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Review Article

Role of Zinc in Reproductive Biology - An Overview

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Abstract

Trace amount of certain metals including zinc are essential for the normal growth, development, reproduction and various other physiological functions in the body. However, their appropriate amount is needed for maintaining steady state mechanism of various functions in the body. Some of the heavy metals even at a very low level are having toxic potential, which might be dependent upon the dose, time and duration of exposure as well as factors associated with host. The available data on zinc level in serum and seminal plasma suggests that zinc has a significant role in spermatogenesis and maintaining the total number of sperms as well as sperm motility and DNA integrity etc. However, significantly higher level (several times of normal level) of zinc may have adverse effects on sperm quality. Zinc is also essential for female reproductive system including embryogenesis and development. Thus deficiency or excess of zinc level might have significant impact on sperm and egg physiology. Zinc has also been involved in antagonizing the effect of various toxicants. Further, data also point the role of zinc supplementation may be useful as one of the adjuvant components for the subjects having sub normal reproductive function with lower seminal zinc level. However, more research is needed on this aspect, as some of the conflicting data also existed.

Keywords: Zinc; Reproduction; Spermatogenesis; Sperm motility; Sperm concentration

Introduction

Human beings as well as aquatic and wild life species are exposed to certain metals and their oxides, through various sources. Some of these metals are toxic to health including reproductive health and few are essential in trace amount for various physiological functions of the body. Thus trace amount of these assisting in maintaining health of various organ systems. All the stages of spermatogenesis and oogenesis would be the potent target of chronic exposure to even low doses of toxic metals. Zinc is reported to be necessary for DNA replication, RNA polymerases, protein synthesis and various metabolic processes. The cell replication, protein synthesis and growth processes etc. are reported to be to some extent dependent upon zinc [1]. Further, zinc is also included in many nutritional supplements [2]. Zinc is a vital trace element found in small amounts in a variety of cells and tissues of organisms and it is a cofactor of more than 300 enzymes reported by Tapiero and Tew [3], and zinc is also involved in several cell functions including signal transduction, transcription and also replication [4]. Further, it has been reported that about three to ten percent of all proteins in mammalian genomes are considered to bind zinc for holding, activity and conformational changes [5].

It is known that the adult human body have about 1–3 g of zinc, and about 0.1% of which is replenished daily [6]. Zinc is recognized as an essential food element required by the body in trace amounts. It is also known that very little zinc in the diet can lead to poor health, reproductive problems, and lowered ability to resist against disease and lot of zinc in diet may also be unfavorable to health [7]. Higher doses of zinc also have the cyto-toxic potential in mice reported by Gupta et al. [8]. Further, the level of zinc that bring health impairments are much higher than the Recommended Dietary Allowances (RDAs) i.e. 11 and 8 mg/day zinc for men and women respectively. If 10-15 times of RDA of zinc are taken even for a short time, it may lead to stomach cramps, nausea, and vomiting. Further, ingesting high levels of zinc for several months may lead to anemia, damage pancreas, and decrease levels of high-density lipoprotein (HDL) cholesterol [9]. It is known that both animals and humans are needed to produce healthy sperm and ova for continuing their species on this earth. This needs formation and maturation of spermatozoa, ova, fertilization, development and production of offspring. In order to achieve this, number of exogenous and endogenous favorable conditions is necessary for the successful of reproductive outcome for the continuation of the species. In this communication, an attempt has been made by analyzing the data available, on zinc and reproduction in order to understand the role of zinc in reproduction.

Material and Methods

In the present paper authors has tried to provide a current status on the role of zinc in reproduction. Searching various databases such as Pub Med, Toxline, Google and certain other websites as well as consulting various journals on reproduction and metal toxicology, assimilated the literature and made certain observations and conclusions. The paper is divided in to four broad headings based on the data available on human male and female reproduction along with relevant experimental studies, its role in in vitro fertilization and oocyte maturation and also data pertaining to understand the mechanism of alterations and preventive potential of zinc against certain reproductive toxicants is also discussed. The data on seminal zinc levels with respect to various seminal parameters has been depicted in Table1.

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Table 1: Correlation of Seminal Plasma Zinc Levels with Different Semen Parameters.

Sr. No	Parameters	Relationship	References
1	Sperm count	r = 0.66, p < 0.05	Madding *et al*. 1986
2	Sperm density	r = 0.6358, p < 0.01	Carreras and Mendoza, 1990
3	Sperm density	r = 0.41, p < 0.01	Xu *et al*. 1993
4	Motile spermatozoa	r = 0.0392, p < 0.0713	Lewis zones *et al*. 1996
5	Sperm concentration Sperm motility Plasma testosterone Sperm morphology	r = 0.33, p<0.05 r = 0.22, p<0.05 r = 0.24, p<0.05 no correlation	Fuse *et al*. 1999
6	Sperm density Sperm motility Sperm viability	r = 0.341, p < 0.0001 r = 0.253, p < 0.0001 r = 0.286, p < 0.0001	Chia *et al*. 2000
7	Seminal pH Other sperm characteristics (Sperm count, motility, etc.,)	r = -0.35, p = 0.0081 No significant correlation	Lin *et al*. 2000
8	Sperm count	r = 0.17 (weak correlation)	Wong *et al*. 2001
9	Sperm count	r= 0.31, p<0.05	Mankad *et al*. 2006
10	Semen volume	r = 0.54, p = 0.09	Meeker *et al*. 2008
11	Sperm count Duration of abstinence Semen volume Sperm motility, viability, morphology, spermatozoa-ZP binding or ZPIAR	r = 0.186, p < 0.001 r = 0.280, p < 0.001 r = 0.178, p < 0.001 No correlation	Liu *et al*. 2009
12	Sperm count Normal sperm morphology	p < 0.01 p <0.001	Colagar *et al*. 2009
13	Sperm progressive percents	r = 0.017, p = 0.885	Rasheed *et al*. 2009
14	Seminal pH	r = -0.193, p < 0.05	Dissanayake *et al*. 2010
15	Hyperviscoelasticity	Lower zinc in hyperviscoelastic samples (p<0.05)	Elzanaty *et al*. 2004

Zinc and male reproductive function

Male infertility can be explained, the incapability of a man to produce a pregnancy in a fertile woman, it is often caused by considerable deficiency in sperm production, concentration, sperm function, deterioration in morphology, sperm DNA damage and integrity and erectile dysfunction also. It is known that zinc is necessary for growth, sexual maturation and reproduction and various other physiological processes. Zinc in human semen might play a noteworthy role in the physiology of spermatozoa. The prostate in small vesicles called protasomes secretes it. Zinc in seminal plasma stabilizes the cell membrane as well as nuclear chromatin structure of spermatozoa. Further, it may also have an antibacterial function [10]. The zinc content of the prostate gland, the seminal fluid and ejaculated sperm are very high and testicular zinc is essential for spermatogenesis [11]. Kvist et al. [12] found a constructive relationship between zinc in sperm nuclei and the resistance of the chromatin to de-condense after exposed to a detergent. They also observed that the infertile men had lesser degree of sperm chromatin stability and lesser sperm zinc content than the fertile donors and suggested that a low content of nuclear zinc would damage the structural stability of the chromatin and thus increases the susceptibility of the male genome.

In a study using spermatozoa of fertile men, adding high zinc concentration (1 mmol L^{-1}) in the culture medium impaired sperm motility as well as sperm penetration of ZP-free hamster oocytes [13, 14]. Addition of zinc in to the culture medium during capacitation of spermatozoa, inhibited spontaneous acrosome reaction (AR) and also the AR induced by the calcium ionophore [14]. Further, seminal zinc concentration has been also linked with sperm count and the duration of abstinence in sub-fertile men whereas in men with normozoospermic semen, elevated seminal zinc concentration may have an undesirable effect on the zona pellucida-induced acrosome reaction [15]. However, earlier study had shown that the zinc level in seminal fluid and serum is not linked with silent male genital tract infection (indicated by seminal leukocytes). Further, it has also been reported that zinc concentration did not affect sperm capability to go through cervical mucus *in vitro* or *in vivo* [16].

A number of animal studies are available on different zinc compounds with respect to reproduction. Treatment of low (12 mg/kg) or medium (120 mg/kg) dose of zinc to rats appeared to improve reproductive function whereas high dose (240 mg/kg b. wt.) of zinc deteriorated the reproductive function [17]. An another study reported that the frequency of sperm with an altered chromatin structure was found to be increased in rats fed with 25 mg zinc/kg/day as zinc chloride for 8 weeks [18]. However, extremely high levels of zinc have been reported to have a detrimental effect on reproduction and its outcome. There are inconsistent reports regarding the levels of zinc in seminal plasma with respect to various semen quality parameters. Seminal zinc level has been reported to be correlated with duration of abstinence [15], volume [19], pH [20], sperm count [21-23], sperm morphology [24] as well as sperm density, motility and viability [25]. Further, Fuse et al. [22] reported a constructive correlation of zinc with sperm concentration, motility and plasma testosterone concentration while there was no link with sperm morphology. Recently, zinc level had shown to be reduced in infertile patients as compared to fertile subjects [26]. Earlier, Ali et al. [27] also reported that zinc might contribute to fertility through its important effects on various semen

parameters. It seems that the assessment of seminal plasma zinc level might be useful in management of infertile males. However, Carreras and Mendoza [28] reported a negative correlation of zinc with sperm motility. Another study had also shown that men with high total zinc intake had 50% lower frequencies of disomy X than the moderate zinc intake group and 39% lower frequencies than the low intake group. There were no steady association found between antioxidant or zinc intakes and sperm aneuploidy [29].

Xu et al. [30] also reported a positive correlation between concentrations of seminal plasma selenium (SeSP) and zinc (ZnSP) with sperm density in normospermic men but not in oligozoospermic men. In addition, Wong et al. [20] demonstrated a weak association between blood plasma zinc concentrations and sperm count, motility, and abnormal sperm morphology. Zinc and magnesium levels in seminal plasma also correlated weakly with sperm count, and copper concentrations in blood plasma with sperm motility. Turk et al. [31] has shown that the male partners of infertile couples had decreased level of anti-oxidative activity, selenium and zinc in their seminal plasma. Mankad et al. [23] from this laboratory estimated zinc and neutral α-glucosidase activity in seminal plasma and reported that the mean α-glucosidase activity was lowest among the azoospermic subjects with respect to oligozoospermic and normozoospermic groups. Mean zinc levels were also lesser among azoospermics compared to oligozoospermic and normospermic groups. A significant constructive correlation was found between zinc levels and sperm count and zinc and α-glucosidase activity in seminal plasma. Dissanayake et al. [32] showed that count, motility, viability, pH and viscosity are affected by seminal plasma zinc variations. They further concluded that seminal plasma total zinc per ejaculate is the better marker for assessing the relationship between zinc and semen quality. Another study had shown that the high molecular weight zinc binding properties is good index of sperm function rather than the total seminal plasma zinc levels [33].

Seminal Zn levels had shown to be poorer in the sub-fertile populations as compared to fertile group [25, 34] whereas no difference has been observed by other investigators [35-37]. Zinc has been shown to have membrane-stabilizing and antioxidant activity and to maintain sperm viability by inhibiting DNAases [38]. Zinc appears to be a effective scavenger of undue superoxide anions produced by defective spermatozoa and/ or leukocytes in human semen after ejaculation [39, 40]. Thus, it seems that seminal plasma, due to its high content of zinc, will exert protective, antioxidant-like activity sufficient to cope with the excessive amount of superoxide anions [41]. Colagar et al. [24] also mentioned that zinc has anti-oxidative properties and plays a significant role in scavenging reactive oxygen species. They have further assessed the relationship between Zn levels in seminal plasma with sperm quality in fertile and infertile men. Fertile subjects irrespective of smoking habit demonstrated significantly higher seminal Zn levels than infertile group. Lower Zn levels were observed in seminal plasma of smokers with respect to nonsmokers. Seminal Zn level in fertile and infertile males correlated significantly with sperm count and normal morphology. They further concluded that reduced Zn nutrition may be a significant risk factor for lower sperm quality and idiopathic male infertility. However, extremely high levels of zinc may inhibit sperm motility and the function of mannose receptor on the sperm head [10]. It has also been reported that high seminal Zn concentrations have a suppressing effect on progressive motility of spermatozoa [42]. Lewis Jones et al. [43] mentioned that zinc concentrations were not influenced by the motile sperm concentration and concluded that seminal plasma zinc is an unreliable marker of spermatogenic activity.

Hunt et al. [44] presumed the important role of zinc in testosterone production and its need in the spermatogenesis. They suggested that serum testosterone levels, seminal volume and total seminal zinc loss per ejaculate are susceptible to short-term zinc depletion in young men. Bedwal and Bahuguna [45] stated that, zinc, copper and selenium are vital metals in male and female reproduction. Zinc is high in the adult testis, while it is higher in prostate as compared to any other organ of the body. It was further suggested that zinc deficiency first impairs angiotensin converting enzyme (ACE) activity, which in turn leads to testosterone depletion and impairments of spermatogenesis. It is known that gonads are the rapidly growing tissues in the body, and some of the essential enzymes involved in nucleic acid and protein synthesis are zinc metallo-enzymes. Defects in spermatozoa are commonly observed in the zinc-deficient rat. Zinc is thought to help in extending the functional life span of the ejaculated spermatozoa [45]. Most of the studies indicate that zinc might play an important role in maintaining the normal male reproductive function. The inconsistent conclusions drawn in various studies may be reflective of different population groups as well as the variations in confounding factors such as age, smoking, dietary status, etc.

Zinc in female reproductive functioning

A few reports exist about the role of zinc in female reproduction. Experimental studies conducted by exposure of rats, mice, and guinea pigs to concentrations as high as 119.3 or 121.7 mg zinc/m^3 as zinc chloride smoke (which also contained other compounds) for 1 hour/day, 5 days/week, for 20 weeks. No adverse effects on the mammary glands, ovaries, fallopian tubes, or uteri were observed at 18 months [46] whereas preimplantation loss increased in rats those were fed with diets containing 200 mg zinc/kg/day as zinc sulfate on gestational days 0-18. However, when the rats received 200 mg zinc/kg/day 21 days prior to mating, no effects on implantation or other adverse reproductive effects were observed [47]. Dietary Zn supplementation throughout pregnancy has shown to protect against fetal dysmorphology and postnatal mortality caused by ethanol exposure in early pregnancy in mice [48].

Zinc requirements during pregnancy and lactation have been estimated from the zinc content of tissues accrued during pregnancy and the zinc content of milk secreted during lactation [49]. The estimated total additional zinc needed for pregnancy is reported to be ~100 mg [50]. In pregnant experimental animals, zinc deficiency has shown to limit fetal growth and, if severe, causes teratogenic anomalies [51]. Earlier Swanson and King [50] mentioned that low maternal serum Zn levels have been associated with pregnancy-induced hypertension, abnormal parturition, and congenital anomalies. During pregnancy, zinc deficiency causes a number of anomalies: spontaneous abortion, pregnancy-related toxemia, extended pregnancy or prematurity, malformations, and retarded growth [52]. The decline in the zinc levels has also been associated to haemodilution, decrease in zinc binding protein, hormonal changes during pregnancy [53] and decline in active transport of zinc from the mother to fetus [54].

The need for zinc increases in women with marginal zinc intakes during pregnancy and lactation because of the better demands for normal embryogenesis, fetal growth and milk secretion [55]. Among Chinese women, Yang et al. [56] reported that fetal growth and birth weight are directly associated to maternal zinc intake, while no relationship was observed between maternal zinc intake during lactation with infant height, weight, or weight gain from birth. Low plasma zinc concentrations have been reported to be associated with pregnancy related obstacles such as prolonged labor, hypertension, postpartum hemorrhage, spontaneous abortion and congenital malformation etc [57]. Pregnant women receiving 0.3 mg zinc/kg/day as zinc sulfate during the last trimesters of pregnancy did not exhibit any reproductive effects (no changes in maternal body weight gain, blood pressure, postpartum hemorrhage, or infection) reported by Mahomed et al. [58].

Little is known about the high levels of zinc affecting the babies or causing birth defects in humans. Rats those consumed very large amount of zinc were either infertile or after becoming pregnant had smaller babies. Too little dietary zinc may also cause poorly developed sex organs as well as retarded growth in men. Zinc deficiency in pregnant woman may have babies that have retarded growth [7]. Zinc insufficiency in the female can lead to complications such as impaired synthesis/secretion of FSH and LH, abnormal ovarian development, estrous cycle disruption, frequent abortion, extended gestation period, teratogenicity, stillbirths, complexity in parturition, pre-eclampsia, toxemia and inferior infant birth weights [45]. Goldenberg et al. [59] reported that daily zinc supplementation in women with reasonably low plasma zinc levels in early pregnancy is linked with greater infant birth weights and head circumferences, with the effect taking place mainly in women with a body mass index less than 26 kg/m^2. It has been shown in a study that maternal plasma zinc levels during antenatal care, labour and infant birth weight in the intrauterine growth retardation infant group were significantly lower than that in normal growth infants. They further concluded that measurement of maternal plasma zinc concentration in the third trimester of pregnancy would suggest mothers at higher risk of delivering intrauterine growth retard babies [60] indicating the importance of zinc in developing fetus. In a study from India, Garg et al. [61] reported that zinc supplements significantly improved foetal growth. The effect on birth weight was superior whenever the supplement initiated in the first trimester, than in the third trimester. Also, the gestational age of the infant increased more with longer periods of zinc supplementation; those who received the supplement from the first trimester had an average gestational age of 39.4 wk, while those supplemented only from the third trimester had a gestational age of 38.8 wk. Femur diaphysis length was superior in fetuses whose mothers received zinc supplements, and the differentiation tended to elevate with gestational age, suggesting the prospective importance of maternal zinc condition for fetal bone growth in humans [62].

Hambidge et al. [63] reviewed the pregnancy outcomes in women with acrodermatitis enteropathica and reported one abortion and two malformations out of the seven pregnancies suggesting the teratogenic effect of severe zinc deficiency on human fetus. Two pregnancies in a patient with acrodermatitis enteropathica were given sufficient zinc to maintain normal zinc concentrations throughout gestation and the pregnancy outcomes were found to be normal [64]. Contrary, to these findings, Iqbal et al. [65] found no relationship between infant birth weight and zinc status. The study by Osendarp et al. [66] on zinc supplementation and pregnancy outcome, found that increased zinc levels in zinc-supplemented mothers did not improve the incidence of LBW. In another study done on 54 women at parturition to determine the relationship between zinc levels and birth weight, it was found that the levels of zinc were higher in maternal blood of low birth weight babies than in those with normal weight babies [67]. The relationship has been shown between low infant birth weight ≤ 2000 g and maternal zinc deficiency as well as infant birth weight and infant zinc levels. Maternal age of ≤19 years has been associated with low infant birth weight and low maternal zinc levels whereas plasma zinc level in mother correlated with plasma zinc level is their offspring [68]. The zinc supplementation was reported to have no significant effect on prematurity, preeclampcia, premature rupture of membranes, stillbirth, gestational age, infant length and head circumference. Moreover, the incidence of low birth weight was significantly low in those under zinc than placebo. Also, pregnancy-induced hypertension and intrauterine growth retardation (IUGR) were observed only in the placebo group [69]. Tuormaa [70] suggested zinc supplementation as a treatment in all cases of anorexia, bulimia, immunodeficiency, alcoholism, and mental depression, both male and female infertility. Furthermore, an optimal zinc status before and during pregnancy is necessary to prevent congenital malformations, premature and low birth weight as well as small head circumference in the off springs.

Zinc in antagonizing the effect of toxicants

Zinc is a crucial element important for growth, the nervous system, as well as the immune system. Zinc insufficiency as well as its levels well over normal, due to high-dose treatment, demonstrated an impaired immune function [71]. Zinc is an essential trace element for humans taking role in electron transfer in many enzymatic reactions [72]. The beneficial role of zinc in providing protection against calcium-, lead-, cobalt- and mercury- induced testicular or other organ toxicity in experimental animals has been reported by various investigators [73-76]. Zinc increases hepatocellular metallothionein (MT) levels and because of their high affinity for metals, MT may play a physiologic role in the absorption, storage and metabolism of important trace metals such as zinc and copper, as well as in the detoxification of certain metals such as cadmium, mercury and chromium [77,78]. There are few reports based on experimental studies that zinc could protest the adverse effects of certain known reproductive toxicants. Zinc has a protective role against lead and cadmium induced toxicity in rats [79]. Saksena et al. [80] reported that Zn, if given prior to or within 2 hours of cadmium exposure, is capable of at least in part reversing harmful effects of cadmium on spermatogenesis, steroidogenesis and fertility of the male rat. Zhang et al. [81], studied role of zinc, copper and selenium on placental cadmium transport. Placental cadmium was significantly higher in women with lower levels of maternal blood zinc than in those with normal zinc levels. This suggests that maternal lower level of zinc might have some role in maintaining the higher levels of placental cadmium. Onyenmechi et al. [82] observed that chronic exposure to chromium VI produces a marked testicular toxicity, which can be prevented by concomitant zinc administration. Zinc could reduce adsorption of fluorine, with the result of decreased fluorine in the

body. Thus it antagonizes fluorotic toxicity by improving the activity of CuZn-SOD and antagonizing lipid peroxidation [83]. Further, appropriate zinc had shown to antagonize male reproductive toxicity of fluorine on molecular level by antagonizing lipid peroxidation, influencing reproduction endocrine, activity of enzyme, and Fas expression [84]. In addition, earlier studies also indicated that administration of zinc reduces the reproductive toxicity of ethanol [85], other metals such as cadmium and mercury also [86-88].

Zinc is essential for spermatogenesis and induction of hepatocellular metallothionein (MT), while it's pretreatment reported to protects animals and cells in culture medium from the acute Cd toxicity [89]. Paksy et al. [90] showed that Zn can induce a significant increase in FSH-supported progesterone synthesis while it was not able to protect against Cd-induced drop in progesterone production. They further concluded that Zn protected against Cd-induced sterility *in vivo*, but it failed to counteract the direct effect of Cd on steroid biosynthesis [90]. Heavy smoking has shown to be associated with low sperm count, motility, morphology and increased seminal cadmium levels. Zinc therapy improved sperm quality and increased seminal IL-4, but reduced TNF-alpha and IFN-gamma while a zinc-deficient diet led to high cadmium testicular accumulation comparable with those supplemented with cadmium [91]. They further concluded that zinc modulates the putative effect of cadmium through its enhancement of T-helper 2 cytokines expression and down-regulation of T-helper 1 cytokines.

Earlier Favier [52] reported the diverse effects of zinc that can be elucidated by its multiple actions on the metabolism of androgen hormones, estrogen and progesterone, together with the prostaglandins. Nuclear receptors for steroids are all zinc finger proteins. Zinc supplementation has already demonstrated beneficial in male sterility and has also been implicated in testicular development, testosterone synthesis and sperm maturation. Zinc also plays an important role in sexual development, ovulation and the menstrual cycle in females and has shown in reducing complications in pregnancy. Both folate and zinc have antioxidant properties that neutralize reactive oxygen species (ROS) [92] thereby maintaining antioxidant and oxidant balance.

Zinc in oocyte maturation/ *in vitro* fertilization

It has been known that an inadequate zinc level can alter gene expression as well as a range of cellular functions with severe consequences on animal health [5]. In the last few decades, major efforts have been made to determine the effect of trace elements on reproduction, but little is known about the role of zinc on the oocyte maturation. The mammalian oocytes are enclosed by cumulus cells that are coupled through gap junctions to the oocytes, during oocyte maturation [93]. These gap junctions connect one cumulus cell to other cell surrounding the oocyte. The function of this communication is to transport relatively low molecular weight molecules, ions, and amino acids to the oocytes [94, 95]. Consequently, this implicates a metabolic support for the oocyte. Moreover, Kim et al. [96] demonstrated that the presence of cumulus cells coupled to bovine oocytes, although was not necessary for nuclear maturation, but plays an important role on the subsequent capability of the oocytes for developing to blastocyst stage. Picco et al. [97] observed that during oocytes maturation, Zn had found to affect intracellular GSH content and DNA integrity of cumulus cells significantly, and improved preimplantational embryo development. They further concluded that optimal embryo development to the blastocyst stage was partially dependent on the adequate Zn concentrations [97].

There are reports which point out that zinc also has an important role in preventing generation of ROS during first embryonic cleavage division. ZnSOD, placed in the cytoplasm, is found in human oocytes and fallopian tubes [98, 99] and in the environment of the pre-implantation embryo: it is also there throughout the embryo's journey in the oviduct [100]. Zinc acts as a co-factor for the various enzymes, that includes carbonic anhydrase enzymes involved in the progression of methylation and deterrence of oxidative stress (Zn superoxide dismutase; ZnSOD) as well as metallothioneins (MT) detaining superoxide and hydroxyl radicals. It is the second-most abundant transition metal following iron and binds strongly to MT (cystine-rich proteins), in that way defending thiol groups and preventing their irregular interactions with iron, which generate free radicals groups. It also stabilizes DNA conformation by contributing in several DNA repair enzymes, especially vital during early embryogenesis reported by a number of investigators [101-103]. Earlier, Picco et al. [104] studied the impact of various zinc concentrations, on the DNA integrity of bovine cumulus cells *in vitro* maturation (IVM) of oocytes. They concluded that different levels of zinc concentration during IVM might have some role on early embryo progress. Later, Juan et al. [105] also studied the effect of zinc on cumulus cells (CC) during *in vitro* maturation and concluded that low Zn concentrations raise DNA damage and apoptosis in CC. However, it has been shown that, adequate Zn concentrations protect the integrity of DNA molecule and lessen the percentage of apoptotic CC. The acute accumulation of zinc during meiotic maturation implicate zinc as a probable player in the cytoplasmic maturation of the oocyte and the fluctuation in zinc during oocyte maturation had long-lasting effects on early embryonic development, connecting the metal ion as a important factor in the maternal legacy from egg to embryo. Thus the results obtained by Kim et al. [106] emphasize on the idea that inorganic physiology is critical in the making of a competent and mature oocyte that is able to sustain the early development of a new organism. Zinc plays a significant role in reproduction, via mechanisms that control genome stability and is an vital co-factor in the folate cycle, involved in the recycling of homocysteine to methionine, both of which have a foremost influence on methylation reactions through s-adenosyl methionine, which is formed in the oocytes and homocysteine impairs both methionine incorporation and normal methylation reactions [107]. Moreover, it has been observed that human oocytes have a very inadequate capability to recycle homocysteine, because the cystathionine β synthase (CBS) pathway is not present and the zinc dependent, betaine homocysteine methyl-transferase (BHMT) pathway, is expressed inadequately [107]. Further, oocytes have shown to express most of the zinc transporters, metallothioneins and metal regulatory transcription factor which may point out a significant role for zinc, in particular with potential linkage toward genome stability during early embryonic development [108].

On the basis of available data it can be inferred that zinc plays a positive role in both male and female reproduction, which depends upon the adequate concentration. Zinc may help in promoting proper cell division, which is necessary during conception, parturition, and

fetal development as well as in lactational stages. In male reproduction, zinc might be necessary for proper spermatogenesis and hormonal regulation, which thereby maintains the sperm quality essential for fertilization. Thus it can be suggested that zinc is important for sexual reproduction and development. However, the appropriate level of zinc is imperative for this aspect. Further, it is hypothesize that in the deficiency of Zn, the possibility of increased oxidative damage would contribute to poor reproductive health of both sexes.

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