**Ministry of Higher Education and Scientific Research**

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**Department of Medical Laboratory Technology**

**Evening Study**

# Effect of Lead Acetate on Spermatogenesis

**A research submitted to the Presidency of the Medical Laboratories Department as Partial fulfillment of the diploma requirements**

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نحن أعضاء في لجنة مناقشة مشاريع التخرج لطلبة قسم تقنيات المختبرات الطبية نشهد أنه بعد قراءة مشروع البحث الموسوم ( effect of lead acetate on spermatogenesis) للطلبة :

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# الاهداء

إلى من أفعمني بصريح العطف و أغدقني بفيض الإحسان ...أبي

إلى التي أشبلتنى بخالص الحب وصدق الحنان ..أمي

إلى الذين آثروني بالإخاء وناصروني في كل أن ..إخواني وأخواتي

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إلى هؤلاء جميعا أهدي ثمرة نجاحي كعربون وفاء وعرفان

# شكر وتقدير

**أتقدم بخالص شكري وتقديري الى الاستاذ الفاضل (م.م. مهند ساجت)**

**كما أتقدم بالشكر والتقدير الى كل من شجعني ووقف الى جانبي في قول وفعل واخص بالشكر اساتذتي الكرام لوقوفهم معي ومساعدتي بالنصح والارشاد وكل من كان لي شرف تلقي العلم على يديه طوال مدة دراستي.**

**كما أتقدم بالشكر والاعتزاز إلى والدي ووالدتي اللذين اضاءا لي الطريق للوصول إلى هذه المرحلة.**

**في الختام اتقدم بالشكر لكل من اسهم ولم يبخل في تقديم المساعدة**
**لكم جميعًا شكري وتقديري**

## Abstract

Spermatogenesis, the complex process of sperm cell development, is highly susceptible to environmental toxins, among which lead acetate has emerged as a significant concern. This comprehensive review examines the multifaceted effects of lead acetate on spermatogenesis, drawing upon a synthesis of experimental data and mechanistic insights.

Lead acetate, a ubiquitous environmental pollutant, penetrates the male reproductive system, disrupting key cellular processes essential for normal sperm production. Through intricate pathways, lead acetate interferes with germ cell differentiation, impairs Sertoli cell function, disrupts hormonal homeostasis, and induces oxidative stress within the testicular microenvironment.

These disruptions manifest in altered testicular morphology, reduced sperm quality, and compromised male fertility. Moreover, the transgenerational effects of lead acetate exposure pose long-term risks to reproductive health across generations. Importantly, this review highlights emerging therapeutic strategies, including antioxidant supplementation, chelation therapy, and environmental remediation, aimed at mitigating the adverse effects of lead acetate on spermatogenesis. However, effective prevention remains paramount, emphasizing the necessity of stringent regulations to limit human exposure to lead acetate in occupational, environmental, and dietary contexts. Overall, this research underscores the urgent need for interdisciplinary efforts to address the public health implications of lead acetate exposure on male reproductive function and fertility.

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# Chapter One

## Introduction

# Chapter One : Introduction

## 1.1 Introduction

Spermatogenesis, the complex process of sperm cell development, is crucial for male fertility and reproductive health. However, various environmental and occupational exposures to toxic materials pose significant threats to this delicate process. Understanding the adverse effects of these substances on spermatogenesis is paramount for safeguarding reproductive well-being (Sengupta, 2010).

Toxic materials encompass a wide array of chemical compounds, including heavy metals, pesticides, industrial chemicals, and endocrine disruptors. These substances have been implicated in disrupting hormonal balance, inducing oxidative stress, and interfering with cellular signaling pathways crucial for spermatogenesis (Jeng and Pan, 2012).

Heavy metals such as lead, cadmium, and mercury have long been recognized for their detrimental effects on male reproductive function. Research suggests that exposure to these metals can impair sperm quality, reduce sperm count, and increase the risk of infertility. Additionally, pesticides like organophosphates and carbamates have been associated with decreased semen quality and altered sperm morphology (Pant et. al., 2014).

Industrial chemicals like bisphenol A (BPA) and phthalates, commonly found in plastics and personal care products, have emerged as significant threats to male reproductive health. These endocrine-disrupting chemicals mimic or interfere with natural hormones, leading to disruptions in sperm production and function.

Moreover, lifestyle factors such as smoking, alcohol consumption, and illicit drug use can exacerbate the adverse effects of toxic materials on spermatogenesis. Chronic exposure to tobacco smoke, for instance, has been linked to impaired sperm motility and DNA damage (Duty et. al., 2003).

Lead poisoning, a significant public health concern worldwide, poses detrimental effects on various physiological systems, including male reproductive health. Accumulating evidence suggests that exposure to lead can profoundly disrupt spermatogenesis, the intricate process of sperm cell development, leading to impaired fertility and reproductive dysfunction in men (Telisman et. al., 2007).

Lead, a heavy metal ubiquitous in the environment due to industrial activities, water contamination, and lead-based products, exerts its toxic effects through multiple mechanisms. Upon absorption, lead can accumulate in various tissues, including the testes, where it interferes with critical cellular processes essential for spermatogenesis.

## 1.2 Importance of the Research

The importance of researching the effect of lead on spermatogenesis lies in several critical areas:

1. Protecting Male Fertility: Understanding how lead exposure impacts spermatogenesis is crucial for safeguarding male fertility. By identifying the mechanisms by which lead disrupts sperm production and function, researchers can develop strategies to minimize these effects and preserve reproductive health in men.

2. Public Health Policy: Research on lead-induced spermatogenic dysfunction informs public health policies and regulations aimed at reducing environmental and occupational exposures to lead. This knowledge helps policymakers establish guidelines for safe lead levels in drinking water, workplace environments, and consumer products, thereby protecting populations from reproductive hazards.

3. Occupational Safety: Occupational workers in industries such as manufacturing, construction, and mining are at increased risk of lead exposure. Understanding the impact of occupational lead exposure on spermatogenesis is crucial for implementing workplace safety measures and regulations to minimize reproductive risks for workers.

4. Reproductive Medicine: Insights into the effects of lead on spermatogenesis are valuable for reproductive medicine and assisted reproductive technologies (ART). Clinicians can use this knowledge to counsel couples undergoing infertility treatment, identify potential contributors to male infertility, and tailor treatment strategies accordingly.

5. Transgenerational Health: Research on the transgenerational effects of paternal lead exposure provides insight into intergenerational health risks. Understanding how lead exposure in one generation affects the reproductive health and development of subsequent generations is essential for identifying and addressing potential risks to population health.

Overall, research on the impact of lead on spermatogenesis is vital for protecting male reproductive health, informing public health policies, promoting occupational safety, advancing reproductive medicine, and safeguarding future generations from the adverse effects of environmental toxicants.

## 1.3 Objectives of the study

1. To elucidate the cellular and molecular mechanisms by which lead exposure disrupts spermatogenesis.

2. To establish dose-response relationships between lead exposure levels and the severity of spermatogenic impairment.

3. To investigate the transgenerational effects of paternal lead exposure on offspring health and reproductive outcomes.

4. To evaluate the efficacy of intervention strategies, such as chelation therapy and antioxidant supplementation, in mitigating lead-induced spermatogenic dysfunction.

5. To assess the susceptibility of different population groups to the reproductive toxic effects of lead exposure and inform targeted prevention and intervention efforts.

## 1.4 Structure of the study

**Chapter 1**, titled "General Introduction," provides an overview of the study subject, outlines the scope of the research, and states the research objectives clearly.

In **Chapter 2**, an extensive literature review is conducted, beginning with an introduction and defining Lead, and Lead Toxicity.

**Chapter 3** focuses on the human spermatogenesis processing.

Finally, **Chapter 4**, the effect of lead acetate on spermatogenesis of human and the conclusion of the study.

# Chapter Two

## Literature Review

## 2.1 Introduction

There are 35 metals that concern us because of occupational or residential exposure; 23 of these are the heavy elements or "heavy metals": antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium, and zinc. Interestingly, small amounts of these elements are common in our environment and diet and are actually necessary for good health, but large amounts of any of them may cause acute or chronic toxicity (poisoning). Heavy metal toxicity can result in damaged or reduced mental and central nervous function, lower energy levels, and damage to blood composition, lungs, kidneys, liver, and other vital organs. Long-term exposure may result in slowly progressing physical, muscular, and neurological degenerative processes that mimic Alzheimer's disease, Parkinson's disease, muscular dystrophy, and multiple sclerosis. Allergies are not uncommon and repeated long-term contact with some metals or their compounds may even cause cancer (Al-Saadi, 2011).

The symptoms of toxicity resulting from chronic exposure (impaired cognitive, motor, and language skills; learning difficulties; nervousness and emotional instability; and insomnia, nausea, lethargy, and feeling ill are also easily recognized; however, they are much more difficult to associate with their cause. Symptoms of chronic exposure are very similar to symptoms of other health conditions and often develop slowly over months or even years (Al-Saadi, 2011). All metals are potentially toxic, yet, many metals are essential for life. Homeostasis is key to survival. Metals are frequently bound to proteins for transport and storage (Mañay et. al., 2008). In small quantities, certain heavy metals are nutritionally essential for a healthy life. Some of these are referred to as the trace elements (e.g., iron, copper, manganese, and zinc) (Al-Saadi, 2011).

## 2.2 Lead

Lead, ubiquitous in the environment as a result of mining and industrialization, is found as a contaminant in humans although it has no known physiological function there (Mañay et. al., 2008). While lead serves no function in our bodies, it is usually found in the body in some amount since it is so common in

the environment. Low levels in adults are not thought to be harmful (Woolf et. al., 2007).

Lead is a dangerous element that can be harmful even in small amounts. It is enters the human body in many ways. It can be inhaled in dust, from lead paints, or waste gases from leaded gasoline. It is found in trace amounts in various foods, notably fish, which are heavily subjected to industrial pollution. Some old homes may have lead water pipes, which can easily contaminate drinking water. Most of the lead we take in is removed from our bodies in urine; however, there is still risk of buildup, particularly in children. If Lead buildup occurs, health problems including damage to the nervous system, mental retardation, and even death, can ensue (Jackson, 2005).The signs and symptoms of lead poisoning in adults may include: pain, numbness or tingling of the extremities, muscular weakness, headache, abdominal pain, memory loss, reproductive impairment in men, constipation, and anemia (Jackson, 2005). Lead level blood, this test is used to screen people at risk for lead poisoning, including industrial workers and children who live in urban areas (Woolf et. al., 2007). In Adults lead Less than 20 micrograms/dL of lead in the blood. Adults who have been exposed to lead should have blood lead levels below 40 micrograms/dL. Treatment is recommended if you have symptoms of lead poisoning, or if your blood lead level is greater than 60 micrograms/dL (Woolf et. al., 2007).

## 2.3 Pollution with Lead

Lead environmental pollution is a major health hazard throughout the world. Several mechanisms of lead poisoning have been identified. The most common are pica, industrial exposure, drinking moonshine liquor, inhalation, gunshot wounds, retained lead pellets or particles, and a variety of folk remedies and cosmetics (Khan et. al., 2009). Studies confirm that exposure to lead causes renal damage, encephalopathy, and impaired cognitive function in children and in adult (Khan et. al., 2009). In adults, the peripheral nervous system is commonly affected (peripheral motor neuropathy). This may lead to irritability, behavioral disorders, low intelligence quotient (IQ), ataxia convulsions, and to wrist drop, foot drop, or lead colic in adults (Khan et. al., 2009). Lead has been classified as carcinogen in

animals. The National Toxicology Program classifies lead, along with its compounds, as being reasonably anticipated to be a human carcinogen on the basis of limited studies in humans and more sufficient animal studies. The International Agency for research on cancer considers inorganic lead compounds as "probably carcinogenic to humans" on the basis of limited evidence in humans (Khan et. al., 2009). An estimated 90-95% of cases reported in the United States in the adult blood lead epidemiology and surveillance program result from occupational exposures. The cars and homes of workers in the lead industry may become contaminated with lead dust, which may be carried on a worker's body, clothes, and shoes. Jobs that may expose a worker to lead include automobile radiator repair, construction, painting, and metal salvaging. The major source of lead is occupational exposure from jobs dealing with lead and lead-based components; there is a high prevalence of lead toxicity in the population exposed to such activities. Occupational exposure of workers is seen in the manufacturing of lead batteries and cables, as well as rubber and plastic products. Soldering and foundry work, such as casting, forging, and grinding activities, are also associated with occupational exposures. Constructions workers involved in painting or paint stripping, plumbing, welding, and cutting are also exposed to lead (Al-Saadi, 2011).

## 2.4 Lead Normal Values

Normal lead values in humans can vary depending on the source of exposure and individual circumstances. However, in general, blood lead levels are typically measured in micrograms per deciliter (μg/dL).

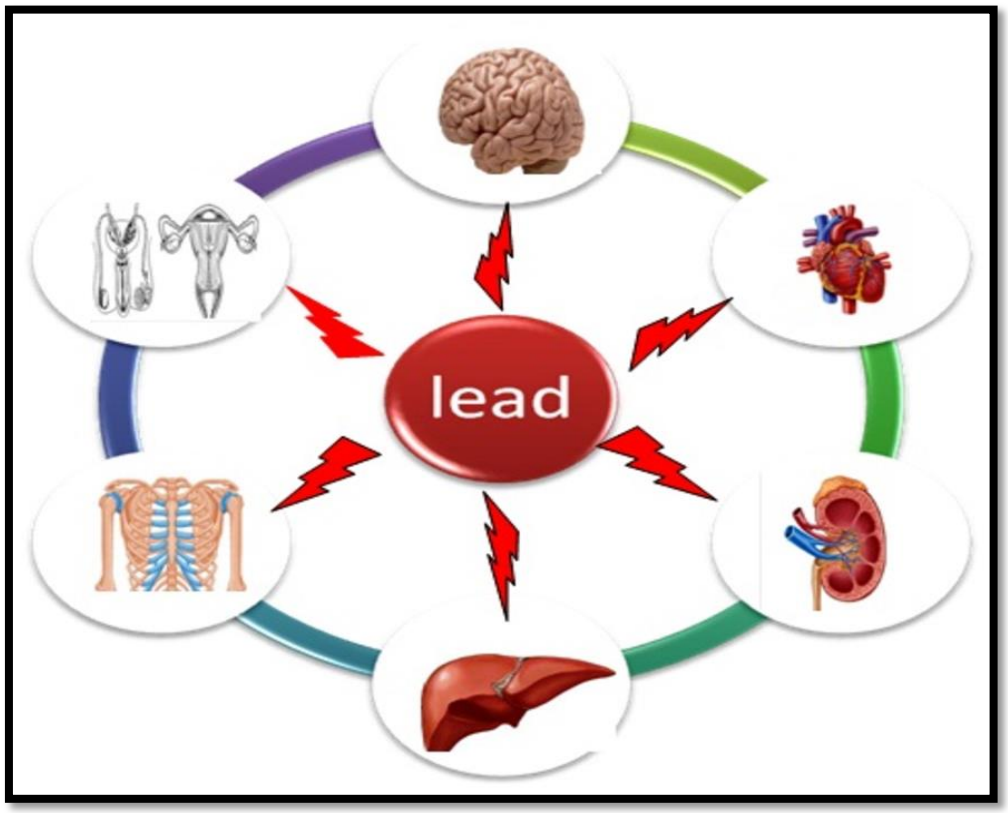
According to the Centers for Disease Control and Prevention (CDC,2020), the reference value for blood lead levels in adults without occupational exposure is less than 5 μg/dL. For children, the reference value is lower, typically less than 3.5 μg/dL.

It's important to note that these values can vary slightly depending on the laboratory and the specific testing method used. Additionally, exposure to lead should always be minimized as much as possible, as even low levels of lead

exposure can have adverse health effects over time. Regular monitoring of lead levels may be necessary for individuals with potential exposure risks.

## 2.5 Lead effects on human

lead poisoning, or plumbism, is well-documented for its multifaceted effects on human health. Here's a breakdown of the disorders related to lead poisoning according to the CDC (CDC, 2019). Picture (2-1) by (Bhattacharjee et. al., 2018) below shows the body parts that could be effected by lead poisoning :




**Picture (2-1):The body parts that could be effected by lead poisoning**

1. Neurological Disorders:

- Cognitive Impairment: Lead exposure can impair cognitive functions such as memory, attention, and problem-solving abilities.
- Behavioral Problems: Lead toxicity is associated with increased aggression, hyperactivity, and other behavioral issues, particularly in children.

- Seizures: In severe cases, lead poisoning can lead to seizures and convulsions due to its neurotoxic effects.

2. Hematological Disorders:

- Anemia: Lead interferes with the synthesis of hemoglobin, leading to decreased red blood cell production and ultimately causing anemia.

3. Renal Disorders:

- Kidney Damage: Lead can accumulate in the kidneys, causing nephropathy and impairing renal function over time.

4. Reproductive Disorders:

- Infertility: Lead exposure has been linked to reduced fertility in both men and women.
- Pregnancy Complications: Pregnant women exposed to lead are at increased risk of miscarriage, premature birth, and developmental abnormalities in their offspring.

5. Cardiovascular Disorders:

- Hypertension: Chronic lead exposure is associated with elevated blood pressure, increasing the risk of cardiovascular diseases.

6. Developmental Disorders:

- Growth Impairment: Children exposed to lead may experience stunted growth and delayed development.
- Neurodevelopmental Disorders: Lead toxicity during critical periods of brain development can lead to long-term neurodevelopmental disorders, including learning disabilities and attention deficit hyperactivity disorder (ADHD).

7. Gastrointestinal Disorders:

- Abdominal Pain: Lead poisoning can cause gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and constipation.

8. Dermatological Disorders:

- Lead lines: Chronic lead exposure can result in the deposition of lead compounds in the gums, leading to the formation of blue-black lines along the gingival margin known as "lead lines."

Understanding the mechanisms by which lead exerts its toxic effects on various organ systems is crucial for developing effective prevention strategies and therapeutic interventions.

# Chapter Three

## Human Spermatogenesis

# Chapter Three: Human Spermatogenesis

## 3.1 Introduction

The union of male and female gametes creates offspring. The production of these vital reproductive cells occurs in the testis and ovary during the processes of spermatogenesis and oogenesis, respectively (Nishimura and L'Hernault, 2017) The primary male reproductive organs, the testes, are located inside the scrotum and function to produce sperm cells as well as the primary male hormone, testosterone. As mentioned above, spermatogenesis is the process by which sperm cell production occurs; the germ cells give rise to the haploid spermatozoa. Sperm production takes place inside the seminiferous tubules, which is a convoluted cluster of tubes located inside the testes. Testosterone production occurs in cells surrounding the seminiferous tubules, called Leydig cells. After being formed, sperm cells travel outside of the tubules into the epididymis, where they mature and prepare for ejaculation.

The complex process of spermatogenesis occurs in three steps. The first step involves mitotic cell division that allows the early cell stage, spermatogonia, to multiply. The second step requires meiosis, in which the diploid cells form haploid cells. A division occurs until a round spermatid formation occurs. The final stage of spermatogenesis includes spermatozoa production, mature and motile sperm cells, from round spermatids, through a process called spermatogenesiss (Kretser, 1998).

Diminished fertility or infertility may result from a decrease in spermatozoa number, alteration in shape, and inefficient motility (Holstein et. al., 2003). The three steps represent the foundation of spermatogenesis. Functional abnormalities may occur in any one of them, which can cause the entire process to fail. These abnormalities can lead to defective or reduced sperm production. In more severe conditions, a complete absence of spermatozoa can result, leading to infertility. Therefore, we must expand our knowledge of spermatogenesis as a whole to provide essential information regarding the regulatory mechanisms. The testicular environment is complex; therefore, the study of spermatogenesis can be quite tricky in most species. To achieve this understanding, experimental studies completed in rodents and primates are the cornerstone of this crucial knowledge (Kretser, 1998).

## 3.2 Spermatogenesis Issues of concern

The necessity for the production of an infinite number of gametes increases the specific requirements needed for spermatogenesis to occur: The reproductive lifecycle of the male requires a large amount of stem cell production. A wide array of particular progenitor cells is necessary for the production of enough gametes to establish fertilization. Certain genes specific to spermiogenesis are required for the differentiation of sperm as well as acquiring sperm mobility. The continuous pool of spermatozoa becomes readily available by an advanced level of control and organization. One of the principal functions in male reproduction is carried out by the spermatogonia stem cells. Spermatogonia need stem cells to maintain their numbers by self-renewal and form the necessary progenitor cells required to proceed with spermatogenesis. Germ cells need constant nutrition to be able to differentiate into mature sperm that are capable of fertilization. Unavailability of these factors can cause spermatogenesis to fail ultimately and lead to sperm cell production (Griswold, 2016) and (White-Cooper, 2010).

Spermatogenesis is far less efficient in terms of quality management. The loss of germ cells occurs quite often. Also, the ejaculate can have extremely high numbers of malformed spermatozoa. Apoptosis or degeneration allows for the loss of about 75% of the developed germ cells. Only 25% of the germ cells reach the ejaculate, and research reveals that about 50% are malformed. Therefore, the spermatogenic potential that is accessible for reproduction is about 12%(Holstein et. al., 2003).

Recent reports have noticed a decline in the spermatozoa concentrations in the ejaculates of healthy males. This decline has occurred over the last decades, and specific factors affecting embryonal development seem to be the cause. These factors include prenatal influences such as hormones, drugs, radiation, metabolites in the drinking water, and nourishment of the mother. Moreover, the spermatogenetic process of the testis is affected by increased temperatures. These negative influences lead to a reduction in spermatogenesis, which manifests as a reduction in the number of mature spermatids or the formation of malformed spermatids.

Additionally, these influences may cause the process of meiosis to be disturbed. An arrest of spermatogenesis may occur after the creation of primary spermatocytes, and apoptosis of spermatogonia can occur. Rescue of spermatogenesis may arise if the spermatogonia survive. If they do not survive, spermatogenesis comes to a halt, and seminiferous tubules will appear as shadows (Holstein et. al., 2003).

Testicular biopsies evaluate the disturbances of spermatogenesis through histological sections. A suitable technique is known to be semithin sectioning of material embedded in epoxy resin. The excellent preservation of the cells much helps the evaluation of the specific details of the cells (Holstein et. al., 2003).

## 3.3 Human testes structure

he human testes, exhibiting an ellipsoid shape, are two reproductive organs that reside in a sac called the scrotum. Each testis is about 2.5 x 4 cm in diameter, surrounded by an active capsule of connective tissue called tunica albuginea. The parenchyma of the testis is divided roughly into 370 conical lobules by thin septula testis. Within the lobules are the seminiferous tubules as well as inter-tubular tissue. This tissue contains groups of Leydig cells and further cellular elements (Holstein et. al., 2003).

The seminiferous tubules consist of entwined loops whose ends unfold into the open space of the rete testis. Rete testis is a network of tubules found in the hilum of the testicle and function to carry collected sperm to the efferent ducts of the epididymis as the seminiferous tubules secrete it. The germinal epithelium constitutes the seminiferous tubule. The invagination of Sertoli cells houses many cells. These cells include germ cells in different developmental stages such as spermatogonia, primary and secondary spermatocytes, and spermatids. The tight junctions of cellular membranes connect Sertoli cells. The specialized zones of tight junctions form the blood-testis barrier. Germ cells pass the hurdle during maturation, where they get protection from the diffusion of external substances.

Sertoli cells are known to be the “biological clock” of the testis. When visualized in histological sections, they manifest rising amounts of lipid droplets

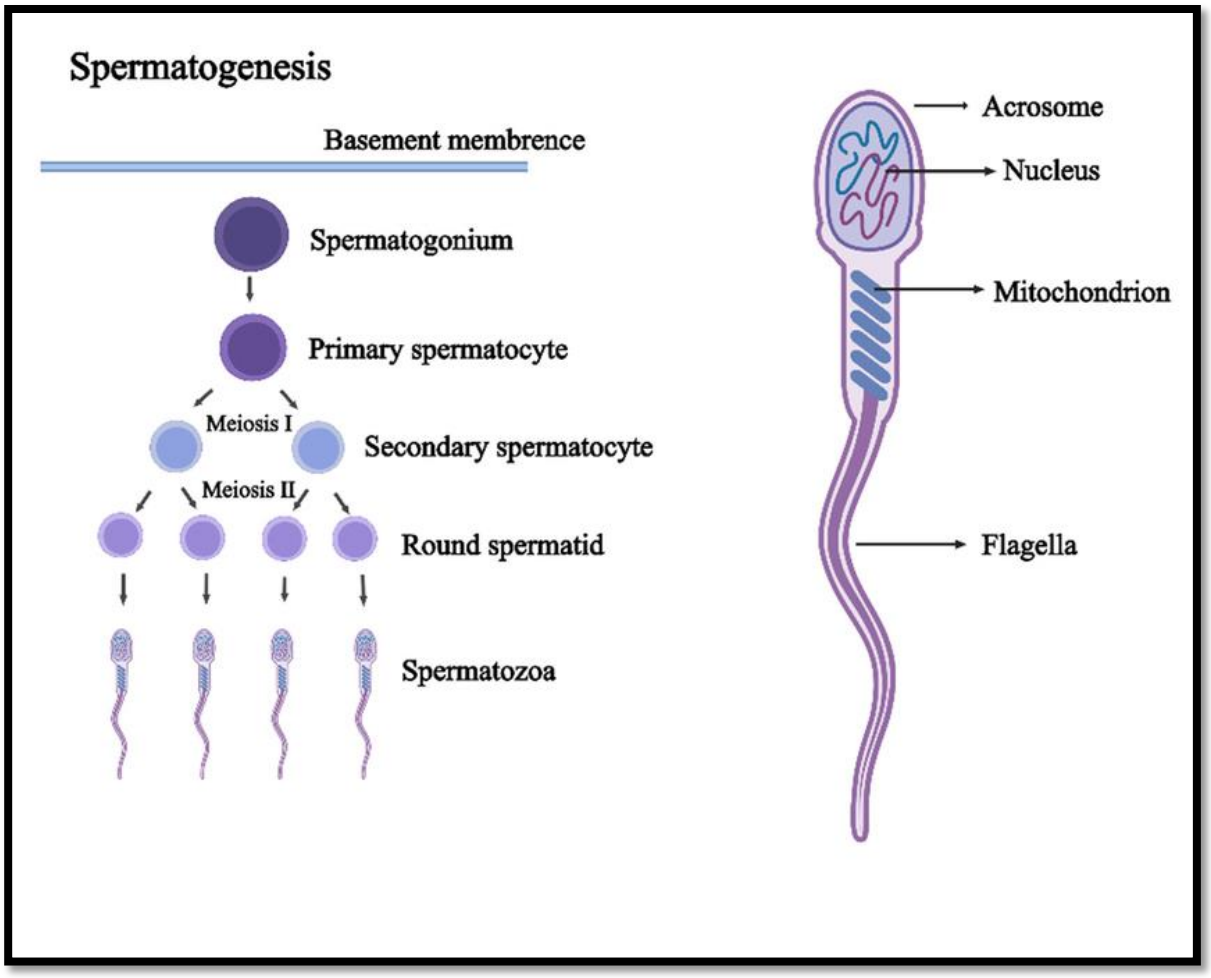
with time. Therefore, the increasing numbers of lipids correlate to the advancing age of the individual (Holstein et. al., 2003).

Other functions attributable to Sertoli cells include providing nutrition for the germ cells, delivering mature spermatids to the tubular lumen, regulating spermatogenesis by producing endocrine and paracrine substances, maintaining the epithelia of the efferent ductal system by secreting ABP (androgen binding protein) as well as interacting with the inter-tubular Leydig cells. The lamina propria of seminiferous tubules, also known as the peritubular tissue, constitutes the basement membrane of the basal lamina and functions to surround the cellular elements. It consists of connective tissue intermingled around five layers of myofibroblasts. These myofibroblasts play a vital role in the peristaltic contraction of seminiferous tubules to allow for the transport of immotile spermatozoa to the hilum of the testis, the rete testis. Peritubular tissue usually is about 8 micrometers in thickness. Alteration of spermatogenesis can increase the width to 12 micrometers by connective tissue (Kretser, 1998).

Leydig cells, which are most prominent in the inter-tubular space, form clusters surrounding the capillaries. They produce and secrete one of the essential male reproductive hormones, testosterone. Testosterone is vital for male reproduction as it activates the hypophyseal testicular axis. It is crucial for the development of male genital organs as well as masculinization and formation of the secondary sex characteristics. Testosterone plays a significant role in initiating, processing, and maintaining spermatogenesis. Hormone production does not correlate with the number of Leydig cells. Immunohistochemically investigations prove that the creation of testosterone only takes place in a few Leydig cells despite their increased number. An increased number of cells occurs in hyperplasia or tumors (Holstein et. al., 2003).

## 3.4 Human testes function

Spermatogenesis involves the following three complex integrated processes initiated at the onset of puberty. Picture (3-1) by (Yan et. al., 2022) shows spermatogenesis process:




Picture (3-1): (Yan et. al., 2022) shows spermatogenesis process

## 3.4.1 Meiosis

Male fertility requires the formation of millions of gametes. Production of functional gametes or sex cells requires a single cell to undergo cell division to reduce the number of chromosomes by half. This process is known as meiosis. Meiosis occurs twice, thereby creating four daughter haploid cells, also known as spermatids. For every diploid spermatocyte, meiotic divisions produce four haploid spermatids.

Mitotic cell division: diploid spermatogenic stem cells differentiate into two sets of diploid primary spermatocytes, also known as tetraploid cells. The largest germ cells found in the germinal epithelium are the primary spermatocytes, containing the largest cell nuclei

### 3.4.2 Meiotic Cell Division I

The division begins with the leptotene stage of prophase. The stage takes place in the germinal epithelium, more specifically, the basal compartment. Spermatocytes enter the ad luminal compartment after reaching the Sertoli cell barrier. Here, further prophase stages continue, and these include the zygotene, pachytene, and diplotene stages. These stages see DNA reduplication, chromosomes condensation, and homologous chromosomes pairing, as crossing over will occur. Each set of diploid primary spermatocytes differentiates into two haploid secondary spermatocytes, where the total number of chromosomes gets reduced to half(Holstein et. al., 2003) and (Lancaster K., 2016).

### 3.4.3 Meiotic Cell Division II

Each haploid secondary spermatocyte differentiates into two haploid spermatids, therefore, resulting in four haploid cells. This process occurs quickly, and no DNA replication takes place (Holstein et. al., 2003).

### 3.4.5 Spermiogenesis

This process is the final phase of spermatogenesis. Spermatids mature and form spermatozoa, fully differentiated sperm cells. This stage ends when the mature cells leave the germinal epithelium. These free cells, at this point, are called spermatozoa. Spermatozoa have a unique shape, which is essential in their movement to the female gamete. The condensed nucleus and the presence of an acrosome needed to establish contact with the female gamete provide them with their unique shape. They exhibit extensive motility as they contain a connected flagellum. As they transform into mature sperm, spermatids undergo a wide array of morphological changes (Holstein et. al., 2003) and (White-Cooper, 2010). It takes about 30 to 40 days for spermatogenic stem cells to generate spermatozoa. (Griswold, 2016) Spermatogenesis is a process that occurs in the seminiferous tubules, and many internal and external factors regulate it. Intrinsic regulation requires the production and release of testosterone, neuroendocrine substances, and growth factors secreted by Leydig cells. They communicate with nearby Leydig cells, blood vessels, peritubular tissue of the seminiferous tubules, and Sertoli cells. They maintain the trophic factors of these cells and participate in the regulation of peristalsis in the seminiferous tubules. These growth factors and neuroendocrine

substances influence the contractility of myofibroblasts to ensure the proper transport of spermatozoa. Intrinsic factors also play a vital role in regulating the flow of blood in the intertubular microvasculature. This process is quite intricate and is mainly investigational in laboratory animals. In humans, it is still unclear (Holstein et. al., 2003).

Extrinsic regulation of spermatogenesis requires stimuli from the hypothalamus and hypophysis. The hypophysis awaits a signal from the hypothalamus to begin the release of LH (luteinizing hormone). This signal is the pulsatile secretion of the hormone GnRH (gonadotropin-releasing hormone). The release of LH stimulates the Leydig cells to produce testosterone. Testosterone has a significant effect on spermatogenesis as well as other functions throughout the body. Sertoli cells are stimulated by FSH (follicle-stimulating hormone), an important signal that allows for the maturation of germ cells. Sertoli cells secrete inhibin that is involved in the feedback mechanism (Holstein et. al., 2003).

## 3.5 Histochemistry and Cytochemistry of Spermatogenesis

The male reproductive organs, the testes, serve two primary functions in the human body, including the production of the male gametes, sperm cells, and testosterone, which is the primary male sex hormone. Located inside the testes are groups of convoluted tubules called seminiferous tubules, where sperm cell production takes place.

At embryonic day ten, the bipotential gonad is first visualized as a thickening of the mesonephros located on the ventral side. Gender specificity acquisition occurs over the next two days, primarily driven by “SRY” gene expression. Expression of this gene allows cells to differentiate and become the Sertoli cells, which are cells of the testis. In contrast with females, if SRY gene expression is absent, granulosa cells will form in a developing ovary. For sex determination to be complete and for male testis formation requires primordial germ cells to interact with embryonic Sertoli cells, myoid cells, and Leydig cells. This process occurs by embryonic day twelve and a half. Primordial germ cells appear within the epiblast at embryonic day six, where they undergo cell migration. They arrive and infiltrate the developing gonadal ridge at embryonic

day 11. Once the cells are in close approximation to one another, they can form the seminiferous cords, which eventually form the seminiferous tubules (Griswold, 2016).

The primordial germ cells undergo mitotic proliferation within the cords of an embryonic testis. They are then called prospermatogonia or gonocytes. After replication of this population of cells, prospermatogonia enter a dormant non-proliferative phase until birth in the rodent. The initial location of the prospermatogonia is closer to the center of the seminiferous cords; however, eventual migration occurs to the periphery after birth. Several essential processes arise at this location, producing the morphologically distinct spermatogonia.

Oocytes in females and sperm in males are derivatives of primordial germ cells. Their production is dependent on a derivative of vitamin A, known as retinoic acid. During fetal development in females, meiosis is initiated by germ cells in the ovary in response to retinoic acid. However, in the testis, germ cells do not receive the signal from retinoic acid. Hence meiosis is not initiated until after birth. The period corresponds to the resumption of male germ cell proliferation and the transition to spermatogonia. Eventually, spermatogenesis occurs, and haploid spermatozoa get created (Endo T., 2019). Sertoli cells produce and secrete an essential regulatory factor called glial cell-derived neurotrophic factor (GDNF). GDNF is critical to the survival and proliferation of the undifferentiated spermatogonia (Griswold, 2016).

## 3.6 Pathophysiology

Occasionally, the seminiferous tubules may contain tumor cells in the basal compartment instead of healthy spermatogonia cells. They can be seen on histological sections differing from spermatogonia due to their noticeable larger size, prominent nucleolus, increased glycogen content, and characteristic peripheral border. The presence of these neoplastic cells attribute to carcinoma-in-situ and can lead to hypo spermatogenesis. The carcinomatous cells characterize the stem cell population for many and most germ cell tumors. Examples include seminomatous as well as trachomatous tumor types. During active spermatogenesis, the tubules may give rise to sporadic tumor cells. However,

spermatogenesis ceases as the cancer cells increase in number, and this results in detachment of the remaining spermatogonia, which then enters the tubular lumen. With the continuous proliferation of the cancer cells, they are also eventually released into the tubular lumen or penetrate the lamina propriety of the seminiferous tubules leading to the formation of inter-tubular tumor cell cluster s(Holstein et. al., 2003). PLAP, which is placental-like alkaline phosphatase, is an immunohistochemically marker used to diagnose pervasive carcinoma in situ. It is manifested exclusively in these carcinomas in situ cells. A score-count system evaluates the histology of the cancer cells and other techniques used for protein and mRNA expression. Testicular biopsies are also recommended and should undergo completion in specialist centers (Bergmann, 2005)

Meiosis is a convoluted process that is vulnerable to many faults and defects. Apoptotic spermatocytes can arise in the process and are known to be frequent. Megalospermatocytes, which are very large spermatocytes, can sometimes appear. In these cells, homologous chromosomes fail to pair in a process called asynapsis, causing the cells to become abortive. Moreover, spermatogenesis can come to a halt at the stage of primary spermatocytes, stopping the morphological changes from occurring in the cells. Primary spermatocytes are seen to border the lumen of seminiferous tubules. They will not develop any further, which will lead to the disintegration of the cells and lack of spermatids production (Holstein et. al., 2003).

The structure of the sperm tail closely resembles the motile cilium in that the axonemal has a 9+2 micro tubular arrangement. Therefore, genetic defects detected in motile cilia can significantly affect the formation of the sperm tail. A genetic disease called PCD (primary ciliary dyskinesia) due to the malformation of motile cilia causes pulmonary disease, increased risk of infections, and male infertility. Many genes are associated with PCD; however, the exact effect these mutated genes have on spermatogenesis is still investigational (Sironen et. al., 2020)

A study on using testicular histology determining the effects of aging on spermatogenesis showed various alterations, including basal membrane thickening, a decrease in the germinal and Sertoli cell number, as well as an exhibition of individual variations. Upon examination of post-meiotic cells, the aneuploidy rate was higher than average during the arrest of spermatogenesis. However, they

concluded that spermatogenesis could still be possible until the male is 95 years old (Dakouane et. al., 2005)

## 3.7 Clinical Significance

In diploid organisms, sexual reproduction requires the union of two haploid gametes. Currently, there are many different methods available for assisted reproduction, founded as a result of the knowledge we have on spermatogenesis. The identification of mature spermatids and spermatozoa occurs through specific morphological processes (Holstein et. al., 2003). Induction of pregnancies can occur through specialized techniques that extract spermatozoa from testicular tissue, followed by injection into the cytoplasm of the ovum. These techniques can significantly enhance and develop the assisted reproductive technologies available today.

# Chapter Four

## Lead Effects on Spermatogenesis

## 4.1 Introduction

Many industrial chemicals are known to have a negative impact on human reproduction (Lahdetie J., 1995), particularly occupational and environmental exposures to heavy metals such as lead. The risk is generally believed to be directly correlated with both increasing concentrations and duration of exposure (Alexander et. al., 1998). At its simplest, increased blood lead levels of 12.5μg/dl versus 6.0μg/dl, have been observed among infertile men when compared to fertile men, respectively (Pant et. al., 2003). Similarly, epidemiological studies on male workers with blood lead levels ranging from 10 to more than 40μg/dl have been shown to increase the risk of infertility (Sallmen, 2000). A study of more than 4000 male workers with blood lead levels higher than 25μg/dl, for example, demonstrated a reduction in the number children when compared to 5000 control subjects (Lin et. al, 1996).

Experimental animal studies, mainly in rats, have also reported that lead is an active element responsible for male reproductive parameter imbalances (Nathan et. al., 1992). On the other hand, a multi-country (Belgium, Finland, Italy, and England) investigation found no association between occupational exposure to lead and lower fertility rates when blood lead concentrations ranged from 29 to 37μg/dl. In addition, studies on lead battery workers were unable to confirm the effects of lead on male fertility among French, Danish and Taiwanese workers with blood lead concentrations of ≤29μg/dl. Although the evidence is not conclusive, a threshold for adverse reproductive effects in men might be in the blood lead range of around 30 to 40μg/dl. Nevertheless, lead's adverse effects on male reproductive function, particularly at low levels (<10μg/dl), has still not been adequately reviewed. Approximately 15% of couples attempting their first pregnancy meet with failure, and contemporary data suggests that male-related factors are responsible for around half of all infertility cases (Oehninger, 2000).

Because human sperm count, normal morphology and functions appear to be in decline (a situation that may potentially jeopardize male fertility) increasing attention has been paid to male reproductive problems in recent years (Oehninger, 2000). On the other hand, an important component of male infertility of unknown etiology may be attributable to environmental and occupational to various

chemical exposures (Oehninger, 2000).. In this article, we provide an overview of epidemiological and experimental studies published in English up to December 2009, available on PubMed (U.S. National Library of Medicine) and that addressed lead toxicity on the male reproductive system. The article is divided into three parts; 1) Spermatogenesis, 2) Sperm functional parameters, and 3), Hormonal disruptions. Our review also elucidates the most likely responsible mechanism of lead on the male reproductive system, as this is still not clearly understood.

## 4.2 Spermatogenesis

The most frequent causes of male infertility are associated with spermatogenesis. Because it is relatively easy to conduct, non-invasive and inexpensive to perform, semen analysis (sperm count, semen volume, sperm morphology and assessments of functional parameters) is one of the first laboratory tests commonly performed for infertile couples. Studies on occupationally lead-exposed men have shown multiple sperm parameters being affected as seminal plasma or blood lead concentrations rise, usually at levels of >40μg/dl, but sometimes even at levels of <10μg/dl. For instance, reductions in sperm count and sperm concentration or density (Alexander et. al., 1998), decreased volume of ejaculation, as well as correlations with asthenospermia, hypospermia, and teratospermia (53μg/dl) (Benoff et. al., 2003) have been reported in male workers. Furthermore, higher percentages of immature and abnormal spermatozoa such as wide, round, and short sperm in lead exposed workers have been reported at both high (40μg/dl) and low (<15μg/dl) blood lead levels (Oehninger, 2000)..

Many studies on reproductive system of male animals have documented lead as a toxicant for testicular tissue and functions (Hsu et. al., 1998) such as significant reductions in the number of spermatozoa within the epididymis in mice administered lead acetate (0.25% and 0.50%) in drinking water (Wadi and Ahmad , 1999) and halted spermatogenesis in rats (Batra et. al., 2001). Many studies suggest spermatogenesis problems caused by lead, although, some researchers have failed to demonstrate correlations between lead and semen volume, pathologic sperm and sperm concentration among workers exposed to high lead

levels (Benoff et. al., 2003), or abnormalities in sperm count and/or the sperm morphology in rabbits (Willems et. al., 1982).

Macroscopic changes in accessory sex organs such as diminished weight of testes, seminal vesicles, epididymis, and ventral prostate have been demonstrated in various studies using experimental animals (Sokol, 1990). Microscopic changes, histological as well as macroscopic ones, have been induced by increasing lead levels in lead exposed male rats including changes in the testicular tissues morphology (Batra et. al., 2001), and decreased germ cells layer population (Batra et. al., 2001). In addition, two studies conducted on lead exposed mice demonstrated seminiferous tubule degeneration, and seminal abnormal cytology. Similarly, electron microscopic analysis has revealed that lead-exposed monkeys, when exposed during infancy, can induce testicular alterations, which persist in later life even when blood lead concentrations had decreased considerably. Due to ethical limitations, many studies on reproductive organs have been performed using high lead levels with experimental animals, which have revealed lead's effect at the cellular level.

## 4.3 Sperm functional parameters

Successful fertilization of an ovum by spermatozoa depends not only on sperm count and morphology but is also relevant to functional parameters. Lead has been shown to incur detectable negative effects on blood, semen and/or spermatozoa quality in workers, such as inducing prolonged liquefaction time and decreasing sperm motility (Benoff et. al., 2003). It has been negatively associated with sperm motility and viability (blood lead levels $\leq 10$ µg/dl) , and a reduction in the functional maturity of sperm among men with mean blood lead levels of 45µg/dl (Sokol, 1990).

On the other hand, concomitantly, significant improvements in the number of motile sperm has been reported after mean blood lead decreased from 42 µg/dl to 20 µg/dl among the lead factories workers . Reduced semen quality such as prolonged latency of semen melting have also been reported amongst lead exposed workers, without directly measuring blood and/or semen lead concentrations. As a general rule however, numerous studies have demonstrated that sperm functional disorders induced by lead, are related to the sperm's interactions with oocytes and

implantation, such as premature acrosome loss (Benoff et. al., 2003), and strong negative correlation between seminal plasma lead levels and artificial insemination rates in humans (Queiroz and Waissmann, 2006).

Two studies of mice and one of rats, have shown that there may be a dose-dependent decrease in the number of sperm attaching to ova (54), reducing the ability of spermatozoa to penetrate the corona radiata and the zona pellucida of the oocyte (Benoff et. al., 2003), and an increased frequency of post-implantation loss of embryos (at 0-2 µg/ml lead acetate, 40 µg/dl blood lead levels and 25-50 mg/kg in chow, respectively). According to these results, lead significantly induces the sperm function disorders in exposure cases before and after ejaculation.

## 4.4 Hormonal disruption

Reproductive hormones play an important and complicated role in the regulation of spermatogenesis and sperm development. The results of experimental studies in rats have shown that the effects of lead involve multiple sites on male reproductive hormones although the most important part of these disorders probably occurs in the hypothalamic-pituitary-testosterone (HPT) axis. For example, depending on lead exposure levels and duration, signals within and between the rat's hypothalamus and pituitary gland appear to be disrupted by lead . In a study of lead-exposed rats hyper responsiveness to stimulation with both gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) was demonstrated (Queiroz and Waissmann, 2006).

Another study on male rats administered lead acetate in water showed a dose-related increase in GnRH mRNA and no effects on the serum concentrations of hypothalamic GnRH or LH, suggesting there may be a compensatory mechanism in the HPT axis. In addition to animal experiments, McGregor (1990) reported a positive correlation between serum LH levels and duration of occupational lead exposure (Queiroz and Waissmann, 2006), a finding which was confirmed one year later in another study of workers with mean blood lead levels of 35µg/dl (Benoff et. al., 2003).

Testosterone, the main male sex hormone, is formed and secreted by Leyding cells in testes in response to stimulation by of LH. Semen lead concentrations at a mean of 2 µg/dl have been reported to be inversely related to serum testosterone among occupationally-exposed men (Alexander et. al., 1998).

Suppression of testicular testosterone levels and increasing steroid binding globulin levels related to increased duration of exposure to lead has been also demonstrated among mice exposed to lead for 30 days. The suppression of testosterone levels in the epididymal cells and increased androgen binding protein levels of rats have been also noted (Nathan et. al., 1992). However, there are some reports describing increased serum testosterone concentrations on lead exposed men from low (median 5 μg/dl)) to relatively high (more than 40μg/dl) blood lead levels.

These findings suggest that it might involve other hormonal and/or hormonal feedback pathway(s) than disruption of testosterone secretion in the reproductive hormonal axis by lead, such as a lack of reflex in response to plasma testosterone, direct inhibitory androgen biosynthesis in Leydig cells , or defects in LH regulation at the pituitary level (Sokol, 1990). Molecular mechanisms underlying histopathological examination have revealed disturbance degeneration in Leydig cells among rats, thereby suggesting Leydig cells as a target for lead intoxication.

On the other hand, due to imbalances in the HPT hormonal axis induced by lead exposure, pituitary cells release inappropriate levels of LH and change the steroid negative feedback loop, usually at the hypothalamus level . Increased concentrations of other reproductive hormones, such as follicle stimulation hormone (FSH), secreted from the pituitary gland, have been observed following lead exposure in men and in lead treated rats. However, unchanged concentrations between workers exposed to high and low-levels lead and unmodified levels in mice treated lead with acetate in drinking water (Sokol, 1990) have also been shown. These differences in FSH secretion levels might relate to differing lead levels and/or the duration of exposure among subjects.

On the other hand, inappropriate inhibin B overproduction in excessively lead exposed subjects may be induced by a Cell of Sertoli dysfunction, which suggests spermatogenesis impairment. On the other hand, research on male monkeys has shown that alterations in Sertoli cell function may occur due to decreases in inhibin/FSH (Benoff et. al., 2003), rather than by a direct effect on the cells. Such findings are consistent with a failure to find significant microscopic alterations in rat's Sertoli cells, except for increased lysosomal size, verified by ultrastructural examination on the rats' cells (Nathan et. al., 1992). Thus, the Sertoli cells may be not a direct target of lead toxicity and lead's effects on FSH

disruption is the more likely cause of reproductive dysfunction rather than by a direct effect on the cells.

## 4.5 Mechanisms of lead reproductive toxicity

At a conceptual level, the mechanisms of lead toxicity on male reproductive system have not yet been fully elucidated. There are a number of probable pathways to explain how lead exposure may reduce male fertility. For instance, multiple calcium and potassium channel isoforms in human testes and spermatozoa, may be involved in early events of acrosome reactions (Vigeh et. al., 2006). In addition, some enzymes activities, such as alkaline phosphatase and sodium potassium ATPase, have been shown to be reduced in the reproductive organs of lead-exposed rats (Batra et. al., 2001). Another issue in lead's reproductive toxicity might relate to the excessive generation of *Reactive Oxygen Species* (ROS), an issue which has been paid more attention recently. ROS inhibits the production of sulfhydryl antioxidants, inhibits enzyme reactions, damages nucleic acids and inhibits DNA repair, as well as initiating lipid peroxidation in cellular membranes. Lead induces oxidative stress and promotes the generation of hydrogen peroxide (Vigeh et. al., 2006).

The negative wide-ranging of effects due to an increase of ROS levels in tissues have been postulated as a major contributor of disorders related to lead exposure. An epidemiological study of the male reproductive system has demonstrated positive correlations between seminal plasma lead and spermatozoa ROS levels (Benoff et. al., 2003).On the other hand, in people with protracted exposure to lead, increased activity of superoxide dismutase has been observed, which suggests an adaptive mechanism against the increased amount of ROS production induced by lead (Queiroz and Waissmann, 2006). This may result in oxidative cell in the damage in reproductive tissues closely associated with ROS production. For example, a study on rat sperm exposed to ROS *in vitro* has demonstrated premature acrosome reactions and reduced penetration rate in the zona-intact (Vigeh et. al., 2006).. However, from low to high doses, there are known to be different responses of lead-induced oxidative stress in various target sites, including sperm (Wadi and Ahmad, 1999). Studies on lead-exposed rats have demonstrated that lead influences sperm function, decreases serum testosterone levels and produces early onset of capacitation by activating pathways of ROS generation (Benoff et. al., 2003). Additional evidence where rats were chronically exposed to lead has reported an elevation in the concentration of lipid peroxide in

reproductive organs (Batra et. al., 2001). Results of studies suggest therefore, that lead-induced ROS is an important molecular mechanism for male reproductive disorders, either in the hormonal stages or during spermatogenesis.

## 4.6 Conclusion

Examination of experimental data from both epidemiological and animal research suggests that lead in different concentrations has a wide spectrum of toxicity on the male reproductive system, including spermatogenesis, sperm functional parameters and reproductive hormones. Although unfavorable reproductive effects usually occur at relatively high levels of lead exposure, lower doses for longer time periods may also alter the male reproductive system in a manner similar to that previously reported at higher doses for shorter periods. Furthermore, regarding dosage level and duration of exposure, there are other potential factors to consider such as individual differences, social conditions, and various environmental factors. As a result of these numerous, potential confounders, it has not been easy nor straightforward to quantify which organ or pathways are involve in lead's adverse effects on male fecundity.

Although, reproductive tissues represent one critically sensitive organs to toxic substances such as lead, some studies have actually failed to demonstrate significant correlations between increased lead concentrations and impairment of the gonads. Additionally, low lead concentrations in the testis, seminal fluid, and epididymis have demonstrated that the blood-testis barrier may protect testicular cells from direct exposed to the high levels of blood lead. As such, there might be other pathways which reduce spermatogenesis among lead-exposed males. Or, on the other hand, spermatogenesis disorders are not completely predictable.

Thus, according to wide spectrum effects of lead at different concentrations on reproductive hormones and the priority of hormones for growth, development, and function of the sex organs and spermatogenesis, the present review suggests that lead's effects the male reproductive system most likely by disrupting hormonal regulations, mostly via the HPT axis, then reduces sperm production in seminiferous tubules of the testes.

The present review of lead toxicity on the male reproductive system also suggests that hormonal disruption might occur at lower levels of blood lead. Despite such findings, it has not been easy to definitively ascertain the correlation

between lead exposure, male fecundity and probable mechanisms of infertility. For these reasons and perhaps because high levels of lead exposure might affect many organs in various ways, aside from the reproductive system, contemporary research has begun to shift more towards studies of low level exposures-particular with blood lead concentrations below the currently accepted worker protection criteria (<10μg/dl) as they may still adversely affect male fertility.

As such, occupational health surveillance must continue to include the assessment of adverse effects on the reproductive system of lead-exposed workers, particularly those with significant environmental exposures. Because laboratory findings cannot definitively ascertain fertility status, this review suggests that future studies should aim to establish more concrete links between lead's effects on reproductive dysfunctions and reduced fertility rates; not only changes in hormonal or sperm characteristics among lead-exposed subjects.

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## الخلاصة

عملية تكوين الحيوانات المنوية، العملية المعقدة لتطوير خلايا الحيوانات المنوية، عرضة للتأثيرات الضارة للملوثات البيئية، من بينها خلات الرصاص التي برزت كمصدر قلق بارز.

تقوم هذه الدراسة بفحص تأثيرات خلات الرصاص على عملية تكوين الحيوانات المنوية من خلال تجميع البيانات التجريبية والتحليل الميكانيكي. يخترق خلات الرصاص، الملوث البيئي الشائع، الجهاز التناسلي للذكور، مما يؤدي إلى اختلال العمليات الخلوية الأساسية الضرورية لإنتاج الحيوانات المنوية بشكل طبيعي.

من خلال مسارات معقدة، يعيق خلات الرصاص تمييز الخلايا الجنينية، ويضر بوظيفة خلايا سيرتولي، ويعطل التوازن الهرموني، ويثير الضغط الأكسدة داخل البيئة الداخلية للخصية. ينعكس هذا الاضطراب في التشوهات الخصية، وجودة الحيوانات المنوية المنخفضة، والعقم الذكوري المضطرب. علاوة على ذلك، تشير تأثيرات خلات الرصاص عبر الأجيال إلى مخاطر طويلة الأمد على الصحة التناسلية عبر الأجيال.

وبشكل هام، تسلط هذه الدراسة الضوء على استراتيجيات علاجية ناشئة، بما في ذلك التكميل بمضادات الأكسدة، وعلاج الكيلة، وتحسين البيئة، بهدف التخفيف من التأثيرات السلبية لخلات الرصاص على عملية تكوين الحيوانات المنوية. ومع ذلك، يظل الوقاية الفعالة هي الأهم، مما يؤكد على ضرورة التنظيمات الصارمة لتقليل تعرض الإنسان لخلات الرصاص في السياقات المهنية والبيئية والغذائية. في المجمل، تؤكد هذه الدراسة على ضرورة الجهود التعددية لمعالجة الآثار الصحية العامة لتعرض الإنسان لخلات الرصاص على وظيفة الإنجاب للذكور والخصوبة.

وزارة التعليم العالي والبحث العلمي
الجامعة التقنية الوسطى – معهد تقني الكوت
قسم تقنيات المختبرات الطبية
الدراسة المسائية

# تأثير التسمم بالرصاص على تخليق الحيوانات المنوية

بحث مقدم الى الجامعة التقنية الوسطى – معهد تقني الكوت – قسم تقنيات المختبرات الطبية كجزء من متطلبات الحصول على درجة الدبلوم التقني في المختبرات الطبية

من اعداد الطلبة :

سجاد هاشم محمد
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سجاد صالح

بإشراف :

المدرس المساعد

مهند ساجت

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