heavy alcohol drinkers were normozoospermic (normal sperm) and most(64%) were oligozoospermic (low sperm count), which is suggestive of progressive testicular damage in relation to increasing daily alcohol intake [39]. Recreational drugs such as marijuana, cocaine, anabolic–androgenic steroids, opiates (narcotics), and methamphetamines are examples of illicit drugs that exert a negative impact on male fertility. The adverse effects of these drugs could impair the hypothalamic–pituitary–gonadal (HPG) axis, testicular architecture, and spermfunction [40].

More than 76% of caffeine consumers had a slight increase in semen volume, whereas fertile vasectomy patients who drank 6 cups of coffee/d presented with higher sperm motility. A recent systematic review involving 19967 men found that in most of the studies, semen parameters were affected by cola-containing beverages and caffeine-containing soft drinks, but not by caffeine intake from coffee, tea, and cocoa drinks. Caffeine intake may impair male reproductive function possibly through sperm DNA damage [41].

A study involving 13 077 men reported that obese men were more likely to be oligozoospermic or azoospermic compared to men within a normal weight range. A population-based study found that as body mass index and waist circumference increased, the prevalence of low ejaculate volume, sperm concentration, and total sperm count were also greater in overweight and obese men of unknown fertility [42]. The presence of excess white adipose tissue in obese individuals causes increased conversion of testosterone to estrogen, and affects the HPG axis leading to a reduction in gonadotrophin release, and impaired spermatogenesis and increased oxidative stress [43]. Similarly, diet such as vegetables and fruits, fish and poultry, cereals, and low-fat dairy products were among the foods positively associated with sperm quality. Diets consisting of processed meat, full-fat dairy products, alcohol, coffee, and sugar-sweetened beverages were associated with poor semen quality and lower fecundity rates [44]. Stress, in its many forms, may be detrimental to male reproductive potential. The classical stress response activates the sympathetic nervous system and involves the hypothalamus–pituitary–adrenal (HPA) axis. Both the HPA axis and gonadotrophin-inhibitory hormone exert an inhibitory effect on the HPG axis and testicular Leydig cells. Men who were significantly stressed had lower levels of testosterone and higher level of FSH and LH than men with normal well-being thus reducing sperm count, sperm morphology and its motility.[45]sleep disturbances may possibly have adverse effect on male fertility [46].

Results and Discussion

Treatment

Semen analysis and assays for sperm chromatin integrity are the most widely utilized and best studied adjunctive diagnostics in male infertility. Sperm DNA fragmentation detects a high level of defective spermatozoa [37]. DNA damage is more common in infertile men than fertile men. If sperm count is less than 40 million, artificial insemination can be recommended. If the sperm count is less than 20 million, the following treatments are recommended.

Assisted reproductive technology: If the sperm counts are less than 20 million but have reasonable motility, in vitro fertilization (IVF) can be carried out. The introduction of IVF in 1978 created a comprehensive shift in the focus of reproductive medicine. Things began to change upon the initial reports of successful surgical sperm retrieval. Invitro fertilization which involves the fertilization of eggs and sperm outside the body in a laboratory setting. Once, an embryo or embryos form, they are placed in the uterus. There are five basic steps in the IVF and embryo transfer process which include the collection of ova, collection of sperms, monitoring as well as stimulating the development of healthy ovum/ova in the ovaries, fusion of nurtured ova and desired sperms in the laboratory by providing the appropriate environment for fertilization and early embryo growth, and finally followed by transferring the embryos into the uterus [47].

First, fertility medications are prescribed to control the ova maturation and to increase the chance of collecting multiple ova during the menstrual cycle referred to as ovulation induction. Multiple ova are desired because some will not develop or fertilize after retrieval. Ovum development is monitored by ultrasound as well as the examination of urine or blood test samples to measure hormone levels. Ova are obtained via laparoscopic or transvaginal ultrasound-guided aspiration [48]. Second follicular aspiration is achieved by retrieving ova through a minor surgical procedure using ultrasound imaging to guide a hollow needle through the pelvic cavity to remove ova from the ovaries.

Third, sperm are obtained via ejaculation and the sperm and ova are placed in incubators located in the laboratory which enabled fertilization. In cases with lower levels of fertilization, intracytoplasmic sperm injection (ICSI) may be introduced. The ova are monitored to confirm that fertilization and cell division are taking place. They are considered embryos after successful fertilization. The embryos are usually transferred into the woman's uterus from 1 to 6 days later, but in most cases the transfer occurs between 2 to 3 days following egg retrieval [49]. At this stage, the fertilized egg has developed into a 2- to 4-cellembryo. The transfer process involves a speculum which is inserted into the vagina to expose the cervix. A predetermined number of embryos are suspended in fluid and gently placed through a catheter into the womb. Intracytoplasmic sperm injection combined with options for micromanipulation revolutionized treatment of infertile couples. The procedure involves injecting a single sperm, even a nonmotile one, directly into theooplasm [49]. These investigators developed a novel static method known as time lapse imaging (TLI) to study artificially fertilized embryo without removing them from the incubator to minimize the exposure of embryo to environmental changes, such as temperature, pH, or humidity. They further suggested that TLI enables continuous monitoring of early embryonic development via acquisition of images every 5 to 20 minutes thus minimizing multiple pregnancies, which is a major problem encounter during traditional morphological evaluation.

Even when men have evidence of spermatogenic dysfunction there is no opportunity to identify those individual sperm with greatest reproductive competence in a given specimen. At present, the only assays that attempt to isolate the most reproductively competent sperm after standard washing techniques have limited clinical data to support their use. Intracy to plasmic morphologically selected sperm injection (IMSI) allows morphology evaluation at high powered magnification. The pregnancy rate was correlated with higher oocyte yields and higher numbers of embryos transferred in the IMSI group compared with the ICSI group, suggesting that the IMSI groups included patients with a better prognosis [50]. Failing injection of single spermatozoa, extraction of testicular sperm can be used.

Karyotyping is important in men with a sperm count<5million/mL. These individuals show a much higher rate of autosomal abnormalities than fertile populations (around4%), while the highest frequency is found in azoospermia men(mostly Klinefelter syndrome). Klinefelter syndrome (47: 47], and XX males [SRY+] and [SRY-] is the most common of the sex chromosomal aneuploidies. The benefits of knowing if there is a chromosomal abnormality are in the planning for therapy and in the future follow-up of the patient. As such, karyotype analysis should be performed prior to either use of ejaculated sperm in conjunction with ICSI or prior to operative testis sperm extraction [51]. The other technique for sperm selection is hyaluronic acid(HA) binding assay. This is based on membrane alterations occurring during normal spermiogenesis resulting of occurrence of HA binding sites. Hyaluronic acid bound sperm showed lower rates of aneuploidy and apoptosis thus increasing ICSI improvements in implantation rates among embryos derived from oocytes injected with HA bound sperm [52].

Herbal Medicine: In traditional medicine, various herbal plants are used to treat male infertility. Cardiospermum helicacabum or "Welpenala" is one such example [53]. The aqueous extract improved sperm count, sperm motility, number of implantations, and viable embryos at 100 and 200 mg/kg dose levels. Similarly, Chinese herbal

medicine such as Ginseng roots (Panax quinquefolius) improves overall fertility; Tribulus fruit (Tribulus terrestris) improves sperm count, morphology, and motility; Maca root (Lepidium meyenii) improves hormonal balance [54].

Conclusions

To combat infertility, it is essential to optimize lifestyle factors in order to maximize fertility. Sedentary lifestyle, obesity, smoking, heat exposure, stress, poor nutrition, and harmful environmental toxicants may all adversely affect sperm count and quality. Hence, it is important to be aware of harmful chemicals, to be more active, and finally, to live a healthy lifestyle. Simply put, just simple lifestyle changes can improve male fertility. However, in other cases, if natural conception is impossible, assisted reproduction techniques can overcome the problem and advanced techniques such as ICSI treatment can be used. Identifying risk factors to improve the management of human wellness and health throughout standardized analysis, which correlates the accumulation of biotoxins in the seminal fluid with semen quality, can be considered in the agenda of public prevention policies.

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