Unraveling the Complexity of Infertility: A Comprehensive Review of Semen Abnormalities, Etiological Factors, and Cutting-edge Approaches in Reproductive Medicine

Jovan Ferrel Reynaldo Siswanto[a*], Zakiyatul Faizah[b], Sri Ratna Dwiningsih[c]

[a]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[b]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[c]Department of Obstetric and Gynecology, Dr. Soetomo General Academic Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[*] Corresponding author: jovan.ferrel.reynaldo-2020@fk.unair.ac.id

Abstract

This literature review delves into the multifaceted aspect of infertility, providing a comprehensive examination of semen abnormalities, etiological factors, and advancements in reproductive medicine, with a particular focus on in vitro fertilization (IVF). The definition of infertility as the failure to achieve pregnancy within 12 months of unprotected intercourse is outlined, emphasizing the distinction between infertility, subfertility, and sterility. Epidemiological insights reveal the global prevalence of infertility, underscoring that males contribute to 20-30% of cases. A historical perspective reveals a concerning decline in sperm quality over the decades, with studies indicating a significant reduction in sperm count, motility, and morphology. Noteworthy findings from diverse regions, including Africa, Europe, Tunisia, and Indonesia, underscore the global relevance of male infertility. Specific semen abnormalities such as oligozoospermia, asthenozoospermia, teratozoospermia, azoospermia, and leukospermia are discussed, shedding light on their clinical implications. The etiology section explores various factors contributing to male infertility, including varicocele, mitochondrial mutations, lifestyle choices (smoking, obesity), and exposure to environmental toxins. The pathophysiology section elucidates how these factors impact testicular function, mitochondrial DNA, and hormonal balance, ultimately affecting spermatogenesis and sperm quality. In the context of assisted reproductive technologies, the paper delves into the role of IVF, with a particular emphasis on intracytoplasmic sperm injection (ICSI). The procedural details of IVF, success rates, and its pivotal role in managing compromised semen parameters are discussed. The abstract concludes by acknowledging the prevalence of female infertility, highlighting key epidemiological insights, etiological factors, and management strategies, underscoring the broader context of reproductive health.

Keywords: Infertility , Semen abnormalities, Reproductive medicine

1. Introduction

Male and female infertility stands as a prominent concern in the landscape of reproductive health, transcending geographical and cultural boundaries. This literature review embarks on a comprehensive exploration of male infertility, embracing facets of semen abnormalities, etiological factors, pathophysiology, and advancements in assisted reproductive technologies, particularly in vitro fertilization (IVF). The conventional definition of male infertility revolves around the failure to achieve pregnancy through frequent, unprotected sexual intercourse within a 12-month timeframe (Vander Borght and Wyns, 2018). This delineation distinguishes infertility from subfertility, where couples face reduced fertility, and sterility, representing a perpetual state of infertility. Significantly, males contribute substantially to infertility, accounting for 20-30% of cases globally (Vander Borght and Wyns, 2018).

Epidemiological insights underscore the pervasive nature of infertility, affecting one in seven couples in Western nations and one in four couples in developing nations (Vander Borght and Wyns, 2018). Regional variations are evident, with higher prevalence in Africa and Central/Eastern Europe (Agarwal et al., 2015). Historical data indicating a decline in semen quality from the 1980s to the present day emphasizes the urgency of investigating contributing factors (Kumar and Singh, 2015). The literature further dissects specific semen abnormalities, including oligozoospermia, asthenozoospermia, teratozoospermia, azoospermia, and leukospermia. Oligozoospermia, marked by decreased sperm count, varies in severity, while asthenozoospermia involves reduced sperm motility (Castañeda et al., 2018). Teratozoospermia, characterized by abnormal sperm morphology, and azoospermia contribute to the complex landscape of male infertility (Castañeda et al., 2018). Leukospermia, marked by elevated white blood cell concentrations, emerges as a significant factor linked to impaired spermatogenesis and subclinical genital tract inflammation (Khodamoradi et al., 2020).

The etiology of male infertility is multifactorial, encompassing genetic, environmental, and lifestyle factors. Varicocele, a common vascular abnormality, is identified as a leading etiological factor (Barak and Baker, 2016). Mitochondrial mutations, influenced by oxidative stress, impact flagellar movement and fertility (Dada et al., 2008). Lifestyle choices, such as smoking, alcohol consumption, and poor dietary habits, compromise sperm quality (Durairajanayagam, 2018). Exposure to environmental toxins contributes to oxidative stress, leading to mitochondrial DNA mutations and sperm abnormalities (Pizzino et al., 2017). Subsequent sections delve into the pathophysiology of male infertility, elucidating how varicocele, mitochondrial mutations, lifestyle factors, and environmental exposures adversely affect testicular function, hormonal balance, and sperm quality. Moreover, a critical exploration of IVF, with a specific focus on intracytoplasmic sperm injection (ICSI), is undertaken to assess its role in addressing compromised semen parameters. In conclusion, this literature review lays the foundation for an in-depth analysis of male infertility, integrating epidemiological data, etiological insights, and advancements in reproductive medicine. By unraveling the complexities of male infertility, this review contributes to a comprehensive understanding of factors influencing male reproductive health, informing future research and clinical interventions.

1. Review Content

2.1 Male Infertility

2.1.1 Definition

Infertility is defined as a failure in having a pregnancy from frequent, unprotected sexual intercourse in a timeframe of 12 months. Subfertility is any form of reduced fertility in couples trying to achieve pregnancy. The difference between infertility and sterility is its time frame. Infertility is restricted to a certain time period, which is 12 months, and sterility is not restricted by a time period, meaning being in a permanent state of infertility. Male infertility by itself is when males are the cause of the failure of pregnancy in couples (Vander Borght and Wyns, 2018).

2.1.2 Epidemiology

It is estimated that one in seven western couples and one in every four couples in developing nations experience infertility. Males are found to be responsible for 20-30% of infertility. A study was done by Agarwal et al in 2015 which showed that in Africa and Central/Eastern Europe, male infertility was the highest. It is estimated that 8-12% of couples worldwide are affected by infertility (Vander Borght and Wyns, 2018). As early as the 1980s numerous studies had been done about the deterioration of semen quality. It can be concluded from numerous articles, between 1938 and 1990, the mean sperm count of healthy men declined by 1%. A significant 50% reduction in the mean sperm count from 113 × 106 mL−1 in 1940 to 66 × 106 mL−1 in 1990 and in the seminal volume from 3.40 to 2.75 mL. A meta-analysis has been done and can be concluded that sperm density has decreased globally by about 50% over the past 50-60 years. It was also found from a study done in Finland that there was a decrease in semen quality in the general population from 1998-2006. Another study conducted in Southern Tunisian between 1996 and 2007 on a sample of 2940 infertile males found a deterioration in semen quality during a 12-year period. A retrospective analysis of 9168 cases of men from ages 20-77 which were collected from the Andrology and Reproduction Laboratory in Cordoba, Argentina over a ten-year period revealed a significant decrease in seminal volume, sperm count, motility, viability, and normal morphology which were related to age. In addition, a study conducted at the Reproduction Biology Laboratory of the University Hospital of Marseille (France) between 1988 and 2007 that included the analysis of semen from 10,932 male partners of infertile couples found that overall population sperm concentration (1.5%/year), total sperm count (1.6%/year), total motility (0.4%/year), rapid motility (5.5%/year), and normal morphology (2.2%/year) were all declining. The same patterns of sperm quality degradation with time were also seen in the group of chosen samples with a total normal sperm count (Kumar and Singh, 2015). In Indonesia, data was taken from dr. Hj. Putri Sri Lasmini, Sp.OG(K) clinic was founded in 2015, 218 couples were infertile, in 2016, 304 couples were infertile, and in 2017, 184 couples were infertile. About 36% of infertility in those couples is caused by males (Susilawati and Restia, 2019). Research was done by Wahyudi, et al in 2020 about the incidence of male infertility in dr, Soetomo hospital in Surabaya. The research shows that from 123 people, there is 1 case (0.8%) of oligozoospermia (0.8%), 2 cases (1.6%) of asthenozoospermia, 30 cases (24.3%) of teratozoospermia, 1 case (0.8%) of oligo-astheno-zoospermia, 4 cases (3.2%) of oligo-terato-zoospermia, and 34 cases (27.6%) of astheno-terato-zoospermia, 21 cases (17%) of oligo-astheno-terato-zoospermia (Wahyudi et al., 2020).

2.2 Semen Abnormalities

2.2.1 Oligozoospermia

Oligozoospermia is an abnormality that happens when the number of sperm in the ejaculate decreases which decreases the odds that one of the sperm will fertilize the oocyte. Sperm under 15 million sperm/ml is considered as oligozoospermia. It is further divided into mild (10-15 million sperm./ml), moderate (5-10 million sperm/ml), and severe (<5 million sperm/ml) (Castañeda et al., 2018).

2.2.2 Asthenozoospermia

Asthenozoospermia is defined as low sperm motility. Sperm motility depends on energy availability and is the flagellum fully functioning or not which will decrease the chance of the sperm to reach the oocyte (Tu et al., 2020). Complete asthenozoospermia, which is 100% immotile spermatozoa, is a very rare case found in about 1 in 5000 men (Castañeda et al., 2018).

2.2.3 Teratozoospermia

Teratozoospermia is an abnormality that is characterized by the abnormal morphology of spermatozoa. It is important to differentiate mixed abnormalities of sperm morphology from those in which all of the sperm show the same abnormality or usually called monomorphic teratozoospermia. Macrozoospermia and globozoospermia are some of the well-known examples of monomorphic teratozoospermia (Castañeda et al., 2018). Macrozoospermia is a very rare condition that is characterized by oversized misshapen heads with multiple flagella which will result in miscarriage when the abnormal sperm combines with an oocyte cell (Ray et al., 2022). Besides macrozoospermia, globozoospermia is also a very rare condition that is characterized by the round head of spermatozoa, lacking acrosome, abnormal nuclear shape, and an abnormal arrangement of the mitochondria (Castañeda et al., 2018). This can affect male fertility since the sperm is lacking acrosome. The acrosome is important for the sperm for gamete fusion, binding, and penetration of the zona pellucida (Berruti and Paiardi, 2011).

2.2.4 Azoospermia

Azoospermia is a condition where there are no presence of spermatozoa in the ejaculate. Azoospermia can be divided into obstructive azoospermia and non-obstructive azoospermia. Obstructive azoospermia is the absence of spermatozoa in the ejaculate despite normal spermatogenesis. Patients with obstructive azoospermia can still be treated by IVF by sperm retrieval since the cause of the absence of spermatozoa in the ejaculate is the obstruction (Baker and Sabanegh, 2013). Non obstructive azoospermia is the absence of spermatozoa in the ejaculate which is caused by failure in spermatogenesis. On the other hand, treatment of non-obstructive azoospermia would be difficult since their spermatogenesis is impaired (Chiba, Enatsu and Fujisawa, 2016).

2.2.5 Leukospermia

Leukospermia is defined as a condition when there is an abnormally high concentration of white blood cells in the semen. Some studies has shown that leukospermia has a negative prognostic factor for infertility. It theorized to be caused by several things, for example leukospermia can impair spermatogenesis and sperm maturation and subclinical genital tract inflammation can lead to impairment of spermatogenesis by altering cytokine levels, which will then impair sertoli cell functions. It has been studied that leukospermia interferes with the acrosome reaction and the fusion of sperm and oocyte. Because of this, the presence of WBC in the seminal plasma is considered as a significant factor in failure of IVF (Khodamoradi et al., 2020).

2.3 Etiology

A research done in Dr. Cipto Mangunkusumo Hospital in Jakarta about the etiologies of male infertility stated that varicocele is the most common etiology. Symptoms include swelling and a dragging sensation in the scrotum (Barak and Baker, 2016). Mitochondrial mutation can cause impairment in flagellar movement. Mitochondrion and mitochondrial DNA (mtDNA) are important in a lot of physiological processes, such as providing energy via oxidative phosphorylation. Thus, any mutation disrupting this energy pathway and further production of adenosine triphosphate (ATP) will reduce impaired flagellar movement. Mutations in mtDNA are proven to be caused by oxidative stress and influence the fertility of an individual (Dada et al., 2008). Lifestyle can also affect sperm quality. Smoking, alcohol, and unhealthy diets will affect sperm quality. Cigarettes contain harmful toxins which will impair sperm function, motility, and morphology (Durairajanayagam, 2018). Obesity can also affect male infertility and cause sperm abnormalities. Several studies have shown that an increase in BMI will cause reduced plasma concentration of sex hormone binding globulin (SHBG) and decreases testosterone while increasing plasma concentration of estrogen. Obesity can also cause the temperature of the scrotum to increase which also harms the process of spermatogenesis (Katib, 2015). Exposure to free radicals such as pollution, heavy metals (cadmium, mercury, lead, and arsenic), certain drugs (cyclosporin, tacrolimus, gentamicin, and bleomycin), cigarette smoke, alcohol, and radiation can cause an increased chance of asthenozoospermia as those free radicals can cause oxidative stress which results in a mutation in the mitochondrial DNA (mtDNA) (Pizzino et al., 2017). An unhealthy diet can also lead to sperm abnormalities. Not having a healthy diet may lead to obesity resulting in sperm abnormalities. Obesity will cause a decrease in testosterone and an increase in estrogen (Katib, 2015).

2.4 Pathophysiology

Varicocele has a negative effect on testicular function. Several theories have been advanced, which include vascular stasis, interference with oxygenation, back pressure, reflux of renal or adrenal products into the pampiniform plexus, ROS generation, and interference with the heat exchange function of the pampiniform plexus (Shlomi Barak and HWG Baker, 2016). The mitochondrion and mitochondrial DNA (mtDNA) are really important in a lot of physiological processes. Oxidative energy supply is controlled by them which are important for growth development and differentiation. Mitochondrial function is controlled by a fine-tuned crosstalk between mtDNA and nuclear DNA. As mitochondria supply energy by oxidative phosphorylation, when a mutation happens, adenosine triphosphate production will be disrupted which results in impaired flagellar movement. Furthermore, the midpiece of the sperm contains a few mtDNA copies, so when a mitochondrial mutation occurs, the sperm will not get enough ATP resulting in a decrease in mobility (Dada et al., 2008). It is studied that obesity will cause an elevated concentration of insulin which results in the suppression of hepatic SHBG. Lower sex hormone-binding globulin means lower testosterone and higher estrogen levels (Cooper et al., 2015). Testosterone is used in the spermatogenesis process, therefore a decrease in testosterone levels will inhibit spermatogenesis, resulting in abnormal sperm. Changes in the levels of sex steroids could feed back at the hypothalamic axis to suppress gonadotropins. FSH, LH, and inhibin B are hormones needed in the regulation of sertoli cell function and spermatogenesis (Katib, 2015). Obesity has a negative effect on the temperature of the scrotum. It is studied that in individuals with obesity, gonadal heat is raised resulting from increased scrotal adiposity. Temperatures within the scrotum will be elevated from the optimal temperature which is 34-35°C, which would harm the sperm cells and it is associated with reduced sperm motility (Katib, 2015).

2.5 In Vitro Fertilization

2.5.1 Intracytoplasmic Sperm Injection (ICSI)

In vitro fertilization has a huge role in the management of female infertility. However, in the treatment of compromised semen parameters, conventional IVF is proved to be not as good of a tool. A breakthrough was done in the treatment of male infertility caused by the development of intracytoplasmic sperm injection (ICSI) (Stephens, Arnett, and Meacham, 2013).

2.5.2 Procedure

IVF begins with the stimulation of the ovary. GnRH are used to eliminate a woman’s LH surge which allows the physician to time oocyte retrieval. Ovarian stimulation is done so that approximately 10 to 20 oocytes are retrieved. There are two main protocols, a long luteal GnRH agonist or a GnRH antagonist cycle. The long luteal GnRH agonist protocol starts with administrating 0.1 mg GnRH agonist daily starting on cycle day 21 in the preceding month. This will turn off the pituitary secretion of LH and FSH during the ovarian stimulation, and then GnRH agonist is continued to be given until the hCG. Gonadotropins are administered starting on cycle day 2. The hCG injection is given when at least three follicles reach 18 mm in size. The GnRH antagonist protocol starts with administrating gonadotropins daily starting on cycle day 2 or 3. The GnRH antagonist will start to block the endogenous LH surge when the lead follicular diameter reaches 14 mm or on the sixth day of ovarian stimulation. When at least three follicles reach 18 mm, hCG is administered. Mature oocytes are retrieved 34 to 36 hours after hCG is given. Oocyte retrieval is done by using ultrasound-guided transvaginal aspiration and intravenous sedation. Ovaries are visualized using a vaginal ultrasound probe and by using a needle guide which helps the physician direct the needle into each follicle and aspirate the oocyte (Choe, Archer and Shanks, 2020). Fertilized embryos are then transferred at the cleavage stage which is 3 days after fertilization or at the blastocyst stage, which is 5 days after fertilization. The embryos are transferred by using a catheter which is passed through the cervix and into the uterine cavity by using ultrasound to guide the placement (Choe, Archer and Shanks, 2020). There are several markers that can show whether a female is considered pregnant or not, which is hcg and progesterone. Both need to be observed since by using only one marker, it is not enough, and it can’t be certain. A female is considered as pregnant when the hcg level is above 25 mIU/mL (Anderson and Ghaffarian, 2020) and progesterone about 80 nmol/L is (Ku et al., 2018).

2.5.3 Success Rate

It has been researched that the success rate of IVF varies, which depends on the age of the female partner. It has been shown that the pregnancy rate of women below 35 years old is 46.2%, 35–37-year-old women with 38.5%, 38–40-year-old women with 29.3%, 41–42 year old women with 19.5%, and women above 42 years old with 9.1% (Stephens, Arnett and Meacham, 2013).

2.6 Female Infertility

2.6.1 Epidemiology

Female infertility is when a couple is experiencing infertility, and the female is the cause of the infertility. Research was done by the National Survey of Family Growth. 12,000 women were interviewed, and it was concluded that as a woman gets older, the chances of infertility increases. Women aged 15-34, infertility rates ranged from 7.3-9.1%, in women aged 35-39, the fertility rates increased to 25%, and women aged 40-44, had 30% chance of infertility.

2.6.2 Etiology

Several etiology of female infertility are ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage, and uterine abnormalities (Walker and Tobler, 2020). Several risk factors of female infertility include poor lifestyle such as having an intense exercise regimen, eating disorders or poor diet, and smoking (Walker and Tobler, 2020).

2.6.3 Pathophysiology

Ovulatory disorders are the most common cause of female infertility. Anovulation is when no oocytes are released monthly resulting in infertility. WHO further categorizes ovulatory disorder into four classes. Hypogonadotropic hypogonadal anovulation for example hypothalamic amenorrhea, normogonadotropic normoestrogenic anovulation for example polycystic ovarian syndrome (PCOS), hypergonadotropic hypoestrogenic anovulation for example premature ovarian failure, and hyperprolactinemic anovulation for example pituitary adenoma (Walker and Tobler, 2020). Hypothalamic amenorrhea is associated with eating disorders and excessive exercise, resulting in a decrease in the hypothalamic GnRH secretion. Decreased caloric intake, associated weight loss, or excessive exercise leads to increased cortisol levels, which causes a suppression of GnRH. The decrease of GnRH results in a decrease in the release of gonadotropins, FSH, and LH from the anterior pituitary gland. This will result in the abnormal growth of the follicle, anovulation, and low estrogen levels (Walker and Tobler, 2020). PCOS is one of the types of normogonadotropic normoestrogenic anovulation. PCOS is associated with the dysfunction of developing a mature follicle. Abnormal pulsation of GnRH is a possible cause (Walker and Tobler, 2020).

Premature ovarian insufficiency and ovarian resistance is one of the types of hypergonadotropic hypoestrogenic anovulation and is associated with females' age. This is due to a steady decline in the quality and quantity of the patient;s oocytes. In terms of quantity, a newborn has 1 million follicles, it is then starting to decrease as they age. During puberty, the number decreases to 300,000 and continues to decrease (Walker and Tobler, 2020). Endometriosis is defined as endometrial tissue outside of the uterine cavity. Endometriosis is commonly found in the pelvis but can also spread throughout the entire abdomen. It is categorized into four stages, stage I being minimal until stage IV for severe. The pathophysiology of endometriosis is believed to change according to the stage. Stage I and II is associated with inflammation with an increase of production of prostaglandins and cytokines, macrophages, and natural killer cells. It impairs ovarian and tubal function which results in defective follicular formation, fertilization, and implantation. Stage III and IV are associated with pelvic adhesions and masses that distort the pelvic anatomy which will impair tubal motility, oocyte release, and sperm motility (Walker and Tobler, 2020). Pelvic and tubal adhesion are caused by infectious processes and the most common is pelvic inflammatory disease (PID). The microorganism that is associated with PID is Chlamydia trachomatis (Walker and Tobler, 2020). Uterine abnormalities are associated with space-occupying lesions or reduced endometrial receptivity. The most found abnormality is uterine septums. It is a congenital uterine abnormality, and it was researched that about 25% of women with a late first trimester or second trimester miscarriages are found to have congenital uterine abnormality (Walker and Tobler, 2020).

2.6.4 Management

Women with a BMI of less than 17 kg/m^2 with a history of intense exercise regimens or women with eating disorders or poor diet, and smoking habits are more likely to experience infertility. Lifestyle changes are needed to treat infertility (Walker and Tobler, 2020). IVF is one of the effective treatments for female infertility. Research was done by collecting pregnancy rates data from several studies. It compares the pregnancy rates between different treatments. Women with infertility who were given no treatment had 1.3-3.8% pregnancy rate, IUI alone had 4% pregnancy rate, clomiphene citrate had 5.6%, clomiphene citrate with IUI had 8.3%, gonadotropins had 7.7%, gonadotropins with IUI had 17.1% and IVF had the highest with 20.7% pregnancy rate (Walker and Tobler, 2020).

2. Conclusion

In conclusion, this literature review provides a comprehensive overview of male infertility, covering semen abnormalities, etiological factors, and advancements in assisted reproductive technologies. The multifaceted aspects of male infertility, influenced by genetic, environmental, and lifestyle factors, underscores the need for holistic clinical approaches. Advances in in vitro fertilization, especially intracytoplasmic sperm injection, offer promising solutions. The global prevalence of infertility and the decline in semen quality over time highlight the urgency for ongoing research and interventions to enhance diagnosis and treatment modalities, ultimately improving outcomes for couples facing reproductive challenges.

Acknowledgements

The authors would like to thank all the supervisors, enabling the successful implementation of this study.

References

Agarwal, A. et al. (2015) A unique view on male infertility around the Globe, Reproductive biology and endocrinology: RB&E. BioMed Central. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4424520/#:~:text=North%20America%20demonst rates%20rates%20of,Table%201 (Accessed: October 2, 2022).

Anderson, J. and Ghaffarian, K.R. (2020). Early Pregnancy Diagnosis. [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK556135/.

Baker, K. and Sabanegh, E. (2013). Obstructive azoospermia: reconstructive techniques and results. Clinics, [online] 68(Suppl 1), pp.61–73. doi:10.6061/clinics/2013(Sup01)07.

Barak, S. and Baker, H.W.G. (2016). Clinical Management of Male Infertility. [online] Nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279160/.

Berruti, G. and Paiardi, C. (2011). Acrosome Biogenesis. Spermatogenesis, [online] 1(2), pp.95–98. doi:10.4161/spmg.1.2.16820.

Chiba, K., Enatsu, N. and Fujisawa, M. (2016). Management of non-obstructive azoospermia. Reproductive Medicine and Biology, [online] 15(3), pp.165–173. doi:10.1007/s12522-016-0234-z.

Choy, J.T. and Amory, J.K. (2020) Nonsurgical management of oligozoospermia, The Journal of clinical endocrinology and metabolism. Oxford University Press. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7566408/ (Accessed: October 2, 2022).

Castañeda, J.M., Miyata, H., Ikawa, M. and Matzuk, M.M. (2018). Sperm Defects. Encyclopedia of Reproduction, 4, pp.276–281. doi:10.1016/b978-0-12-801238-3.64778-5.

Cooper, L.A., Page, S.T., Amory, J.K., Anawalt, B.D. and Matsumoto, A.M. (2015). The association of obesity with sex hormone-binding globulin is stronger than the association with ageing – implications for the interpretation of total testosterone measurements. Clinical endocrinology, [online] 83(6), pp.828–833. doi:10.1111/cen.12768.

Dada, R., Shamsi, M., Kumar, R., Bhatt, A., Bamezai, R.N.K., Kumar, R., Gupta, N. and Das, T. (2008). Mitochondrial DNA mutations in etiopathogenesis of male infertility. Indian Journal of Urology, 24(2), p.150. doi:10.4103/0970-1591.40606.

Durairajanayagam, D. (2018). Lifestyle causes of male infertility. Arab Journal of Urology, [online] 16(1), pp.10–20. doi:10.1016/j.aju.2017.12.004.

Katib, A. (2015). Mechanisms linking obesity with male infertility. Central European Journal of Urology, 68(1). doi:10.5173/ceju.2015.01.435.

Khodamoradi, K., Kuchakulla, M., Narasimman, M., Khosravizadeh, Z., Ali, A., Brackett, N., Ibrahim, E. and Ramasamy, R. (2020). Laboratory and clinical management of leukocytospermia and hematospermia: a review. Therapeutic Advances in Reproductive Health, 14, p.263349412092251. doi:10.1177/2633494120922511.

Ku, C.W., Allen Jr., J.C., Lek, S.M., Chia, M.L., Tan, N.S. and Tan, T.C. (2018). Serum progesterone distribution in normal pregnancies compared to pregnancies complicated by threatened miscarriage from 5 to 13 weeks gestation: a prospective cohort study. BMC Pregnancy and Childbirth, [online] 18. doi:10.1186/s12884-018-2002-z.

Kumar, N. and Singh, A. (2015). Trends of male factor infertility, an important cause of infertility: A review of literature. Journal of Human Reproductive Sciences, [online] 8(4), p.191. doi:10.4103/0974-1208.170370.

Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., Squadrito, F., Altavilla, D. and Bitto, A. (2017). Oxidative Stress: Harms and Benefits for Human Health. Oxidative Medicine and Cellular Longevity, [online] 2017(8416763), pp.1–13. doi:10.1155/2017/8416763.

Ray, P., Kherraf, Z.-E., Cazin, C., Lestrade, F., Muronova, J., Coutton, C., Arnoult, C. and Thierry-Mieg, N. (2022). From azoospermia to macrozoospermia, a phenotypic continuum due to mutations in the ZMYND15 gene. Asian Journal of Andrology, 24(3), p.243. doi:10.4103/aja202194.

Stephens, S.M., Arnett, D.M. and Meacham, R.B. (2013). The use of in vitro fertilization in the management of male infertility: what the urologist needs to know. Reviews in urology, [online] 15(4), pp.154–60. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3922320/.

Vander Borght, M. and Wyns, C. (2018). Fertility and infertility: Definition and epidemiology. Clinical Biochemistry, [online] 62, pp.2–10. doi:10.1016/j.clinbiochem.2018.03.012.

Wahyudi, A., Supardi, P., Narulita, P., I'tishom, R. and Lestari, S.W. (2020). Male Infertility: An Epidemiological and Clinical Profile at the Andrology Unit of Dr. Soetomo Hospital, Surabaya, Indonesia. Journal of Global Pharma Technology, 12(06).

Walker, M.H. and Tobler, K.J. (2020). Female Infertility. [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK556033/.