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THE EFFECT OF SILVER NANOPARTICLES (AGNPS) ON THE LIVER ENZYMES OF PREGNANT MICE (MUS MUSCULUS) AND THE DEFORMATION OF THEIR FETUSES

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ABSTRACT
Exposure to silver nanoparticles (AgNPs) causes accumulation in various organs of the body, including the liver and kidney, with potentially negative physiological and histological effects. This study aims to determine the toxicity of AgNPs on some liver enzyme parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), as well as investigate the fetal malformation in pregnant mice. In this study, 20 pregnant female Swiss albino mice were injected with a solution of silver nanoparticles with diameters of 30 nm and concentrations of 0.2, 0.4, and 0.6 mg/kg BW AgNPs per day. One week after administration, the level of some liver enzymes was measured. The results of the study showed a significant increase in the activity of liver enzymes in the blood serum. The mice fetal displayed morphological and phenotypic changes such as flatulence, protrusion of the umbilicus and umbilical cord, micromelia of the forelimbs and lack of phalangeals, hind limb enlarged and bent at the knee joint, with posterior end flexed and fused phalanges visible, aquiline tail, and the appearance of folds in the skin. The highest percentage of deformities were observed at the 0.6 mg/kg concentration, including the fetus's small size, trunk curvature with swelling of the navel, torsion tail, congestion of the abdomen and flank with swelling of the abdomen, and the observation of the bending of the forelimbs at the elbow, the sagging of the ear, swelling in the face, the upper lip being cleft, and atrophy of the optic follicle, the short lower jaw with the femoral epiphysis, and foot enlargement. According to the results, the consumption of AgNPs has a negative impact on liver enzymes and physiological parameters in the blood, as well as on pregnant mice fetuses.

Keywords: AgNPs, ALT, AST, ALP, liver enzymes, silver nanoparticles

Introduction:

Silver nanoparticles are commonly used in the manufacturing of medical 1, industrial 2, and household products 3. These nanoparticles, which have a wide range of antibacterial and antimicrobial properties, are widely used in medicine 4. According to studies, AgNPs can cause significant cytotoxicity, including

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oxidative stress in human pulmonary epithelial cells as well as anti-inflammatory effects, mainly hepatotoxicity in laboratory rats, and enzyme imbalances (GOT, GPT, and ALP) 5, as there are few studies showing toxic side effects 6. Nanomaterials cause cytotoxicity by generating reactive oxygen species (ROS) and releasing cytokines 7. Placenta and breast milk have been identified as the two main routes of transmission of AgNPs to offspring upon maternal exposure, although infants can be directly exposed to AgNPs through milk bottles, textiles, toothbrushes, and drinking cups 8. The placenta is an organ that allows the exchange of substances between the bloodstream of the mother and the fetus and provides the fetus with nutrients 9, where accumulation of AgNPs was detected in the placenta and fetal organs during pregnancy, such as they kidney, lung, liver, spleen, and brain 5,10 . AgNPs of small size can pass through the septum and cause structural changes in the placenta, and deposition of AgNPs in the placenta causes vacuolization of nuclei, agglomerated chromatin, nuclear lysis, and focal necrosis in this organ 11. Placental injuries induced by AgNPs can increase the permeability of nanoparticles and the efficiency of placental transport of AgNPs depends on the stage of embryonic and placental maturation in a mouse pregnancy where fetal days are defined as a critical path, after which blood flow and placental barrier function mature leading to a significant decrease in exposure. embryo of nanoparticles 12. The thickness and permeability of the human placenta differs from that of the mouse placenta as the embryonic stages change, as the septum becomes thinner and more permeable during the third trimester compared to that during the first trimester, and this leads to an increased risk of exposure of fetuses to AgNP in late pregnancy 13. The transport mechanism of AgNPs into the placenta is not yet clear. The placental septum consists of multinucleated cytotrophoblasts, stroma villi, and endothelial cells of fetal capillaries 5. As demonstrated by previous studies, AgNPs cross the placental barrier via cellular pathways (phagocytosis, clathrin-mediated endocytosis, cavernosa-mediated endocytosis, and megakaryocytes) and paracellular pathways 14. Although placental trophoblasts possess phagocytic activities, endocytosis has been suggested to be the most prevalent pathway mediating placental transport of nanoparticles 8. Uteroblastoid ducts are narrow, highly branched tubular ducts of 15–25 nm that allow the transport of very small nanoparticles 5. Interestingly, both silver ions and AgNPs could be detected in the fetal circulation after perfusion as well as AgNPs can be formed upon perfusion of $AgNO_3$ into the maternal and fetal circulation, raising the question of which Ag species dominate transport of AgNPs across the placenta 15. Several studies have also shown that breastfed infants are exposed to AgNPs through milk when their mothers are exposed to them, as well as that AgNPs can cross the placenta and cause resorption, growth retardation, and histological and functional abnormalities in the fetal central nervous system, reproductive system, immunological system, and other systems and organs 8.

Materials and Methods:

Preparation of silver nanoparticles

By reducing silver nitrate ($AgNO_3$) with sodium citrate ($Na_3C_6H_5O_7$), silver nanoparticles of 30 nm diameter were produced 16. 250 ml of a 1 M solution was placed in a round-bottom flask. While being stirred, this solution was heated to boiling under reflux. Then, 10 mL of a 1% sodium citrate solution

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was instantly added to generate 30 nm-diameter Ag nanoparticles, and the mixture was allowed to boil for 60 minutes. Three distinct concentrations of the nano-solution, prepared at 17, 34, and 51 mg/ml, correspond to doses of 0.2, 0.4, and 0.6 mg/kg BW, respectively.

Preparation of Animals

20 female Swiss albino mice belonging to the Mus musculus strain were used in this experiment. The mice were divided into two experimental groups and treated with AgNPs nano-solutions with diameters of 30 nm; each group was injected with AgNPs at concentrations of 0.2, 0.4, and 0.6 mg/kg BW, respectively, and a negative control group was injected with distilled water for week.

Biochemical Parameters

The Mindray Biochemistry analyzer BS-120 was used in combination with a Mindray (German company) test kit to perform liver enzyme assays (ALT, AST, and ALP) in accordance with the Mohammed & Mohamed method 17.

Statistical Analysis

The data were analyzed using the Statistical Analysis System (SAS) program 18. The arithmetic means of different doses were compared using Duncan's Multiple Range Test at a probability level of $p < 0.5$ to evaluate the effect of AgNPs on liver enzyme parameters (ALT, AST, and ALP) and fetuses, as well as compare them to the control sample.

Results and Discussion:

Ag NPs Morphology

The appearance of the olive color in the reaction mixture revealed the formation of silver nanoparticles. Fig. 1 shows a TEM picture of Ag NPs with diameters of 30 nm.

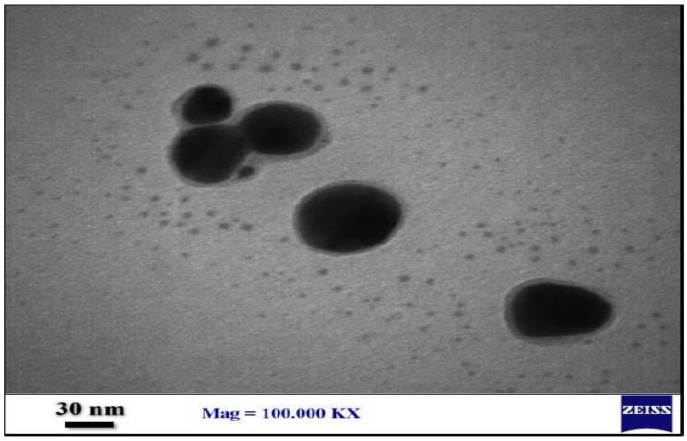

Figure 1. TEM image of 30 nm Ag NPs.

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Liver enzyme activity

The activity of the liver enzymes ALT, AST, and ALP in the blood serum of mice treated with 30 nm AgNPs for one week at concentrations of 0.2, 0.4, and 0.6 mg/kg body weight was significantly different at the $P < 0.05$ level when compared to the control group, as shown in Figs. 2, 3, and 4.

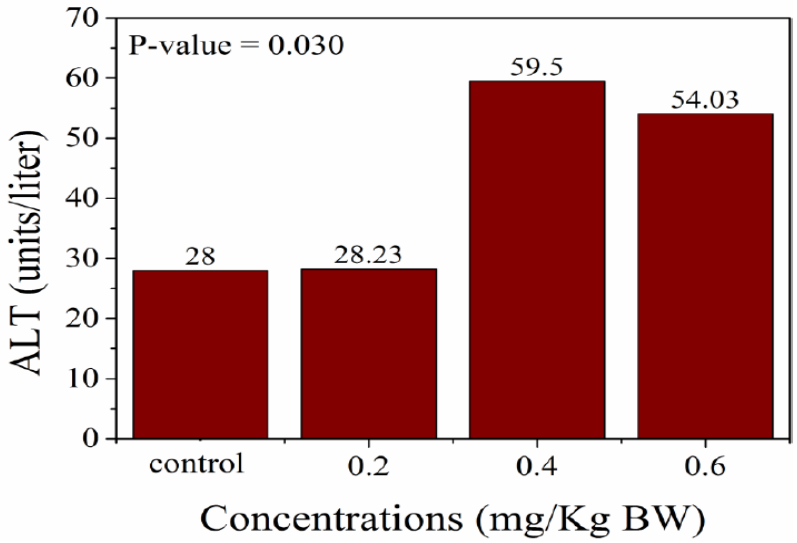

Figure 2. Effect of 30 nm diameter AgNPs on alanine aminotransferase (ALT) enzyme.

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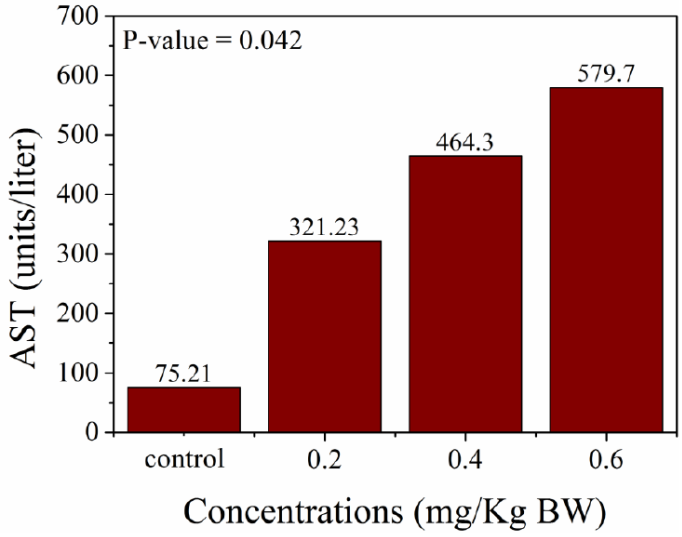

Figure 3. Effect of 30 nm diameter AgNPs on aspartate aminotransferase (AST) enzyme.

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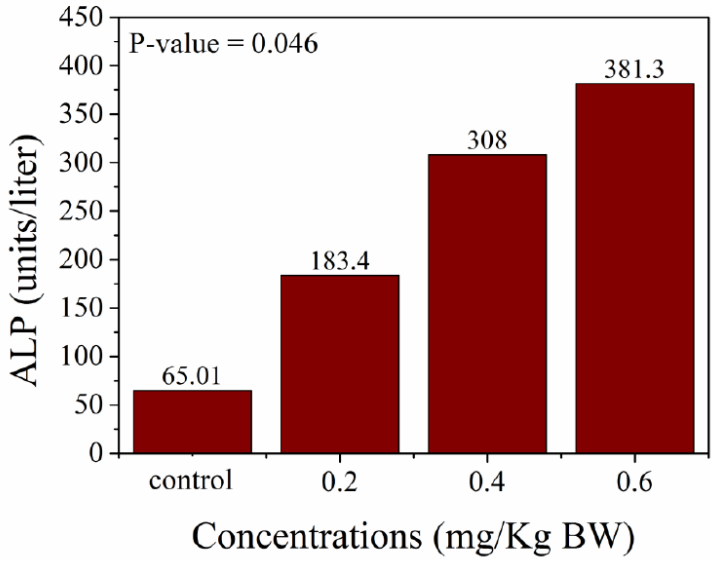

Figure 4. Effect of 30 nm diameter AgNPs on alkaline phosphatase (ALP) enzyme.

Appearance changes of embryos treated with silver nanoparticles

The findings of this study revealed that pregnant mice treated with 30 nm diameter AgNPs for one week at a concentration of 0.2 mg / kg body weight had an appearance, prominence, and congestion in the nose, as well as short and straight front limbs bent at the leg joint, and the tail curving towards the abdominal side, as shown in Fig. 5. Fig. 6 shows a curvature of the tail and skin folds, as well as a bending of the posterior end and the emergence of merged phalanxes and flexion of the hind limb.

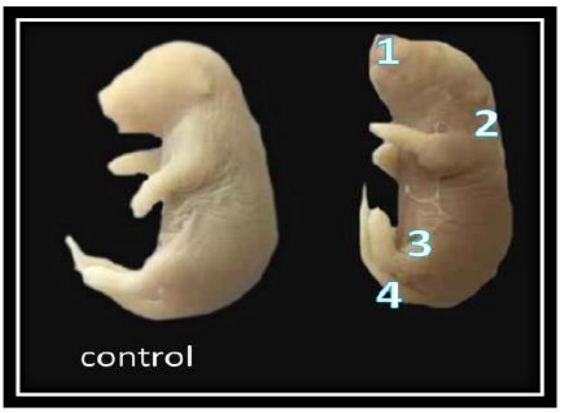

Figure 5. Shows (1) Nasal congestion and prominence, (2) short and straight forelimbs, (3) bending of the forelimbs at the leg joint, (4) curvature of the tail towards the ventral side

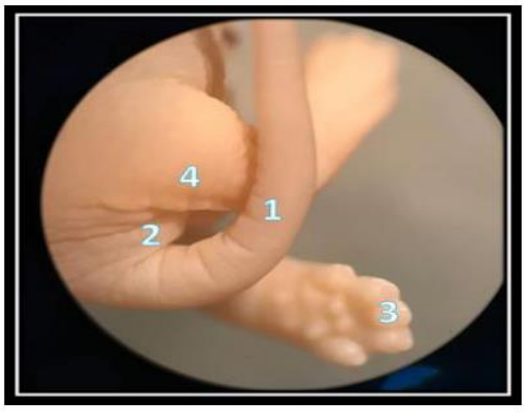

Figure 6. Shows (1) Curvature of tail, (2) folds of skin (3) (4) flexion of hind limb

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Figs. 7 and 8 clearly show the appearance of a bulge in the abdomen with the curvature of the tail, the protrusion of the umbilicus, and the umbilical cord, as well as the fusion of the fingers, a long hooked tail, and an enlarged and bent posterior end at the knee joint. Additionally, the skin fold is formed in association with the shortness of the front end.

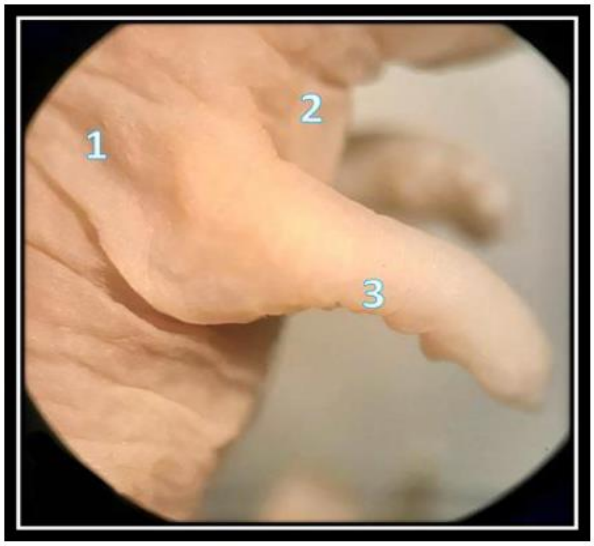

Figure 7. Shows (1) Grooves of skin in the abdomen and shoulder region and (2) grooves in the neck and mandible, (3) wrinkle on the ventral side of the forelimb.

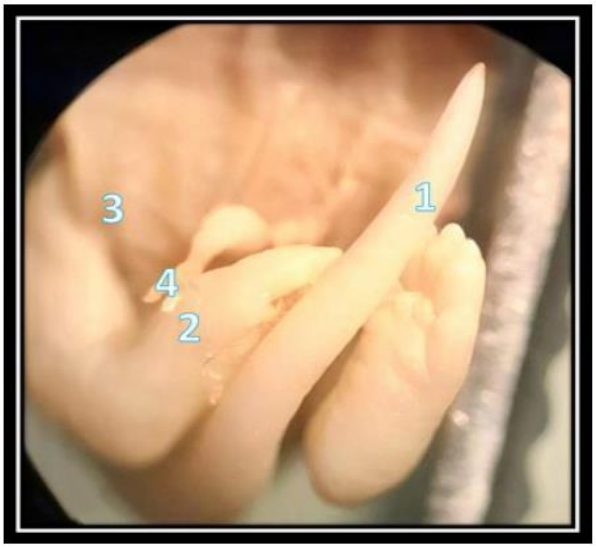

Figure 8. Shows (1) A long, hooked tail (2) enlarged hind limb and bent at the knee joint (3) skin fold, with a Short hind limb and a lack of phalanxes.

The study's findings revealed that treating pregnant female mice with 30 nm-diameter AgNPs for one week at a dose of 0.4 mg/kg body weight revealed numerous deformations. Fig. 9 depicts a tail curvature with swelling of the abdomen, protrusion of the umbilicus and umbilical cord, and syndactyly fusion. Fig. 10 shows a thickening of the anterior limb with adhesion of the phalanges, curvature of the tail towards the abdomen, and wrinkles in the skin. Fig. 11 shows abdominal congestion with folds in the abdomen skin, auricle disc protrusion, loss and atrophy of the loin, curve of the tail with sagging of the ear disc, and bending of the limb to the right at the wrist. The protrusion of the umbilicus, enlargement of the abdomen, blueness, flexibility of the hind limbs, and interphalangeal adhesion were all shown in Fig. 12. The tail is curved, the skin on the hind limb thickens, the back end touches the tail, and the fingers get longer, as shown in Fig. 13. In contrast, the mandible was enlarged with skin folds and a skin groove in the neck, as indicated in Fig. 14.

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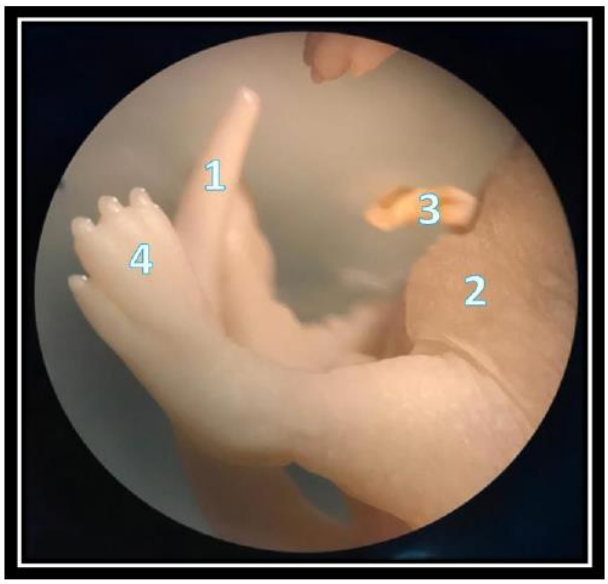

Figure 9. Shows (1) Curvature of the tail, (2) swelling of the abdomen, (3) protrusion of the umbilicus and umbilical cord, (4) fusion of the syndactyly.

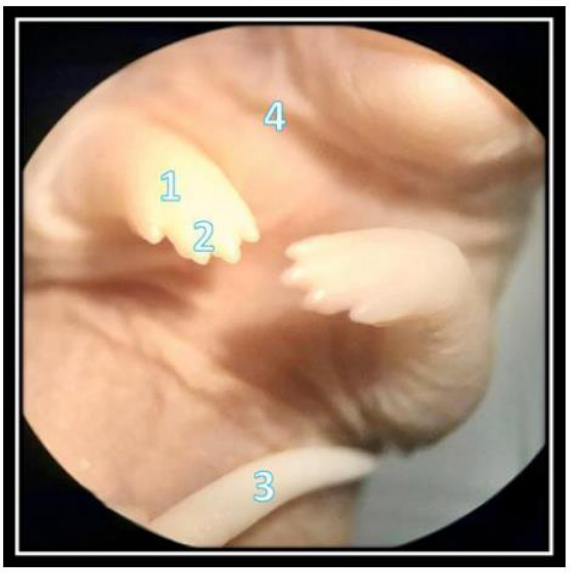

Figure 10. Shows (1) thickening of the anterior limb (2) adhesion of the phalanges (3) curvature of the tail towards the abdomen (4) wrinkling of the skin.

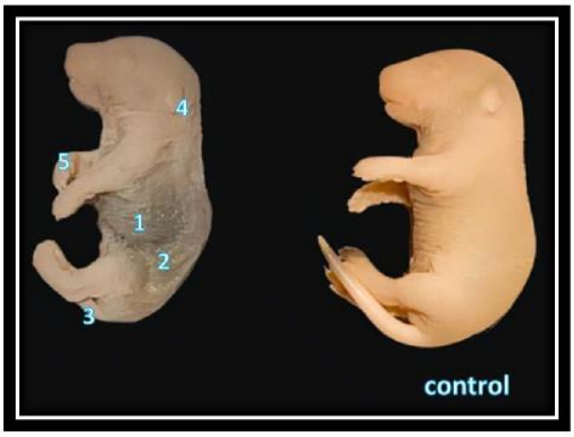

Figure 11. Shows (1) congition of the abdomen, (2) folds in the skin of the abdomen, protrusion of the auricle disc, , loss in the loin and its atrophy (3) curvature of the tail, (4) sagging of the ear disc (5) bending of the limb to the right at the wrist.

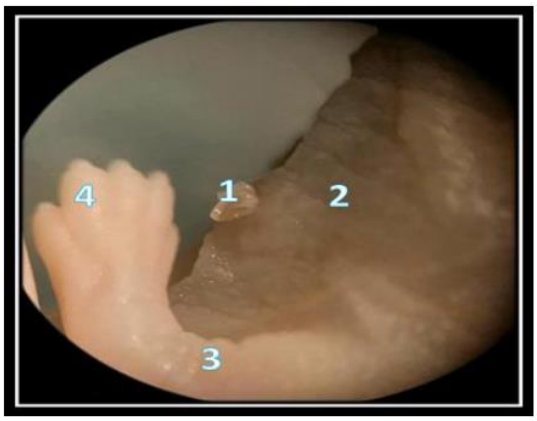

Figure 12. Shows (1) The protrusion of the umbilicus (2) enlargement of the abdomen, and blueness, (3) flexibility of the hind limbs (4) interphalangeal adhesion.

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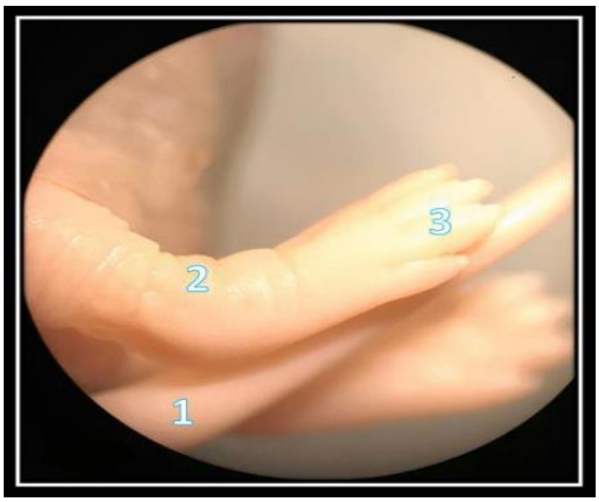

Figure 13. Shows (1) Curvature of the tail, (2) thickening of the skin at the posterior end, contact of the posterior limb, (3) hypertrophy of the fingers.

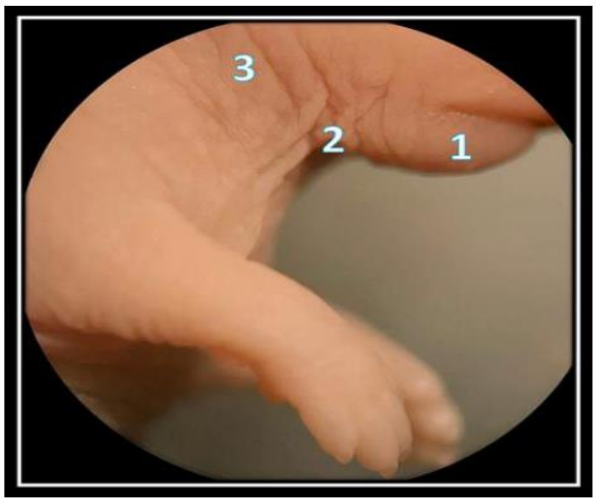

Figure 14. Shows (1) Enlargement of the lower jaw (2) skin folds in the neck (3) cutaneous grooves in the neck.

The treatment of pregnant mice with 30 nm-diameter silver nanoparticles at a concentration of 0.6 mg / kg for a week showed fetal deformities such as a mummified embryo with trunk curvature, protrusion of the placoid of the ear and its congestion, a caudal curvature, belly swelling, and a head as in Fig. 15. Fig. 16 also showed a deformation of the face, macrocephalus, swelling of the ear, the appearance of bloody congestion around it, micromelia, belly swelling, and a curvature of the trunk.

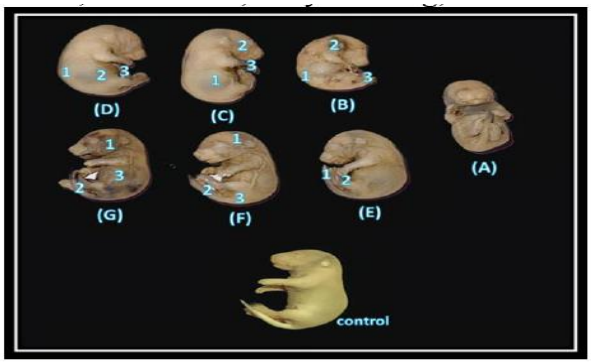

Figure 15. In which (A) the fetus Mummified embryo B- 1belly swelling 2. Swelling of the face and head 3.Shortness of the forelimb.C-1. Fetal arching dorsally 2. belly swelling 3. caudal curvature D- 1. 2. Abdominal congestion. 3. Rear end E-1. a caudal curvature 2. Short rear end F-1. Skin congestion 2. a caudal curvature 3.protrusion the placoid of ear.

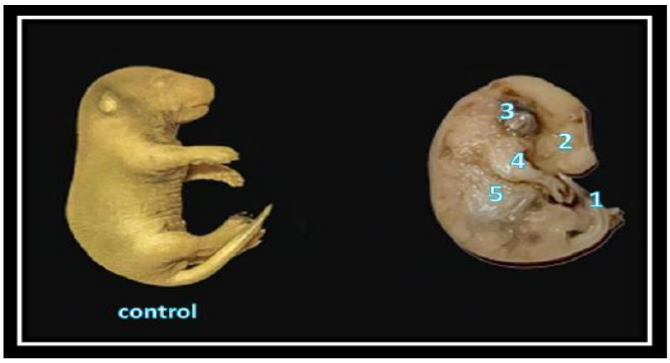

Figure 16. (1) acaudal curvature (2) macro cephalus (3) Skin congestion (4) Micromelia (5) belly swelling.

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Fig. 17 shows a wrinkling of rough skin and caudal curvature, as well as the swelling of the umbilicus and adhesion of the syndactyly to the peritoneum. Fig. 18 shows congestion of the skin, as well as a hooked tail with swelling and congestion of the syndactyly at the posterior end.

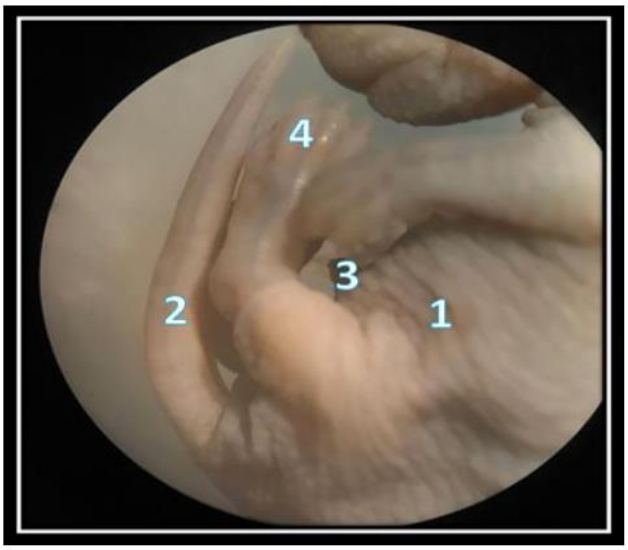

Figure 17. Shows (1) rough skin (2) caudal curvature (3) cervical skin folds, (4) syndactyly to the peritoneum

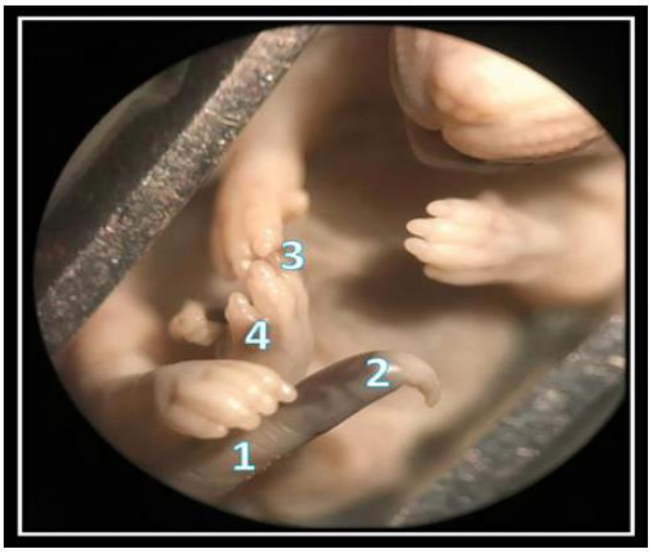

Figure 18. Shows (1) the congestion of the skin, (2) caudal Aquiline (3) congestion of the syndactyly the posterior.

Impairment of hepatic enzyme parameters can be a useful tool for monitoring health status and disease detection, and for tracking disease progression and response to treatment. In this study, the effects of AgNP on the enzymes of female albino mice were investigated. The study showed a significant increase in the levels of ALT, AST, and ALP at concentrations of 0.2, 0.4, and 0.6 mg/kg compared to the control group. These results agreed with Forouhar and his coworkers 19 when they treated Fish were treated with AgNP at concentrations of 0.1 mg/L, 0.2 mg/L, and 0.4 mg/L to assess and determine some parameters of liver enzymes and red blood cells. ALT, AST, and ALP were significantly higher compared with the control group. It was concluded that silver nanoparticles cause significant changes in blood parameters in rainbow trout and that the toxicity of NPs is due to special chemical and physical properties such as size, chemical modification of the surface, and the release of ions. Previous studies in vivo indicated that different types of nanoparticles tend to settle in the liver with different toxic effects, as the liver is the primary organ responsible for detoxifying the body 20. Naguib and her colleagues 21 observed a significant increase in serum enzyme activities such as AST, ALT, and ALP in C. gariepinus exposed to AgNPs for 15 days. The results agreed with 12,19 who observed a significant increase in the AST, ALT, and ALP activities of rainbow trout (Oncorhynchus mykiss) after exposure to silver nanoparticles. These results are in agreement with Abdel-Khalek and his colleagues 22 who reported a significant increase in serum enzyme activities (AST, ALT, and ALP) of Nile tilapia O. niloticus after exposure to copper oxide nanoparticles. The higher levels of AST, ALT and ALP in the

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cytoplasm of hepatocytes as a result of liver injury leading to increased permeability of cell membranes 23. This study recorded several phenotypic deformities of female albino mice embryos after treatment with AgNPs at concentrations of 0.2, 0.4 and 0.6 mg/kg compared to the control group. These results agreed with24 in study of the dangerous effects of AgNPs on the maturation of mouse ovum, in vitro fertilization, and post-implantation and embryo development, as data from in vitro experiments revealed that AgNPs impair mouse oocyte maturation and reduce fertilization rates and the effects of infection on subsequent embryonic development to a large extent, when injected AgNPs at a concentration of 5mg/kg body weight led significantly reduced mouse oocyte maturation with impairment of early embryonic development in vivo. The results of the study25 did not record any significant differences, and indicated that the potential effects of AgNPs on fetal growth of pregnant mice at concentrations of 0, 100, 300 and 1000 mg/kg/day have not yet been determined. No changes in organ weight, pregnancy index, fetal mortality, fetal and placental weights, sex ratio, or morphological changes were observed between groups.

Conclusion

Despite the many benefits that enter into the use of silver nanoparticle (AgNPs) technology medically, veterinary and industrially, it has toxic health effects that may interfere with the functions of some organs and fetuses in living organisms. The results of our study showed a significant increase in the activity of liver enzymes (ALT, AST, and ALP) in the serum of mice treated with 30 nm diameter AgNPs for one week at concentrations of 0.2, 0.4, and 0.6 mg/kg body weight, when compared to the control group. The embryos of female albino mice recorded morphological and phenotypic changes when the females were treated with 30 nm diameter AgNPs for one week at concentrations of 0.2, 0.4, and 0.6 mg/kg body weight. Curvature of the tail and skin folds with flexion of the posterior limb and the appearance of combined phalanges Abdominal distension, Prominence of the umbilicus and the umbilical cord, with a long hooked tail and a posterior end enlarged and bent at the knee joint, with a short anterior end and a lack of phalanges. The curvature of the trunk, with swelling of the umbilicus curvature of the trunk, curvature of the tail, discoloration of the abdomen and flanks with swelling of the abdomen, and noticing the bending of the front end at the elbow With drooping ears and a short front end, with folds and swelling of the face, a cleft upper lip, optic atrophy with cervical skin folds, mandibular shortening, and hyperemia, describes mutations and folds associated with thigh sagging and foot enlargement, This demonstrates the detrimental side effects of AgNPs nanoparticles as proven by the findings of our study.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in University of Kirkuk.

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