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Review Article

# Effect of Metals on Semen Decline

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## ABSTRACT

There are some regions where the population is declining. This may be secondary to increasing infertility, largely due to a worldwide deterioration in semen quality. Metal concentrations in semen play an important role in male infertility. Metals such as Al, V, Pb have a negative effect on ART outcomes, such as embryo cleavage, blastocyst rate and even embryo quality, all leading to a decrease in pregnancy rate. There is currently no doubt about the effect of metals on semen quality. Measures should be taken to improve the environment and reduce the presence of metals. This knowledge allows us to take clinical action to minimize consequences.

**Keywords:** Metal; Semen; Infertility; Embryo

## INTRODUCTION

Despite the world's population has doubled in the last fifty years, and the Total Fertility Rate (TFR) is above 2.1 births per woman, there are regions where two-thirds of the population has a fertility rate below that threshold and birth rates are downturned. Europe's population is expected to drop by seven percent, while in other regions, such as Central, Southeast, South Asia, Latin America, Caribbean, and North America, the population is expected to continue to grow and peak before 2050 [1], bringing the global TFR to 1.66 by 2100 [2].

This population drop may be secondary to infertility, it is obvious that it is a social problem in many countries worldwide. It affects one in ten couples, with consequences not only physical but also psychological and social, leading to marital instability, depression, anxiety, low self-esteem, and many other issues such as violence, divorce, social stigma, and emotional distress [3,4].

## LITERATURE REVIEW

On the other hand, there are studies that support a loss in semen quality worldwide. This could be one of the reasons for the population downturn and the infertility increased. For instance, Levine et al. [5], found in a meta-analysis that sperm count, whether measured by Sperm Concentration (SC) or Total Sperm Count (TSC), fallen significantly among men in North America, Europe, and Australia from 1973 to 2011, with a fifty to sixty percent reduction in males not selected for fertility [6].

Karavolos et al. [7], consider hormonal, congenital, genetic, iatrogenic, behavioral, environmental and lifestyle factors as the main predisposing factors for male infertility. The influence of multiple environmental exposures may be related to the reduction of SC and other sperm parameters [6]. In addition, lifestyle factors such as dietary habits and obesity, alcohol consumption and smoking, and stress may have an impact on its weakening [8]. Several factors such as air pollution, chemicals, bisphenols, pesticides, Heavy Metals (HM), excessive heat, etc., could cause reduced sperm concentration and motility, abnormal morphology, and increased sperm DNA fragmentation [9]. These include HM, which affect testicular morphology, sperm production and sperm quality [10], by inhibiting sertoli cells and steroidogenesis in leydig cells, causing Oxidative Stress (OS) and suppression of spermatogenesis, resulting in reduced reproductive performance [11].

Xu et al. [12], found that seminal plasma may be a better biological specimen to assess male reproductive health and environmental exposures. Several authors observed that lower semen levels of Copper (Cu), Iron (Fe), Selenium (Se), and higher Chromium (Cr) were positively associated with altered seminal parameters risk [13], with an association between Zinc (Zn) and Se exposure and sperm concentrations [12], and Chai et al. [14], had obtained a positive association between Silver (Ag) and increased sperm quality, while

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Vanadium (V) may have detrimental effects on sperm morphology.

Understanding the impact of metals on reproduction, is a key issue in infertility screening. If we were able to know the positive or negative effects that each metal has on reproduction, we would be able to implement protocols to treat and improve fertility.

## DISCUSSION

### Metal effects on male fertility

Semen metal concentrations play an important role in male fertility [11], with a range of beneficial and adverse effects on spermatogenesis, sperm motility, sperm fertilization capacity, and embryo development [15], as well as on implantation rate.

These changes in semen samples appear to be relatively recent and may be related to lifestyle or higher concentrations of pollutants and environmental toxins in developed countries. Toxicological, epidemiological, biochemical, and physiological evidence shows that toxins and pollutants have adverse effects on spermatogenesis [16], and on genetic and epigenetic damage [17]. Some metals are necessary, some are always toxic, and some are toxic but necessary at lower levels [18], (Figure 1).

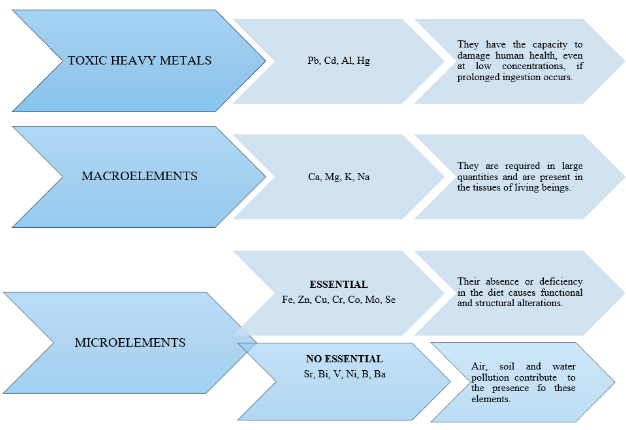


**Figure 1:** Metals that affect human health.

Occupational exposure to metals has been found to have a significant effect on sperm concentration, in such a way that these subjects have lower sperm concentration [19]. In this context, the function of spermatozoa is highly dependent on the exchange of ions between the cells and the environment in which they are immersed [20]. These mechanisms are controlled by multiple channels, exchangers, and active transport systems that act on the cell plasma membrane. The transport systems play a critical role in triggering events essential for sperm fertilization, including capacitation, hyperactivation, and the acrosomal reaction. Some of these transporters are unique to sperm and are structural variants or isoforms that differ from those found in somatic cells. Sodium (Na), Potassium (K), and Calcium (Ca) are involved in these processes [21].

However, there are elements that are indispensable, such as essential metals like Zn, Ca, or Magnesium (Mg), and some that can affect sperm quality at certain levels, such as Cadmium (Cd), Lead (Pb) and Mercury (Hg), Zn and Boron (Bo), Fe and Ca, among others. The occurrence of metals in the environment is shown in Figure 2.

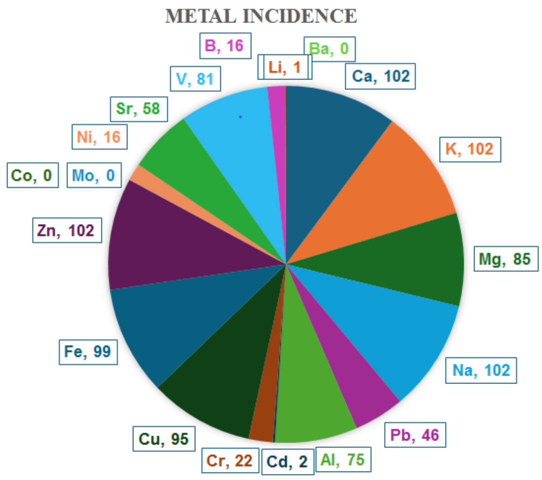


**Figure 2:** Metal incidence (n: 102). **Note:** (■): Li, (■): Ca, (■): K, (■): Mg, (■): Na, (■): Pb, (■): Ai, (■): Cd, (■): Cr, (■): Cu, (■): Fe, (■): Zn, (■): Ni, (■): Sr, (■): V, (■): B.

It has been shown that Cd and Pb are found at higher levels in infertile males, with a significant inverse relationship between concentration and sperm motility and sperm count. These metals are two of the most important reproductive toxic metals which could cause an alteration in the hypothalamic-pituitary-gonadal axis [22].

HM can cause infertility by altering endocrine function, or spermatogenesis, through the production of Reactive Oxygen Species (ROS) [23], and diminish antioxidant defense. This fact induces cellular changes, such as DNA damage, lipid peroxidation and, finally, apoptosis [24].

ROS are known to be required at low levels for normal sperm function, but in excess can affect sperm motility, morphology, and viability [25]. To protect sperm from these ROS, Seminal Fluid (SF) contains enzymatic antioxidants, particularly Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and Catalase (CAT), as well as non-enzymatic antioxidants such as Ca, Fe, Zn, and Se, and some vitamins such as vitamin C and E [26], (Figure 3).

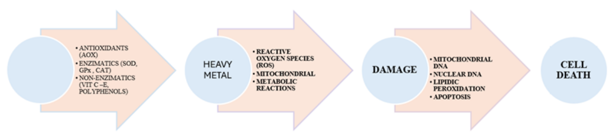


**Figure 3:** HM effects on ROS.

In previous studies by the authors, the influence of seminal metals on sperm quality (Table 1) and on the results of Assisted Reproductive Techniques (ART) has also been demonstrated [19,27], (Table 2).

**Lead (Pb):** Pb is one of the main pollutants that accumulate in the male reproductive system, reducing semen quality, decreasing fertility, and increasing male infertility [28]. Regarding the effects of Pb, a review showed that men exposed to Pb had statistically significant reductions in semen volume, TSC and SC, as well as total sperm motility [29]. However, in contrast to other authors, the authors did not observe a relationship between sperm parameters and Pb levels in semen [19].

Table 1: Effect of semen metals on semen analysis [19].

| Metal mg/kg | Normal | Altered | p-value |
|---|---|---|---|
| Zn | ↑ | | p=0.066 |
| Ca | ↑ | | p=0.047 |
| Mg | ↑ | | P=0.048 |
| Fe | | ↑ | p=0.032 |
| Ni | | ↓ | p=0.070 (trend) |

Table 2: Metal effect on ART [27].

| Metal | Fertilization | Cleavage | Blastocyst | Implantation | Embryo Q | Pregnancy |
|---|---|---|---|---|---|---|
| Al ↓ | - | - | ↑ (p=0.042) | - | ↑ (p=0.087) | - |
| K ↑ | - | - | - | - | - | ↑ (p=0.002) |
| Na ↓ | - | - | ↑ (p=0.002) | | - | - |
| Na ↑ | - | - | - | ↑ (p=0.001) | - | - |
| Mg ↑ | - | - | - | ↑ (p=0.017) | - | ↑ (p=0.009) |
| Fe ↑ | ↑ (p=0.164) trend | - | - | ↓ (p=0.043) | - | - |
| Ca ↑ | - | - | - | ↑ (p=0.033) | | ↑ (p=0.013) |
| Zn ↑ | - | - | - | - | - | ↑ (p=0.004) |
| V ↑ | - | ↓ p=0.032 | - | - | - | - |
| V ↓ | ↑ (p=0.039) | - | - | - | - | - |
| Pb↑ | - | ↓ p=0.052 | - | - | - | - |

**Note:** Q: Quality.

Toxicity is directly related to the ability of Pb to bind to Zn in human P2 protamine, which protects sperm DNA during spermatogenesis. This affects the integrity of sperm chromatin, reducing reproductive capacity, causing DNA damage and abnormal spermatogenesis [30]. Regarding the influence on ART, it has been reported that high levels of Pb interfere with embryo cleavage, as Bloom et al. [31], found, although recent studies did not find any relationship and estimated that Pb may interfere with embryo division, as it could inactivate intracellular antioxidant molecules, increasing OS, with failure in mitosis and alteration of embryo development [28].

**Cadmium (Cd):** Recently, different authors have shown that Cd is associated with sperm DNA fragmentation and ROS production [32], thus having a deleterious effect on sperm quality, mainly by altering the process of spermatogenesis, either by disrupting intercellular junctions or by altering testosterone concentrations [22]. On the other hand, Papalardo et al. [33], have shown that Cd exposure has a detrimental role on both the motility parameters and the fertilization potential of human spermatozoa, due to the stable and irreversible binding of Mg. The authors of the present study have found no relationship between Cd and spermiogram or ART results. [19,27].

**Aluminum (Al):** Al can be toxic to reproduction [34], because it increases the level of lipid peroxidation in spermatozoa with a reduction in their antioxidant capacity. These results support the possibility that the deleterious effects of Al in semen are induced by OS [35].

Surprisingly, in a study by the authors, most patients have Al in semen (73.6%), and it was found that patients with high occupational metal exposure had higher Al levels [19]. The authors have also demonstrated a negative relationship between the presence of Al in semen above a level and a reduction in embryo quality in ART, which also reduces the percentage of blastocyst stage [27], (Figure 4).

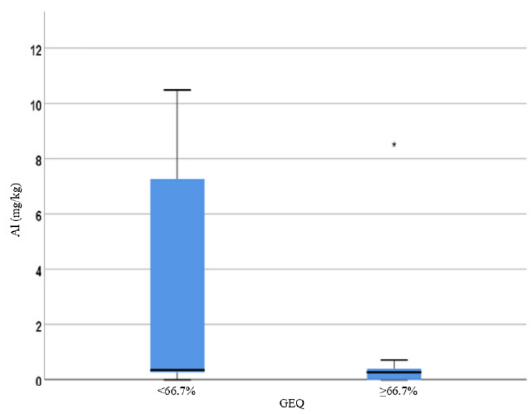


**Figure 4:** Seminal Al effect on Good Embryo Quality (GEQ) and Blastocyte Rate (BR) in Assisted Reproduction Treatment (ART) [27].
**Note:** (■): Bromine (Br).

**Mercury (Hg):** Some authors found no adverse effects of Hg on the male reproductive system [36], but others [37], in *in vitro* and animal model studies, have found a negative effect, specifically by inducing DNA breaks in spermatozoa leading to a falling-off in sperm motility and viability, and they also found that blood Hg levels were slightly higher in men with abnormal sperm parameters [38]. Exposure to Hg induced hormonal disruption, sperm DNA damage, abnormal sperm morphology, and motility [37]. Studies are conflicting and more research is needed on the effects of Hg on sperm quality [39]. Since Hg was not detected in the author´s study, it was not possible to determine its influence on ART [27].

**Calcium (Ca):** Ca is a valuable element that acts as an intracellular second messenger and can be a mediator of oxidative damage, inducing lipid peroxidation, and is significant in sperm cell motility, capacitation, and the acrosome reaction and hyperactive sperm motility [40]. Ca in seminal plasma is one of the elements considered most serious for male fertility, and the authors have found a positive relationship not only with spermiogram quality, but also with implantation and pregnancy rate, with Ca being an important element in normal semen [19].

**Magnesium (Mg):** ATP $Mg^{2+}$-dependent ATPase, generates the energy for sperm motility or fertilization capability and disorders of the fertilizing potential of spermatozoa which are closely associated with dysfunction of ion-transporting ATPases, $Ca^{2+}$, $Mg^{2+}$-ATPase [41].

Mg has been shown to be essential for sperm capacitation, acrosomal reaction and hyperactivation of sperm motility [42]. The authors have found that higher Mg levels are present in normozoospermic men, with Mg having an important role in the embryo implantation rate and in achieving a pregnancy [27].

**Sodium (Na):** The $Na^+$ ATPase plays an important role in establishing the resting sperm membrane potential and in maintaining the electrochemical gradients for $Na^+$ across the sperm plasma membrane [43].

In the same way as K, Na is involved in the regulation of the internal pH and the plasma membrane potential of spermatozoa [20].

In a study by the authors Na has an important role on good semen quality, and on the ART results, in this way, when the Na levels are low, the blastocyst rate improved, and when higher favors implantation [27].

**Potassium (K):** K is involved in the regulation of the internal pH and plasma membrane potential of spermatozoa [20]. K supports sperm motility during the late stages of capacitation, especially during membrane hyperpolarization, and K channels are essential for human sperm motility. The presence of the ion $K^+$ in the seminal plasma is necessary to maintain sperm volume, intracellular pH, and sperm motility [44].

It is known that the membrane potential of human spermatozoa needs to be hyperpolarized to fertilize an oocyte, and this hyperpolarization depends on the SLO3 $K^+$ channel, and the hyperpolarization correlates with IVF success [45]. This may be the reason why the authors found that high K levels correlated with high pregnancy rates [27].

**Iron (Fe):** Fe is a non-enzymatic antioxidant and enzyme cofactor (enzymatic Fe-catalase), which performs the breakdown of hydrogen peroxide [18], with an important role in sperm function, but, in excess of Fe has a negative effect on sperm damage and even on embryo development [46], and it contributes to an increased lipid peroxidation ratio in sperm plasma membranes and impaired motility [18]. In this regard, the authors observed an antagonistic effect of Fe levels, such that elevated levels (0.61 mg/kg) were detected in SF in pathological spermiograms, and on the other hand, low levels below 0.33 mg/kg also showed signs of sperm pathology [19], (Figure 5). In conclusion, it has been observed that excessive exposure to Fe can reduce semen quality and, as the authors also found, sperm concentration and total sperm count were positively correlated and showed inverted "U" shapes in univariate analysis [47].

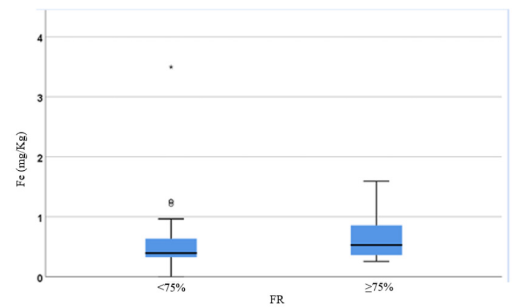


**Figure 5:** Fe and Fertilization Rate (FR). **Note:** (■): Francium (Fr).

**Zinc (Zn):** Zn plays an important role in the maintenance of germ cells, the progression of spermatogenesis and the regulation of sperm motility. Several studies have shown that fertile men have high levels of Zn [12], as the authors also found a significant relationship between higher Zn levels and normozoospermia [19].

Given it antioxidant and anti-inflammatory effects, Zn plays a fundamental role in the elimination of ROS and is involved in the production of antioxidant enzymes for cell protection [48,49]. It also acts by activating the epidermal growth factor receptor and the G protein-coupled receptor. Its deficiency has been associated with OS, sperm apoptosis, and consequently a reduction in sperm quality [50], although other authors have found that it may play a negative role on sperm quality at toxic levels [51], and even on the development of the embryo.

**Copper (Cu):** Cu acts as a cofactor of enzymes and its damage depends on the copper-containing superoxide dismutase. Cu acts as antioxidant and has a positive effect on sperm parameters [52], although low levels of Cu have been detected in semen with diminishing motility [53].

The true influence of Cu on fertility is unknown, as some publications report a positive relationship between its blood concentration and sperm motility, while others have observed a high Cu level in infertile groups. This discrepancy in results may be due to the redox activity of Cu [54].

**Vanadium (V):** V is a ubiquitous transition metal found in soil, water, and the atmosphere. The general population is exposed through ingestion of contaminated food, drinking water, and inhalation. It can be found in seminal plasma and, an association has been found between higher levels of V was found and a waning in fertilization rate (Figure 3), but not with semen parameters [19,27], as no difference in levels of V was found between the normozoospermic and pathological semen groups, and as other authors found no difference in levels of V between the normozoospermic and pathological semen groups [55], and unlike Wang et al. [56], who reported an association between low sperm concentration and V (Figure 6). One of the findings of a work by the authors indicates the correlation between higher values of V and a lower fertilization rate in ART, as well as a decrease in cleavage rate [27].

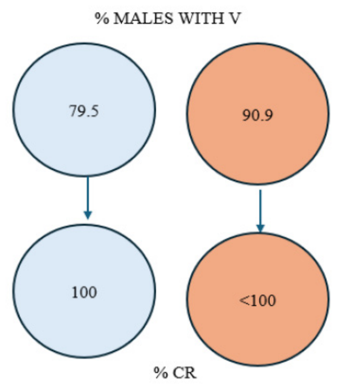


**Figure 6:** Effect of V in semen on Cleavage Rate (CR).

**Nickel (Ni):** The mode of action of Ni in the male reproductive tract includes balancing ROS *via* Zn metabolism, which affects the structure of protamine [57]. In studies by the authors, a significant relationship was found between the level of occupational metal exposure and Ni, and patients with oligozoospermia tended to have lower levels of Ni, but no differences in normal sperm parameters or oligo/asthenozoospermia were reported [58]. Thus, Chai et al. [14], also found that Ni may have adverse effects on sperm morphology and was negatively correlated with sperm concentration, total sperm count, and progressive motility [47].

## CONCLUSION

Males exposed to HM have lower semen quality, which is associated with infertility, highlighting the existence of a significant correlation between exposure to HM and lower semen quality, which is associated with lower fertility rates, or a decrease in good embryo rate, implantation, or pregnancy rate. Reducing chemical exposure can prevent the adverse effects of semen quality and thereby the incidence of male infertility. Metals such as Al, V, Pb have a negative effect on ART outcomes such as embryo cleavage, blastocyst rate and even embryo quality, all of which lead to a decrease in pregnancy rate. Policies should be implemented to improve the environment by reducing the presence of metals.

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