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Extended Essay
Biology

A Review of Selected Factors That
Are Currently Thought to Be
Significant Contributors to Increases
in Human Male Infertility.

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Abstract

Human infertility is increasing worldwide but the exact causes are not yet known. Male infertility, which currently accounts for approximately half of all cases, is increasing faster than female. This essay reviews and assesses the validity of key lifestyle and environmental factors that may be influencing this rise in male infertility. These factors include heat stress, obesity, environmental toxin exposure, and the contribution of genetics to male infertility. Studies have shown that afflicted men suffer lower sperm counts, reduced sperm motility and morphologically abnormal sperm. Whilst each factor contributes to male infertility, each also influences the effect oxidative stress has on sperm. Oxidative stress is caused by free radicals of oxygen atoms; these highly reactive species interfere with normal cell routine, by reacting mainly with native DNA in the mitochondria. Although free radicals are necessary and a natural occurrence in the body, each of the main factors discussed affects the balance of free radicals present and the capacity for DNA damage. In the case of obesity and a range of environmental toxins, oxidative stress was identified as causing damage to sperm. The mechanisms and general understanding of the effect of these factors are still sparse in some areas. This in itself is recognized as a problem, because humans cannot be easily surveyed in a controlled environment. As a result it is strongly encouraged that research continues these areas with in vitro cell tests and animal models but perhaps more critically, research into antioxidants and a greater understanding of the effects of reactive oxygen species on sperm, is a more beneficial way of finding solutions to human male infertility.

(Word count: 268)

A Review of Selected Factors That Are Currently Thought to Be Significant Contributors to Increases in Human Male Infertility.

Introduction

Over the last few years, infertility has been a focus topic with the media worldwide. It is reported that between 15 to 20% of couples are infertile and male infertility is increasing faster than female. The World Health Organisation (WHO) defines infertility as the inability to conceive after one year of unprotected sex.¹ Although the media is often accused of over amplification, it would seem that there is growing peer reviewed scientific evidence to suggest that humans as a species are experiencing a marked decline in fertility rates.

For many Western countries infertility is on the rise and population growth on the decline. Yet there is a lot that the general public does not know about infertility. In 1999, a survey showed that about two-thirds of the people interviewed thought that infertility was related to the woman's fallopian tubes.² There is uncertainty as to the current level of knowledge but many people worldwide still believe that infertility is due to the woman. Awareness of the incidence of male infertility is minimal and yet male infertility accounts for approximately half the cases, which only demonstrates a need for further publication of information on male infertility.

Researchers in reproductive medicine do not know exactly why male infertility is increasing, as there appears to be no exact or defined causes apart from physical issues. However the most commonly accepted ideas are attributed to our changing lifestyles. Research is difficult, as humans cannot be compared to laboratory animals because of

¹ (Zegers-Hochschild, F, et al. 2683-2687)

²("Ignorance over male infertility.")

their differing genetics and variance in lifestyles. Therefore comparative data has to be carefully examined with regard to these variables. While there is a huge variety of factors that affect infertility, this essay will look at possible causes of the current rise in male infertility, which are linked though the lifestyle and environment in which we live in that cause damage on a cellular level.

Heat Stress

Today it is a commonly accepted that increased temperatures of the scrotum affect spermatogenesis, or the formation of sperm. The human male genitalia are located outside the body, going against a common evolutionary strategy in mammals that vital organs are better protected on the inside. It is thought that this is because the scrotum can remain cooler by being physically separated from the body core temperature. This is considered beneficial because sperm are stored, often over many days or weeks, in the epididymis, particularly the cauda epididymis, which resides at the coolest location within the scrotum. The temperature range for spermatogenesis is critical such that lower temperature reduces metabolic rate and sperm can be stored for longer.³ Activities such as taking a hot bath speed the metabolic reactions, aging the sperm. Sperm are produced on a continual basis and therefore the fertilisation capacity of the sperm will only be temporarily affected, assuming these are not habitual long-term activities. There are other factors in normal lifestyles that are not so well considered, but are likely causes of an increase in male infertility of a more permanent nature due to excessive heat exposure.

Certain occupations are a major factor in male infertility. Some jobs put workers in situations of heat exposure. Welding, where extreme heat is used, is an example. A

³ (Ivell 2)

study was recently conducted whereby 17 men were exposed to radiant heat ranging from 31.1 to 44.8 degrees Celsius whilst welding for about 5 hours a day over the course of 6 weeks. The study recognized that these welders are representative of a possible cause of infertility and that they may be exposed to more radiant heat than the average man. The results showed after the six weeks that although there was no significant reduction in sperm count or sperm motility, normal morphology of the sperm declined noticeably and during a holiday break increased again. These results were compared to two reference groups that “comprised 54 non-welding metalworkers enrolled in a previous study.”⁴ This study does have a weakness in that welders are also often exposed to toxic chemicals that could interfere with spermatogenesis. The authors do acknowledge that variables in the experiment that would cause change in sperm morphology would be either the exposure to heat or toxins from welding fumes. Chromium concentrations were tested via urine sample analysis and were found to increase as well, although the experiment did not deem this a likely cause of the abnormal sperm due to minimal exposure. The workers had additional use of exhaust ventilation, as well as compressed air respirators and insulating mats were provided that “in particular [protects] the upper part of the body, against exposure to radiant heat”⁵. Despite the small study group for this study, the findings proved that the occupational environment of these welders had a negative but reversible effect on their semen quality. Heat exposure is thought to reduce sperm motility but sperm motility was unaffected.⁶

⁴ (Bonde 7)

⁵ (Bonde 6)

⁶ (Jung, and Schuppe 203)

Therefore chemical toxins were probably the underlying effect that caused abnormal sperm morphology. In this example, heat exposure was not a potential risk.

Occupationally, welding along with other manual labour jobs that are exposed to radiant

BMI	Normal Weight	Overweight	Obese
Increase in low Sperm Count	5.32%	9.52%	15.62%
Increase in low Motile Sperm count	4.25%	8.93%	13.28%

Fig 1 Male obesity and alteration in sperm parameters

heat, or possible toxins only accounts for a small percentage of the population. However risks faced by men in certain occupations may apply to more than we first assume. In the welding study, the men were required to wear protective insulation from the heat. This situation may have kept the testes in an even hotter environment, as opposed to breathable materials. More research has shown that the clothing men wear today may also be a cause of infertility due to heat. Jung,⁷ like many other scientists claims that “tight fitting, thermally insulating clothing” has an “unfavourable effect”. Another study looked at temperature differences between boxer shorts and brief style underwear. They found that “ the hyperthermic effect of brief style underwear was exaggerated.”⁸ Noting that there was no significant temperature difference in a study of 97 men. The validity of this trial is questionable, as there was not a appropriate use of control groups. The distinction was made on boxers or briefs, regardless of material. It is likely that clothing can have an effect but there are

a number of contributing factors that need to be explored further.

⁷ (Jung, and Schill 31-3)

⁸ (Munkelwitz, and Gilbert 1329-1333)

Heat is still a concern and potentially a mitigating factor in conditions of prolonged exposure. Although reversible, in conjunction with other factors, the heat effect may be cumulative. However, heightened awareness could change lifestyle and the statistical profile that leads us to believe infertility is on the rise.

Obesity

Aside from clothing, insulation obesity presents issues for male fertility. Obesity is on the rise in the western world. As mentioned previously driving, sitting down for long periods of time, and working on laptops have all shown that they can be transiently detrimental to fertility due to an increase in scrotal temperature.⁹Obesity is often associated with people who are generally less active, which could roughly mean periods of prolonged sitting. However more directly, an increase of fat in areas such as the abdomen, and thighs provides insulation that has the proven effect of raising the temperature enough to cause damage. In a more general sense, infertility in couples with overweight male “ might include behavioral, sexual dysfunction or semen quality factors”¹⁰

A study, which analysed such factors, looked at a group of 526 men over 2 years, who were all approximately in their thirties. They found that incidences of oligozoospermia (low sperm count) increased with BMI. 5.32% at normal weight,

9.52% who were overweight, and 15.62% that were obese. Additionally, incidences of low progressively motile sperm count had 4.25% at normal weight, 8.93% overweight, and 13.28% who were obese.

⁹ Increase in scrotal temperature in laptop computer users.
¹⁰ (Hammoud, Wilde, Gibson, Parks, Meikle, and Carrell 2222-5)

This suggests quite an apparent relationship of obesity as a cause of infertility. Possible reasons include the fact that obesity reduces blood flow in the vessels and capillaries; less sperm are produced as a result. Additionally, combined with heat stress effects could be longer term and significant but further studies need to be done.

Abnormal spermatogenesis in men is often hormone related. Obesity can cause problems in the endocrine system too, with a lack in the production of the necessary male androgens needed for reproduction and adversely, an increase in Estradiol levels. As “The hypoandrogenemia is directly proportional to the degree of obesity”¹¹ As a result Estradiol, a female sex hormone has a deleterious effect on sperm, enhanced by the lack of normal male hormones. Contributing to a lower overall sperm count, which in turn affects fertility adversely, shown by the statistics of oligozoospermia or low sperm count in the study.

DNA fragmentation is the process in which chromatin DNA is cleaved during apoptosis, or when a cell dies. Other studies have even found that sperm DNA fragmentation increases with BMI. DNA fragmentation and infertility share a direct correlation. In overweight (27-25.8%) and obese men (28.5-27%) the index was higher compared to normal weight (19-19.9%), as measured using the flow cytometry method (this flows microscopic particles such as chromosomes past a single wavelength) for sperm chromatin integrity. (335)¹²

However, although there is sufficient evidence to support lowered sperm count and DNA fragmentation due to obesity, there is little to yet understand why the sperm morphology appears to be affected, as in some studies there is not enough evidence to

¹¹ (Mola 333-46)

¹² (Hammoud, Gibson, Peterson, Meikle, and Carrell 897-904)

support a relationship. Furthermore, the clinical relationship is not understood between consistent morphological changes in the sperm head and infertility.

Additionally fatty tissue accumulates toxic substances, which constitutes some risk, as endocrine disruptors. These interfere with the hormones in the body, disrupting normal production. Many toxins are soluble in the fatty tissues and with a higher deposition of such tissues, these men are placed at more risk.

Genetics

Disease caused from genetic or inherited factors, may also count for a large percentage of infertile males. Genetic factors are important to consider, as we have seen factors such as obesity may be interfering with DNA. In these cases, the necessary genes are often found deleted on the Y chromosome. The study of epigenetic factors is now opening the door on the role of the environment and lifestyle in many afflictions that manifest themselves in later life, including infertility.

According to Poongothai, genetic abnormalities have been discovered in men with little no to sperm and/or those with structural changes to the chromosome head. Chromosomal disorders are sometimes well known causes of infertility, Klinefelters syndrome with XXY for example). Within this, there are three types of common genetic problems: Monogenic disorders, microdeletions of the Y chromosome, and Mitochondrial DNA mutations.¹³

Monogenic disorders result from an error of a single gene. It can be based on dominant and recessive alleles, or it can be X-linked. There are an estimated 50 disorders that affect male infertility. Mendel's Law can predict these disorders, as they follow the

¹³ (Poongothai, Gopenath, and Manonayaki 336-47)

general pattern of inheritance. The majority of disorders are X-linked; therefore males are more susceptible, as they only carry one copy of the X and Y chromosome.

The mitochondria of sperm cells are essential to successfully carrying out its function. More specifically is its effect on sperm motility. Mitochondria have their own DNA, which is inherited directly from the mother. This would suggest that any defect prevalent, could be received by the son and might affect his fertility in the future as the mitochondria might not provide the energy needed for the sperm to swim and penetrate the egg, if IVF was used as a treatment. However Mitochondrial DNA is known to mutate during one's lifetime, yet it is not typically passed on.¹⁴ Particular mutations may produce "potentially harmful molecules called reactive oxygen species."¹⁵ This is apparently harmful to the mDNA, and can cause further mutations because of the mitochondria's lack of ability to repair itself. In some instances, elsewhere in the body, the inability to repair can be a cause of cancer.

Specifically the microdeletions of the Y chromosome have been proven to have a significant effect on male fertility. Until recently it was believed that "sex determination was the sole function related to the Y chromosome". But as genetics, the field itself, continues to leap forward, so does the mapping of the Y chromosome. As of yet, prevalence of microdeletions varies per study from 1% to 35%¹⁶ when looking at a group of infertile men. This makes it hard to determine the extent to which the cause may impact the population. Regardless, it has been linked to the genes that cause low sperm count and can be pinpointed and determined whether a deletion has occurred.

¹⁴ ("Genetics Home Reference")

¹⁵ Ibid.

¹⁶ (Foresta, Moro, and Ferlin 226-39)

This could be a cause for concern due to the potential for a rise in numbers. As these men are not entirely infertile, they may choose to undergo IVF with the partner. In this case, the specific genes would not be removed from the gene pool and would be passed on. Eventually this could account for a large percentage of the population unable to reproduce naturally, rendering them infertile.

Environment toxins

One suspected cause of male infertility that has gained significant popularity is toxin exposure in the environment. As our society has progressed over the last century, the human race has increased its exposure to unnatural chemicals and radically changed its diet to highly processed foodstuffs. This is supported by differences in infertility found regionally.¹⁷ As mentioned previously, occupation is a key way of determining an environment that the individual is exposed to every day.

A study conducted specifically looked at possible toxins and the number men who had a low sperm count with large percentage of sperm that were slow swimming and/or abnormally shaped, that were exposed to a variety of toxins on a daily basis. From the results, the number of men that suffered from oligoasthenoteratozoospermie as summarised by a low count with many immotile and abnormal sperm are exposed to “glues, solvents or silicones, metals and physical agents” was significantly more than the control.

Additional to the toxin issue, is exposure of men to hormones from the food chain. Livestock in the U.S. is often treated with hormones to promote growth, whereas in other countries, these farming methods are banned. “These oestrogenic compounds can

¹⁷ (Mendiola, Torres-Cantero, Moneno-Grau, Ten, Roca, Moneno Grau, and Bernanbeu 842-50)

accumulate to some extent in fat”.¹⁸With obesity levels on the rise, retention of female hormones in excess adipose tissues in men will likely contribute to male infertility although this is not proven.

Oxidative Stress

Oxidative stress has a profound effect on male infertility. This is caused in humans by an imbalance of reactive oxygen species (ROS). ROS are free radicals containing oxygen atoms that are produced inorganic or organically/enzymatically that are extremely reactive when near unpaired valence shells. They are produced by sperm and leukocytes in small amounts, and are necessary for a wide range of functions. For instance, phagocytes use this type of free radical to destroy foreign material that is dependent on oxygen. Yet too many free radicals from any source cause unnecessary damage to the spermatozoa.¹⁹ Additionally free radicals are used in redox signaling. Redox signaling is how messages are communicated to cells, and is in control of cell apoptosis. The effects of oxidative stress on fertility are numerous. In men, oxygen species can reduce sperm motility and damage DNA in the mitochondrial and nuclear genome likely due to its inability to repair sufficiently.²⁰ Sperm are vulnerable because of the amount of unsaturated fatty acids they possess, which react easily with free radicals with only a small number of antioxidant enzymes that are designed to deal with typical ROS generated.²¹ These fatty acids found in the membrane effectively lose their integrity and hence their function, as they can no longer fuse with an oocyte.²²

¹⁸ (Sharpe 630-42)

¹⁹ (Badia et al. 355)

²⁰ (Aitken, and Krausz 492-506)

²¹ (Baker, and Aiken)

²² (Aitken, Clarkson, Hargreave, Irvine, and Wu)

Although not everything is understood about why DNA damage occurs, it is known that men who do not have enough protamines, leave their DNA chromatins unprotected, whereby free radicals directly attack the deoxyribose structure and pyrimidine and purine bases.²³ The other way this is caused, is by free radicals starting apoptosis in the sperm cell, the self-destructing cell destroys the DNA. Fragmented DNA, or replication errors occurs naturally during the lifespan, the more cell divisions that occur the more reading frame errors are made and so older men tend to be at more risk or producing more genetic errors, and are more likely to have children with genetic defects. The problem lies when, due to oxidative stress, more men have fragmented DNA. The DNA may not be read and subsequently successful conception does not take place or runs the risk of a genetic defect, as proteins are either missing or not produced.²⁴

Oxidative stress can be caused by numerous factors. However what is extremely interesting is the fact that raised scrotal temperatures, occupational and environmental hazards involving heavy metals, and obesity all cause an increase in oxidative stress. Oxidative stress even causes disruption in DNA. Therefore it is important to look at how these common factors causing infertility are all linked.

Heavy metals are known to cause a variety of issues by their toxic effects. Whether it is in the brain or causing cancer, everyone knows that metals are toxic. Common toxic metals include: arsenic, lead, cadmium and mercury. They are all extremely common in the work place but are also linked by their reactive oxygen species. Their redox properties mean that not only are they extremely reactive with biological

²³ (Tremellen 243-58)

²⁴ (Aitken, and Krausz 492-506)

components, they are also hard to successfully contain. This is due to their readiness to 'lose' an electron and as such create ROS.

There are multiple ways in which toxins and other agents may come to affect sperm. The blood-testis barrier serves to keep the "spermatozoa and the immune system separate"²⁵ It allows water, fat and water-soluble substances to pass through.²⁶ However to what extent certain known toxic compounds can pass through is not entirely known and further work needs to be done to understand the mechanism and any role in infertility. A study testing for lipid peroxidation among workers exposed to lead found the blood epididymis barrier did not stop exposure to the lead.²⁷ Again, the welders were not only exposed to extreme heat, but also chromium, which although not toxic in its own right, is adversely implicated in redox reactions in the human body. In the study conducted, the welders were all found to have increased chromium concentrations in their urine. Although, they discounted chromium poisoning as a possible cause of reduced sperm motility due to ventilation, there may be a combination effect. As its conclusion it found morphological problems with the sperm rather than the typical motility and reduced sperm problems normally associated with heat stress. We do know however, that oxidative stress can cause such problems, and was not evaluated. Again, this only stresses the need for further research given there are multiple factors.

Conclusion

From what research is available on humans, it would seem that there are multiple factors of lifestyle and the environment. Heat stress, obesity, and environmental hazards

²⁵ ("uhmc.sunysb.edu")

²⁶ ("Encyclopaedia Britannica")

²⁷ (Marchlewicz 37-51)

have been reviewed here. All of these presented detrimental effects to male fertility, but there is a factor linking them: oxidative stress. Although oxidative stress is a natural occurrence in the body, the side effects of these environmental and lifestyle factors contribute to the problem that appears to be rendering men infertile.

Chromium is “used in metal alloys and pigments for paints, cement, paper, rubber, and other materials²⁸”. Other metals too are used in a wide range of purposes that we do not automatically assume. The survey looking at abnormal sperm motility and morphology found, that more than anywhere else, there was a larger percentage of people with such characteristics working with “glues, solvents or silicones, metals, and physical agents”. Again, although not specific we know this to involve multiple heavy metals, which pose the same risk of ROS.

Obesity can also increase the production of ROS. A higher presence of lipids may be found, based on what we know is able to pass through the barriers. Although this is speculation the concern stems from the risk that the macromolecules; lipids are. Found in the sperm plasma polyunsaturated fatty acids possess a weak carbon-hydrogen bond that makes it easier to lose this hydrogen. This process, named lipid peroxidation, has shown a strong correlation between the produced byproduct and sperm impairment.²⁹

Diet, a factor that contributes to obesity is something that should be carefully considered for the future regardless. New research in the last year has begun to pursue more in depth the benefits of antioxidants. While research carries on to further understand

²⁸ ("Water Treatment Solutions LENNTECH")

²⁹ (Makker, Agarwal, and Sharma 357-67)

the effects, it is thought that even in its consumption antioxidants are helpful in reducing oxidative stress and maintaining fertility.³⁰

Heat stress and oxidative stress share a complicated relationship. One of the most common causes of temperature increases to the scrotum is due to varicoceles. This was not addressed earlier as this is a solvable condition. They can be surgically removed and does not commonly make men infertile. Varicoceles are the swelling of blood vessels in the scrotum, and are extremely painful. The problem reside of varicoceles in this context is the increased blood flow to the scrotum, raising the temperature. While heat stress has multiple negative effects anyway, it appears to have beneficial factors to the side effects of varicoceles. Varicoceles are also known to cause elevated oxidative stress levels, but proteins produced from heat shock, stop ROS from causing the self destruction in cells.³¹ This appears counterintuitive, as we might expect that as temperature increases, so does metabolic rate and would speed up the process of oxidation. Yet this is beneficial when exploring treatment, but heat stress with its own negative effects on fertility is not an ideal approach.

However, research into infertility is not sufficient to draw any conclusions about the cause of the rise of cases, calling for a more cohesive and in-depth approach,that links mechanisms to the clinical condition .

Firstly, much of the research conducted, and presented in this essay demonstrates flaws. Due to the nature of humans trials and taking surveys, it is difficult to obtain reliable results and true comparative data. Not being able to control variables in these tests also shows us that there are many possible factors attributed to causing a particular

³⁰ (Kefer, Agarwal, and Sabanegh 449-57)

³¹ (Benoff, Hurley, Yuan, Xu, and Marmar 106-107)

result. It is possible that this is a cumulative effect, or that some factors have little relevance at all. Either way, further research to differentiate factors is necessary.

Hypothesizing which factors may have the largest impact relies on our understanding of the mechanisms involved. Even now, it is still not clear of the processes taking place on a molecular level. In the case of oxidative stress on the body, without further understanding and tracking of its effects, no treatment can exist.

Perhaps we can potentially solve many of the sources of these problems by changing habits but the human condition demands that there is a need for a significant threat to start the process and the consequences of infertility have yet to really impact the world populous. On the other hand, we can also turn to IVF and genetic analysis but these techniques are still in their infancy with regard to efficacy. Interestingly, we do not know whether or not these treatments will render the children from IVF couples infertile. Therefore from what has been found so far, although there is no quick and easy answer, further research into oxidative stress, its mechanisms, and potential cures, may be the best chance to significantly increase worldwide fertility.

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