



Some Teratogenic Outcomes in Rats Exposed to Zinc Chloride Pre and Post Pregnancy

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A B S T R A C T

The aim of present study was to evaluate the possibility of teratogenicity in rats when exposed to zinc chloride (ZnCl₂) pre and post pregnancy. To achieve this goal, a total of 40 mature Albino Wistar female rats were divided equally into four groups as follows: T1, dosed 0.7 mg/day ZnCl₂ for two months before mating and till to the day 5th of pregnancy, the females of this group were mated with males dosed 0.7 mg/day ZnCl₂ for two weeks before mating; T2, dosed 0.7 mg/day ZnCl₂ for two months before mating and till to the day 16th of pregnancy and then were mated with control males (not exposed to any level of ZnCl₂); T3, dosed 0.7mg/day ZnCl₂ for two months before mating and till the end of pregnancy and were mated with control males; Control, dosed with water free from ZnCl₂ along the period of experiment and were mated with control males. At the end of each pregnancy phase, results revealed that alpha fetoprotein serum levels were significantly ($P<0.05$) higher in all treatment groups compared to the control group, and the most prominent increase was observed in the T3 group. All treatment groups showed a significant ($P<0.05$) decrease in gestation, viability, and lactation indices when compared to the control group, with the T3 group showing the most significant decrease. Additionally, on days 1, 4, 7, 14, and 21 of lactation period, there was a significant ($P<0.05$) decrease in mean pup body weights in treated groups compared to the control group, with T3 group having the most prominent body weight decrease. The findings of this study revealed that ZnCl₂ at a daily dose of 0.7 mg may cause teratogenic defects in rats at various stages of pregnancy, particularly at the third stage. As high-risk groups, pregnant women and children should use Zn supplementation carefully, whether as a food additive or for self-medication. Simultaneously, evaluating effect of low-dose Zn supplementation over a longer duration is required.

Keywords: zinc chloride, rat, teratogenicity, gestation, lactation, pups

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INTRODUCTION

Heavy metals, either being essential or non-essential nutrients, can be hazardous at certain levels as they are not biodegradable and hence have a high potential for

bioaccumulation. Bioaccumulation in a biological organism describes an increment in a chemical concentration through time comparing to the concentration in the environment (1). When compounds are taken up and stored more rapidly than they are metabolized or excreted,

they may build-up and persist in living organisms. Toxicity of heavy metals may cause mental and central nervous system damage, as well as lower energy levels and damage to the liver, kidneys, lungs, composition of blood, and other major organs (2). Long-term exposure has been shown to mimic Alzheimer's disease, Parkinson's disease, muscular dystrophy, and multiple sclerosis by inducing slow physical, muscular, and neurological degradation. Allergies are prevalent, and prolonged exposure to certain metals, or their compounds can result in cancer (3).

Zinc chloride and its hydrates are chemical substances with the formula $ZnCl_2$. Textile processing, metallurgical fluxes, chemical synthesis, and medical usage are only a few of the applications for $ZnCl_2$ (4). The main routes of $ZnCl_2$ exposure include oral, dermal, and inhalation. CRIP, a cysteine-rich intestinal protein that sequesters zinc (Zn) inside enterocytes before active transport into plasma, is responsible for gastrointestinal zinc absorption (5). Zn^{2+} absorption is influenced by nutritional status, with calcium, phosphorus, and phytic acid inhibiting Zn absorption, whereas dietary protein facilitates it. It has been reported that rats absorb around 8% to 10% of the dietary Zn, with the majority excreted in the faeces (6). The rat's placental barrier can be crossed by Zn. Wilson et al. (7) reported that when pregnant C57Bl/6 J female mice were fed 10 mg/kg Zn, the amount of Zn absorbed within 24 h by the entire fetus increased as a function of application time of pregnancy (between days 15-21). Numerous animal studies on the effects of various Zn compounds on reproduction are available. Grzeszczak et al. (8) showed that the effect of Zn is dose dependent, where reproductive performance in rats was improved when received Zn at 12 mg/kg BW (low dose) and 120 mg/kg BW (medium dose) whereas a dose of Zn at 240 mg/kg BW had a deterioration effect.

We have found that zinc excessive intake through water and, or feed caused various teratogenic defect in human and animal. We have previously detected various levels of Zn compound in Iraqi body water such as the Tigris, the Diyala River, and the Shatt al-Arab, thus we are planning to investigate the teratogenic effect of $ZnCl_2$ in rat model.

MATERIALS AND METHODS

Chemicals

$ZnCl_2$ (99.99% purity) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and stored at room temperature. Xylene and ketamine for anesthesia were purchased from BDH (England). Methylene blue for vaginal smear was purchased from Promega (USA). For alpha fetoprotein assessment, a kit was purchased from MyBioSource® company (USA).

Animals of Study

The study was carried out with the approval of the Scientific Committee in the Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq in accordance with ethical standards of animal welfare.

A total of 40 mature female and a certain number of male Albino Wistar rats of variable ages (2-3 months) and weights (180-230 g) were obtained, housed, and maintained at Animal House, College of Veterinary Medicine, University of Baghdad on $22-24^{\circ}C \pm 2^{\circ}C$, relative humidity 50%-55%, and a 14 h:10 h light-dark cycle (5 a.m. to 7 p.m., lights on). For two weeks, animals were acclimatized and both water and standard diet were provided *ad libitum*. All animals received $ZnCl_2$ at a dose of 0.7 mg/rat/day, estimated based on the rats' daily water intake of polluted water. Animals were divided randomly into four equal groups and certain number of adult male rats have been involved and assigned as follows: T1, adult females were dosed 0.7 mg daily $ZnCl_2$ for two months before mating and till the day 5th of pregnancy and mated with male dosed 0.7 mg daily of $ZnCl_2$ for two weeks before mating; T2, dosed 0.7 mg daily $ZnCl_2$ for two months before mating and till the day 16th of pregnancy and then mated with control male (not exposed to any level of $ZnCl_2$); T3, dosed 0.7 mg daily $ZnCl_2$ for two months before mating and till to the end of pregnancy and were mated with control male (as in T2); Control, dosed with water free from $ZnCl_2$ along the period of experiment and were mated with control male).

Insurance of Pregnancy

The pregnant female rats were examined daily after conception for five days. Vaginal smears stained with methylene blue were prepared to detect di-estrus phase. Pregnancy was detected by observation pale mucous membrane of vagina in the third day after conception (9).

Blood Samples

Blood samples were obtained from anesthetized rats, administered i.m. ketamine and xylazine at 90 mg/kg BW and 40 mg/kg BW, respectively, using the heart puncture technique. Blood samples (approximately 2 mL) were collected and kept in tubes for 10 min before being centrifuged at 2500 rpm for 15 min. Sera were collected, aliquoted, and refrigerated ($-20^{\circ}C$) until they were analyzed.

Parameters

Alpha fetoprotein

Assessment of alpha fetoprotein (AFP) was performed at the end of each phase of pregnancy according to (10). A

commercially available kite (MyBioSource® Company, USA) was used for measurement.

Gestation index (%)

Gestation index (GI%) was calculated according to (11) as following:

Gestation index= percentage of pregnancies resulting in live litters

Lactation index (%)

Lactation index (LI%) was calculated as the percentage of the offspring alive at day 4 that survived till the day 21st of lactation period (11).

$$\text{Lactation Index (\%)} = \frac{\text{No. survival neonates (days 5 - 21)}}{\text{Total No. remaining of neonates}} \times 100$$

Viability index (%)

Viability index (VI%) of the offspring for 1-4 day after parturition was calculated according to (11) as follows:

$$\text{Viability Index (\%)} = \frac{\text{No. offspring alive till day 4}}{\text{Total No. offspring}} \times 100$$

Body weight offspring (g)

Body weight was measured after the offspring were born (the total weight of the brood divided by the number).

Statistical Analysis

The general linear model (GLM) approach in SPSS software version 22.00 (IBM SPSS Inc., Chicago, IL, USA) was used to analyze the collected data as a one-way ANOVA. At $P \leq 0.05$, the Fisher's least significant differences (LSD) post hoc test was used to separate the means (13). The results are presented as a mean \pm standard error of the mean (SEM).

RESULTS AND DISCUSSION

Alpha Fetoprotein

The result of AFP showed significant differences ($P < 0.05$) between all groups of the experiment at the end of each phase of pregnancy. There were significant increases ($P < 0.05$) in alpha fetoprotein of T1, T2, and T3 groups compared with control group, but the most prominent increase was observed in the T3 group which has dosed 0.7 mg daily ZnCl₂ for two months before mating and till the end of pregnancy (Table 1).

Gestation, Lactation, and Viability Indices

The current results showed that there was a significant ($P < 0.05$) decrease in GI%, VI%, and LI% in all treated groups as compared with control group, also it showed a significant difference between the treated groups (Table 1).

Table 1. Alpha fetoprotein (AFP ng/mL), gestation index (GI%), viability index (VI%), and lactation index (LI%) of Albino Wistar female rats treated orally with 0.7 mg/day zinc chloride at different phases of pregnancy¹

Group	Reproductive parameters			
	AFP (ng/mL)	GI (%)	VI (%)	LI (%)
T1	20.13 \pm 0.20 ^c	82.50 ^b	91.3 \pm 1.94 ^a	89.60 \pm 1.08 ^b
T2	24.68 \pm 0.34 ^b	62.80 ^c	83.9 \pm 0.94 ^b	82.00 \pm 0.90 ^b
T3	30.22 \pm 0.16 ^a	58.70 ^d	69.5 \pm 0.45 ^c	75.70 \pm 0.76 ^c
Control	15.50 \pm 0.25 ^d	100.0 ^a	95.0 \pm 1.87 ^a	100.2 \pm 2.37 ^a
LSD	4.80	15.4	10.2	4.80

¹Mean \pm SEM, n=10. ^{a-d}Means within a column lacking a common superscript differ significantly ($P \leq 0.05$). T1, dosed 0.7 mg/day ZnCl₂ for two months before mating up to day 5 of pregnancy, females of this group were mated with males dosed 0.7 mg/day ZnCl₂ for 2 weeks before mating; T2, dosed 0.7 mg/day ZnCl₂ for 2 months before mating up to the day 16 of pregnancy, mated with control males; T3, dosed 0.7 mg/day ZnCl₂ for two months before mating up to the end of pregnancy, mated with control males; Control, dosed with ZnCl₂-free water along the period of experiment and were mated with control males

Since trace minerals, such as Zn, are not generally deemed to be hazardous to humans or animals, the acute or chronic deficiency adverse effects are usually given more emphasis (14). High Zn consumption via self-medication or diet as food additives has, however, been documented in some cases (15). In this study, the results showed that female rats exposed to 0.7 mg/day ZnCl₂ exhibited significant ($P < 0.05$) reduction in reproductive outcome, where there was disturbance in time of birth (GI%), and reduction in VI% of pups (except for T1) and LI% in all treated groups compared to control. According to statistical analysis, the most deleterious effect was recorded in rats received 0.7 mg/day ZnCl₂ for two months before mating and till to the end of pregnancy and mated with control males (T3). It has been revealed by some studies that absorption of Zn increases in humans and animals' lactation period (16). According to Jackson et al. (17), absorption of Zn was high in lactating Brazilian mothers with low-income, ranging from 59% to 84%. The women's chronically low Zn intake (128 μ mol/day) and the increased need for Zn during lactation could explain the elevated fractional absorption. Moser-Veillon et al. (18) reported further evidence about the increase absorption of Zn during lactation where the authors found that lactating women in the United States consuming 8 mg Zn/day from diverse diets had a mean fractional absorption of less than 0.35, compared to less than 0.20 fractional absorption of nonlactating postpartum mothers with the similar Zn intake. Six lactating mothers absorbed 83% more fractional Zn than seven women who had never been pregnant. As a result, it appears that one of the mechanisms used to meet the increased Zn demands during lactation is an increase in intestinal Zn absorption. During the second and third trimesters of pregnancy, there was a 30% increase in fractional Zn absorption. This minor increase, although not statistically significant, shows that a change in intestinal absorption is one of the mechanisms to provide the additional Zn required for growth of fetal, possibly prior the lactation process begins (19). Johnson et al. (16) confirmed the findings of the current study, reporting that mild toxic effects on the endpoints of reproductive and liver function were associated with ZnCl₂

supplementation in adult rats. Supplementing ZnCl₂ additionally resulted in abnormal development in F1 offspring. In light of these findings, as well as those published in a two-generation study of Zn toxicity in rats (20) and in a study of subacute toxic effects of Zn in rats (21), where they found that F2 pups' viability and weaning indices, or sex ratios were not affected by ZnCl₂ treatment, there may be a need to reevaluate the risks of excessive Zn supplementation, particularly in infants and pregnant women).

Body Weight of Offspring

Table 2 shows the results of the pup body weights. On days 1, 4, 7, 14, and 21 of lactation period following ZnCl₂ treatment, there was a significant ($P<0.05$) decrease in mean pup body weights in the treated groups compared to the control group.

Table 2. Body weight (g) at different lactation periods of newborn pups birthed by Albino Wister female rats treated orally with 0.7 mg/day zinc chloride in different phases of pregnancy¹

Group	Lactation period (days)				
	1	4	7	14	21
T1	5.3±0.03 ^b	9.20±0.20 ^b	13.5±0.10 ^b	25.4±0.20 ^b	40.1±0.24 ^b
T2	5.1±0.01 ^b	8.10±0.10 ^b	12.2±0.08 ^b	22.7±0.10 ^b	38.6±0.40 ^b
T3	4.8±0.02 ^b	6.90±0.21 ^c	10.6±0.13 ^c	20.1±0.23 ^c	31.5±0.30 ^c
Control	7.1±0.10 ^a	10.3±0.30 ^a	15.2±0.25 ^a	27.8±0.41 ^a	44.1±0.33 ^a
LSD	2.83	2.78	3.10	5.43	6.54

¹Mean±SEM, n=10. ^{a-c}Means within a column lacking a common superscript differ significantly ($P\leq 0.05$). T1, dosed 0.7 mg/day ZnCl₂ for two months before mating up to day 5 of pregnancy, females of this group were mated with males dosed 0.7 mg/day ZnCl₂ for 2 weeks before mating; T2, dosed 0.7 mg/day ZnCl₂ for 2 months before mating up to the day 16 of pregnancy, mated with control males; T3, dosed 0.7 mg/day ZnCl₂ for two months before mating up to the end of pregnancy, mated with control males; Control, dosed with ZnCl₂-free water along the period of experiment and were mated with control males

Results of a two-generation ZnCl₂ study conducted by (22) on rats were similar in terms of food intake and utilization reduction. Zn intake that is adequate and balanced before, during, and after pregnancy is necessary for the fetus's and offspring's optimal growth and development (23).

ZnCl₂ supplemented to pregnant females at 7 mg/daily for two months caused significant reduction in weight gain and the efficiency of feed conversion during gestation. This demonstrates the association of ZnCl₂ excessive supplementation with appetite reduction through development of fetal and it could be attributable to poor pregnancy outcomes. All dams supplemented with ZnCl₂ showed significant reduction in the total number of pups, pups per litter, and live pups per litter. It was reported that females exposed to ZnCl₂ at 7.5 mg/kg/day (low dose) did not show significant effect on the number of miscarriages, although significant reduction was noted in the implantation efficiency. On the other hand, females exposed to medium and high doses of ZnCl₂ exhibited significant increase in the number of miscarriages without effecting the efficiency of implantation. Such findings could imply that the effect of ZnCl₂ on reproductive functions follows a dose-dependent manner, where the rate of fetal resorption

was increased by low supplementation of ZnCl₂, while the rate of fetus death was increased by medium and high supplementation. As a result, it is the general nutritional condition of a mother that can play a significant role in both maternal and perinatal mortality and morbidity throughout pregnancy (24). Previous studies suggest that dams adequately supplemented with ZnCl₂ nutrition at low and high doses showed, respectively, reduction in implantation and increasing in stillbirths. This shows that in susceptible people, Zn deficiency or excess serve the same vital function. It has previously reported that offspring negative effects (25) such as fetal resorption elevated rates, litter size reduction, and congenital anomalies have all been associated with moderate to severe deficiency of Zn in experimental pregnant animals (20).

In conclusion, results from this study showed that ZnCl₂ at dose of 0.7 mg/day may have teratogenic defects at various stages of pregnancy in rats especially at third stage of pregnancy which represents the major physiological and developmental and minor organogenesis. It is recommended thus that pregnant women and children as high-risk groups must carefully use Zn supplementation, whether it is used as a food additive or in self-medication.

Additionally, water sources must be subjected to strict control and detect water contamination.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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بعض المعطيات المسخية في الجرذان المعرضة لكلوريد الزنك قبل وبعد الحمل

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الخلاصة

إن الهدف من هذه الدراسة هو تقييم إمكانية المسخية لكلوريد الزنك في الجرذان البالغة المهقاة قبل الحمل وبعده. ولتحقيق هذا الهدف تم تقسيم 40 أنثى جرد بالغة بالتساوي إلى أربع مجموعات على النحو التالي: المجموعة الأولى جرعت 0.7 مجم كلوريد الزنك فمويًا من خلال ماء الشرب يوميًا لمدة شهرين قبل التزاوج وحتى اليوم الخامس من الحمل. تم تزاوج أنثى هذه المجموعة بجرعة ذكر 0.7 مجم يوميًا من كلوريد الزنك لمدة أسبوعين قبل التزاوج، المجموعة الثانية جرعت 0.7 مجم يوميًا من كلوريد الزنك لمدة شهرين قبل التزاوج وحتى اليوم السادس عشر من الحمل ثم تم التزاوج مع ذكور غير مجرعة من كلوريد الزنك (سيطرة). المجموعة الثالثة جرعت 0.7 مجم كلوريد الزنك يوميًا لمدة شهرين قبل التزاوج وحتى نهاية الحمل وتم تزاوجها مع ذكر سيطرة (كما في المجموعة الثانية). مجموعة السيطرة جرعت بالماء الخالي من كلوريد الزنك طوال فترة التجربة وتم تزاوجها مع ذكر ضابط. أظهر مؤشر بروتين ألفا فيتوبروتين فروق معنوية ($P < 0.05$) بين جميع مجموعات التجربة في نهاية كل مرحلة من مراحل الحمل. أظهرت مؤشرات الحمل والحيوية والرضاعة انخفاضًا معنويًا ($P < 0.05$) في جميع المجموعات المعالجة مقارنة بمجموعة السيطرة، كما أظهر فرقًا معنويًا بين المجموعات المعالجة. أيضًا، كان هناك انخفاض معنوي ($P < 0.05$) في متوسط أوزان الجراء لوحظ في المجموعات المعالجة مقارنة مع مجموعة التحكم خلال الفترات المختلفة. لذلك، يُقترح استخدام الزنك بعناية، خاصةً من قبل الفئات المعرضة للخطر مثل الأطفال والنساء الحوامل على الرغم من استخدامه كمضافات غذائية أو في العلاج الذاتي. في الوقت نفسه، من الضروري إجراء مزيد من البحث والبحث في هذه السمية للزنك مع إعطاء جرعة منخفضة على المدى الطويل.

الكلمات المفتاحية: التشوهات المسخية، الجرذان، كلوريد الزنك، قبل الحمل، بعد الحمل