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Effect of Ochratoxin-A on Mouse Embryos

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Abstract:

This study sought to determine malformation caused by Ochratoxin-A (OTA) on mouse embryos. Twenty adult female white Swiss mice (*mus msculus*) were divided into four groups, with five females per group, and with one male placed with two females in a cage. Avaginal plug was observed in the early morning and the day of mating was considered as day of pregnancy followed by the first day of pregnancy. Three sub lethal concentrations of OTA were applied to the respective groups (other than the control), 1mg/kg, 2mg/kg and 4mg/kg. The animals were given 0.1 ml per 10 gm body weight per concentration of OTA once a day during days 7-14 of pregnancy. The control group animals were given distilled water. The pregnant mice were dissected, and the embryos were extracted in order to identify the effects of the OTA. Number of parameters were studied including, difference in body weight of the mice before mating and after the end of the experiment, the weights and lengths of embryo, as well as a study of embryo malformation.

The study shows no significant differences in the mean body weight of the pregnant mice in the 1 mg/kg group, compared to control group. A significant ($P<0.01$) decrease in the body weight of the treated mice was observed in the 2mg/kg and the 4mg/kg groups. As for the weight of the embryos, there was a significant ($P<0.01$) decrease in the body weight of the embryos in the mothers treated with OTA in the 1 mg/kg and 2 mg/kg treatment groups. The embryos of the 4mg/kg group of pregnant mice could not be recorded since they had been resorbed into their mothers uteri. Similarly, the results of the study showed a significant difference in the mean length of the embryos bodies in the 1mg/kg and 2mg/kg groups, compared with the non-treated control group.

Many malformations induced in the embryos in those groups where it was possible to examine the embryos 1mg/kg and 2mg/kg compared to control mouse embryos, included loss of tail, lack of eyes, cleft lip and exencephaly, as well as spina bifida, curvature of the trunk and there were also reduction defects of the limbs. The study concluded that OTA have teratogenic effects on mice embryos.

Keywords: Mycotoxins, Ochratoxin-A, embryonic malformation.

Introduction:

Fungal toxins are vital compounds produced by fungi when growing and with the ability to produce secondary metabolites (1). These secondary metabolites of fungi are active biological compounds although they may be toxins, they are not antigens in the sense that their molecular structure is free of the components that drive organisms to form antibodies (2). These compounds are mostly toxic to humans, animals, plants and microorganisms. The nutrients in human and animal food can encourage the growth of the fungi that release mycotoxins whether during the different stages of production or when transported or during storage (3).

There are many fungal species such as *Aspergilus*, *Pencillinium*, *Fuzarium*, *Alternaria*, etc., that have the ability to release various fungal toxins (4). The genus *Aspergillus* and *Pencillinium* produce Ochratoxins as well as other toxins. Ochratoxin-A causes, foetal malformation and has been classified as carcinogenic to humans because of its ability to affect DNA (5), to initiate the immunomodulations in both humans and animals and its relationship to the occurrence of chronic nephritis . Some studies also referred to the oxidative action of OTA in brain regions during the stages of the formation of the nervous system (6).

Zank *et al.* (7) demonstrated the role of OTA in apoptosis induced by the formation of free radicals. OTA is also associated with many congenital

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malformations in animal embryos during foetal formation (8).

Chemical research, meanwhile, has shown that OTA inhibits the production of proteins and cellular respiration, and has an oxidative effect in various tissues (9). Although it is easily eliminated by the bile-hepatic circulation, it can survive for up to 840 hours in the human body and accumulates in the body's tissues, especially the liver and kidney (10), as well as having the ability to penetrate blood, brain, placenta, and lactic glands on account of its small molecular weight (11) .

OTA causes many pathological effects in the tissues and organs of animals after exposure to fungal toxins in contaminated food and foodstuffs. The present study was conducted to investigate the effects of OTA on embryos of Swiss white mice.

Materials and Methods:

Twenty female Swiss *(Mus musculus*) were used with ages ranging from 10 to 8 weeks and weights ranging from 25 to 30 grams. They were obtained from the Animal House of the Biotechnology Research Center/Al- Nahrain University. The females were divided into four groups, (5 females per group), and a male and two females were placed in each cage. The animals were observed daily in the early morning and once mating was confirmed the mating day was considered to be day zero of pregnancy, followed by the first day of pregnancy (12). Oral doses of OTA were based on the lethal dose 50 (LD50) for (48-58mg / kg) (13) (14).

Three sublethal concentrations of OTA, 1mg/kg, 2mg/kg and 4mg/kg were selected. The OTA was weighed and dissolved in corn oil (15). The animals were orally administered with 0.1ml/10 gm body weight for each OTA concentration once a day between days 7-14 of gestation, using a gavage tube. The control group animals were administered with 0.1ml/10gm of distilled water. The weight of mothers was taken before mating and after the end of the trial period. Mothers were dissected on day 18 of pregnancy, the uterus was removed and extracted from the embryos. Numbers, weights, lengths and malformation of embryos were recorded.

Results and Discussion:

The results in Table 1 show ahighly significant ($p < 0.01$) decrease in body weight in the pregnant mice treated with 2mg/kg, 4mg/kg concentrations of OTA, compared with the pregnant mice in the untreated control group. This was inferred to be due to the toxic effect of OTA, which has been shown to cause many abnormalities in mice weights (16). This also agrees with (17), that a decrease in the weight of pregnant rats weights treated with OTA 5mg/kg, was due to a reduction in the eight of their embryos. For the pregnant mice in this study, the highly significant ($p < 0.01$) decrease in the case of the 4mg/kg concentration,was because their embryos were resorbed into the mothers' uteri. These results agree with Bowen (18), who observed that the treatment of pregnant rats with OTA at 8mg/kg caused embryonic resorbtion and an associated reduction in their mothers weights, compared with an untreated control.

The results showed no significant ($p < 0.01$) differences in the mean body weight of pregnant mice treated with the 1mg/kg, concentration, compared to the non-treated pregnant mice (Table 1). OTA may be non-oxidation in lower concentrations.

This result agrees with (19) who showed that treating mothers with low concentrations (1 mg/kg for 4 weeks) of FumonisinB1 does not reduce pig embryo weights, although the mothers' weight did decrease with 5mg/kg and 10 mg/kg treatment.

Table 1. Effect of different concentrations of OTA in the body weight of pregnant mice

	Mean ± standard error (gm)	
Concentration(mg/kg)	Weight before experiment	Weight after experiment
Control	25.51± 0.26 a	38.94 ± 0.04 a
1	26.19± 0.18 a	38.31± 0.08 a
2	26.12± 0.16 a	36.39± 0.62 b
4	26.57± 0.34 a	25.63± 0.46 c
LSD value	NS 1.291	1.271**

• Similar letters in the same column mean that there are no significant differences at (P <0.01).

Embryos weights, meanwhile, were found to be decreased significantly ($p \leq 0.05$) in the groups treated with 1mg/kg and 2mg/kg concentrations of OTA, compared to the control group (Table 2). OTA has also been shown to reduce the weights of rat embryos, compared to a control group, after mothers were orally administered with a 0.75mg/kg concentration of OTA between days 1-20 of pregnancy, which was attributed to OTA's oxidative effects and consequent increased levels of peroxides in embryonic cells (20).

A previous study (21) has demonstrated that oral administration in pregnant rats of OTA at a concentration of 120 mg/kg for 60 days caused reducing embryos body weight. The enhanced induction of oxidative stress observed with OTA could also be relevant to explain the molecular basis of cells induced by this mycotoxin, that formation of 8-oxoguanine and free radicals (ROS) Reactive Oxygen Species, which inhibits many functions of liver, kidney and muscle.

Another study (22) found that protein levels decreased as levels of OTA, increased along with inhibition of protein synthesis and energy production, induction of oxidative stress, DNA adduct formation, as well as apoptosis, necrosis and cell cycle arrest.

The process of carbononylation occurs due to oxidative processes leading to changes in tissue composition and may reach the cytoskeleton effect.

In this study, meanwhile, the pregnant mice treated with the 4mg/kg concentration of Ochratoxin-A experienced embryonic resorption Fig. (11, 12, 13).These results agree with (23) where pregnant rabbits treated with a mixture of 0.5mg/kg of OTA and 1mg/ kg concentration of Aflatoxin B1, daily between days 6 and 18 of pregnancy experienced embryonic resorption, and reduction in embryo body weights, as well as anomalies in embryos, such as, tail loss and digital malformation.

The statistical results in Table 2 reveal significant differences in the mean body length of embryos of mothers treated with 1mg/kg and 2mg/kg concentrations of OTA, compared with embryos of the control group.

Similarly, Sinha *et al*. (24) demonstrated that the mean embryo length of rabbits was significantly reduced with a 0.100 mg/kg dose of OTA daily between days 6-18 of gestation, compared with a control group. This result also agreed with observations of multiple skeletal and visceral malformations in rat embryos, after subcutaneous injection of one OTA dose of 1.75mg/kg on the seventh day of pregnancy (25). This outcome, might be due to inhibition of cellular macromolecule synthesis, mainly that of protein, and was similar to that reported by other scholars in the case of rats treated with OTA.

Pregnant mice treated with the 4mg/kg concentration of Ochratoxin-A experienced increased incidence of embryonic resorptions, compared to the other untreated groups of pregnant mice. Ochratoxin-A provokes resorptions or dead foetuses due to its high toxicity, causing DNA damage and chromosomal deformation (26). Free radical effects, including hydroxyl radicals and nitric oxide, have been shown to interfere direcly with the nitrogen bases of DNA, causing many mutations that lead to abnormalities in foetal lengths (22).

Table 2. Effect of different concentrations of OTA in the rate of fetal weights and length

	Mean ± standard error (gm)	
Concentration(mg/kg)	Weight (gm)	Length (cm)
Control	1.435±0.08 a	2.16 ±0.07 a
1	0.862±0.01 b	1.92±0.03 b
2	0.583±0.01 c	1.33±0.03 c
LSD	0.162**	0.159**

• Similar letters in the same column mean that there are no significant differences at (P <0.01).

Oral administration of 1,2 and,4 mg/kg of OTA on days 7–14 of gestation resulted in this study in increased rates of malformation, including exencephaly and anomalies of the eyes, face, digits, and tail. The most severe malformations were cleft lips associated with exencephaly, and eye defects. Head lesions were observed in the embryos of mice treated with 1mg/kg and 2mg/kg of OTA. The absence of neural tube closure resulted in cleft lip, (Fig. 2), congestion in the neck, Fig. (4), exencephaly,(Fig. 5), exthphalmia, Fig.(7), large head size and deviation from the normal level,(Figure 8), brain projection,(Fig. 3,9), a lack of eyes, (Fig. 8,9), as well as congestions near the brain, eyes and ear,compare with control group (Fig. 1).

O'Brien *et al*. (27) showed that, when administered to mothers, OTA has the potential to cross the placenta and reach and accumulate in the embryo tissues, causing various congenital malformations in different animal embryos such as rats, mice, hamsters, chickens and rabbits. (28) demonstrated that OTA in pregnant mice causes mortality, reduced mother body weight gain hepatic pathology in the mother, increased plasma oxidant enzymes, increased embryos resorptions, reduced number of live offspring and increased embryo anomalies. (29) demonstrated that OTA may interfere with organ development and increase the risk of disease and cancer later in life. OTA has been proven to induce diverse toxic effects including teratogenicity, carcinogenicity, immunotoxicity and potential endocrine disruption. Wee and Solk (30) recorded several abnormalities in cranial and craniofacial bones of mouse embryos after oral administration of a single dose of (3mg/kg) of OTA, which included craniofacial deformities, cleft lip, mid-facial dissection clefting, lack of eyeball (synophthalmia) and integration of brain introduction holoprosencephaly.

Furthermore, a study (17) showed many mutations in swine embryos, including facial bones, eye abnormalities, multiple fingers,and, malformation of jaw and skin. These changes were due to the effect of fungal poison, which inhibits bone formation. In another study, (31) pregnant

golden hamsters were injected with OTA into the peritoneal membrane at a concentration of 20 gm/kg of body weight. Several abnormalities were observed in the embryos, such as micrognathia, oligodactyly and syndactyly, short tail, cleft lip, and defects in the formation of the heart. Hack *et al*. (32) suggest that OTA is unlikely to act through a single, well-defined mechanism of action but that a combination of protein synthesis inhibition, oxidative stress and the activation of specific cell signalling pathways is responsible for OTA carcinogenicity. From a risk assessment perspective, it has to be noted that the mechanisms proposed above depend mainly upon gene expression and enzyme activation.

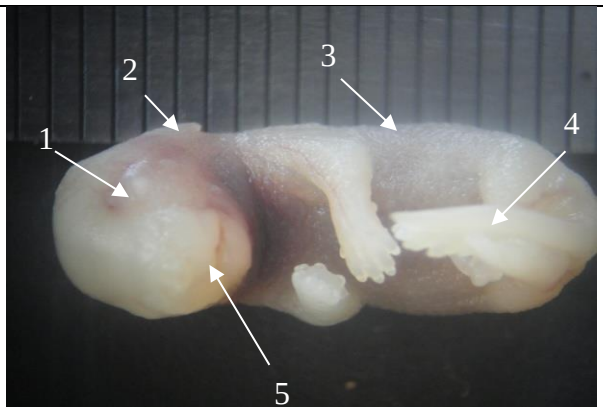

Figure 1. Front view of control (non treated) embryo mouse showing: Eye (1), Ear Pinna (2), Trunk (3), Tail (4), Mouth (5).

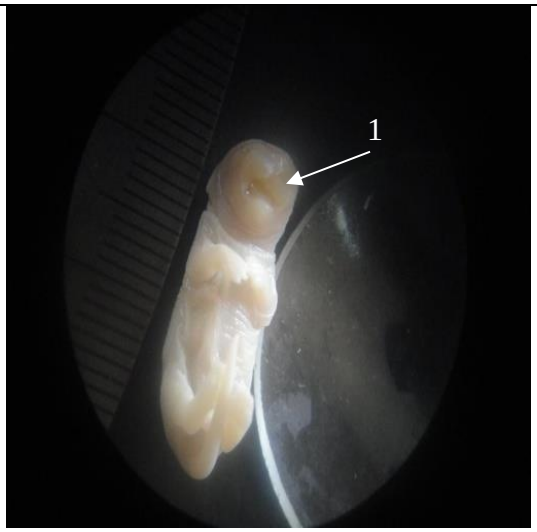

Figure 2. Embryo mouse treated with mg/kg showing: lip cleft(1).

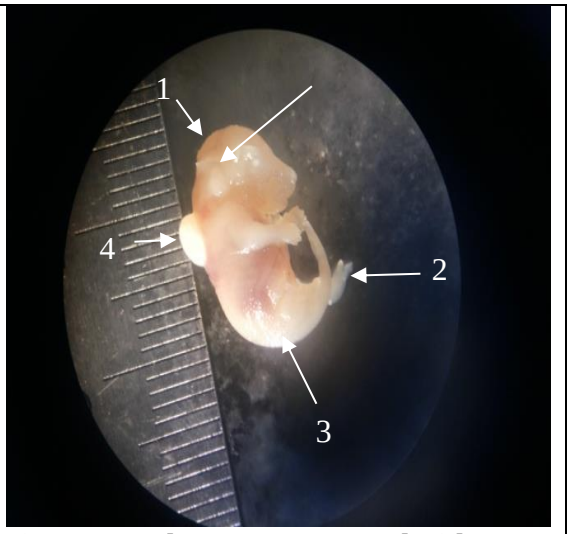

Figure 3. Embryo mouse treated with OTA 1mg/kg showing: brain projection (1), reduction in number of fingers (2), leg atrophy (3), Spina bifida cystica (4).

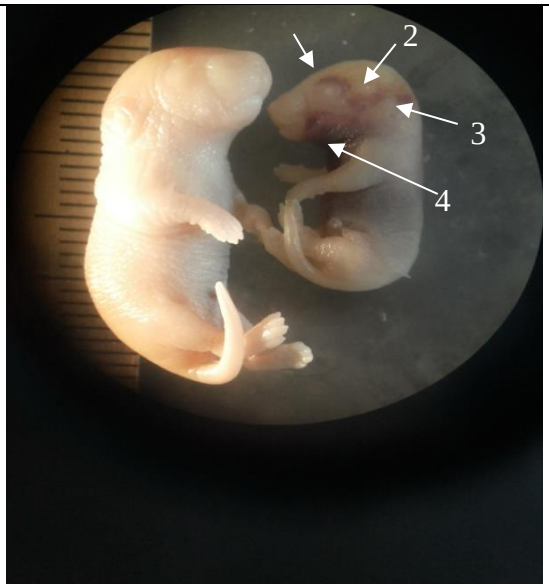

Figure 4. Comparison between the control mouse embryo on the left and mouse embryo treated with OTA 1mg/kg showing: Congestion around, eye (1), ear (2), back of ear (3), in neck (4) .

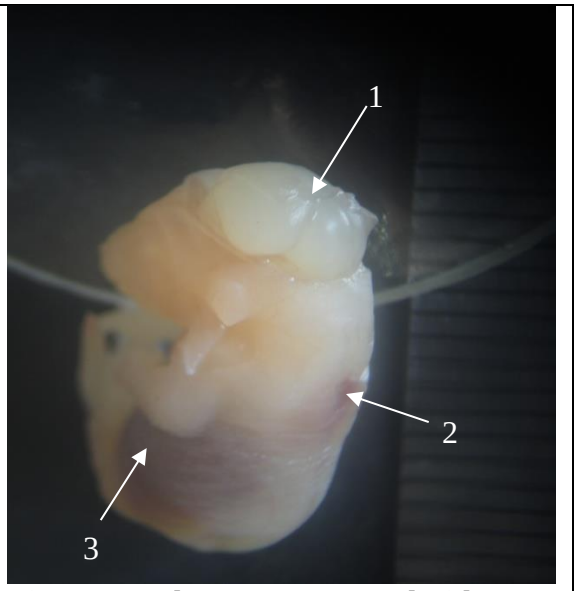

Figure 5. Embryo mouse treated with OTA 1mg/kg showing: Exencephaly (1), Spina bifida(2), Abdominal congestion (3) .

Overall, the results show that OTA is a teratogen causing Neural Tube Defects (NTD) in embryos, when pregnant mice are exposed to 1mg/kg and 2mg/kg on days 7-14 of pregnancy.The number of abnormalities observed in the trunk of embryos, such as spina bifida cystica, (Fig. 3), several congestions in different areas of the trunk,(Fig. 4,5), Spina Bifida, (Fig. 5), torsion of the trunk, (Fig. 6, 7), warped club foot, (Fig. 7), limb atrophy, (Fig.7,3), absence of anterior limbs, (Fig. 8), as well as paddle foot, (Fig. 6, 9), compare with control group, (Fig.1).

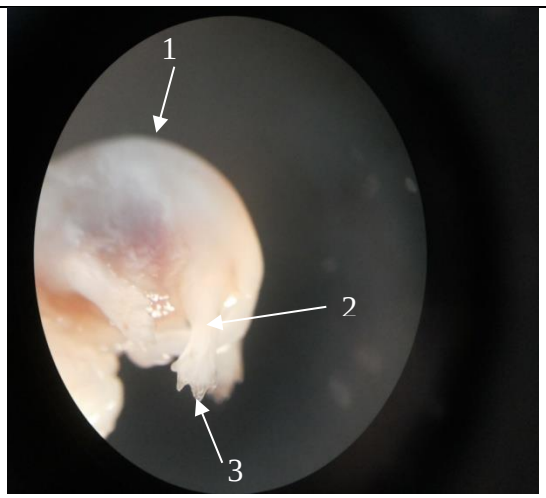

Figure 6. Embryo mouse treated with OTA 2mg/kg showing: trunk curvature (1), paddle foot (2), reduce the number of toes.

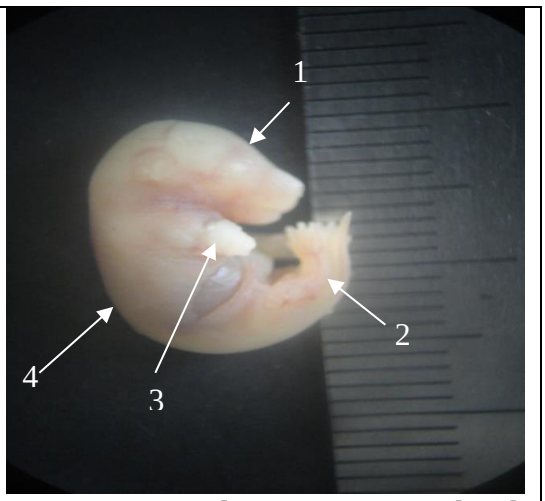

Figure 7. Embryo mouse treated with OTA 2mg/kg showing: Exothphalmia (1), warp foot (2), limb atrophy (3), trunk curvature (4) .

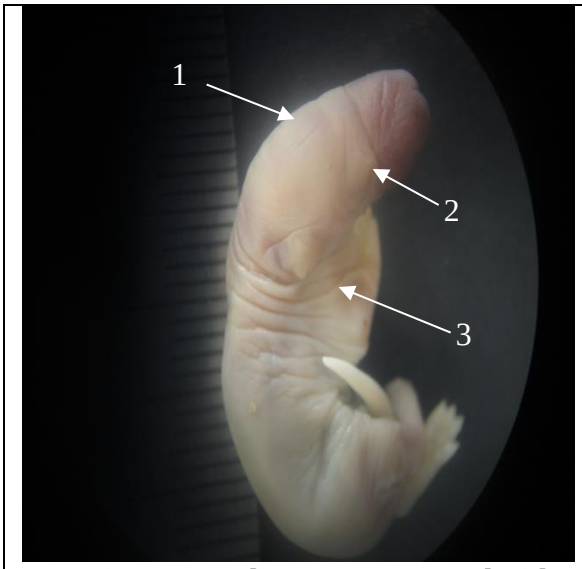

Figure 8. Embryo mouse treated with OTA 2mg/kg showing: large size of head (1), absence eye (2), absence of anterior limbs (3).

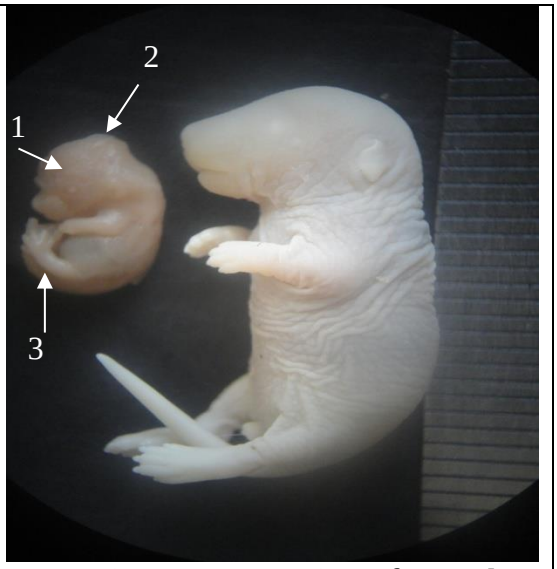

Figure 9. Comparison of control mouse embryo on the right and treated embryo mouse with OTA 2mg/kg showing: absence eye (1), brain progestion (2), paddle limb (3).

OTA has also been shown to enhance the lipid peroxidation results of free-radical-mediated toxicity,when zebra fish were treated with OTA at 0.20 µmol/L during the organogenesis period (33). Several abnormalities were also observed in the body and limbs of chicken embryos (34). Jarnail and Roland (35) confirmed these abnormalities following the oral treatment of mice with 3-mg/kg of OTA between days 8 and 18 of gestation, which resulted in a lack of protein build-up in the mother's body.

Finally, pregnant mice treated with OTA at 4mg/kg exhibited an increase in the number of embryos resorptions, (Fig.11, 12, 13), compared with control mouse embryos, (Fig. 10). Braun *et al*. (36) note an increased incidence of rat embryo resorption when mothers were given OTA (at 1,2,4 mg/kg) on gestation days 6-15, with any unresorbed embryos weighing significantly less than control embryos, many with open eyes, deformed snouts, and other major alterations including, wavy ribs and agenesis of the vertebrae. When the dose increased to 8mg/kg of OTA, embryos were either dead or resorbed.

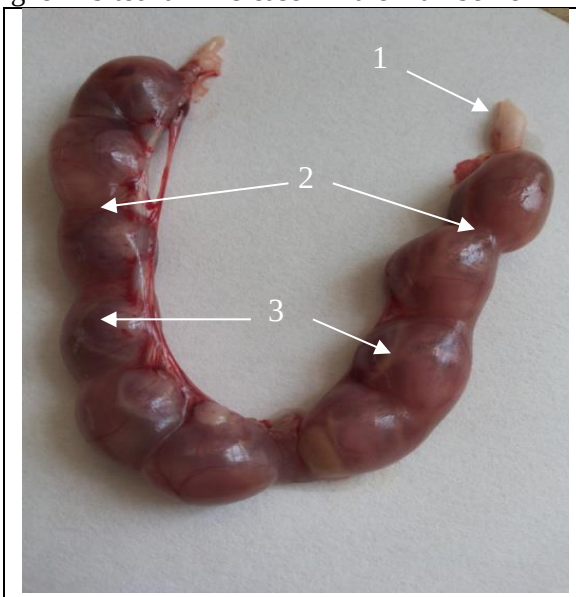

Figure 10. Reproductive system of control pregnant mouse showing: ovary (1), uterine horns (2) ,embryos (3) .

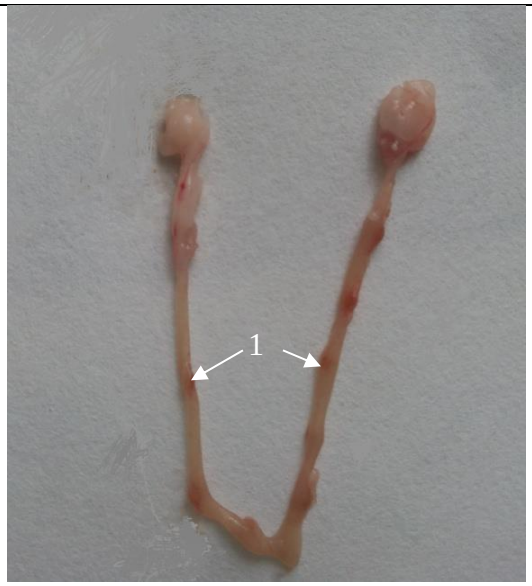

Figure 11. Reproductive system of pregnant mouse treated with OTA (4mg/kg) showing: resorption of embryo in uterine horns (1) .

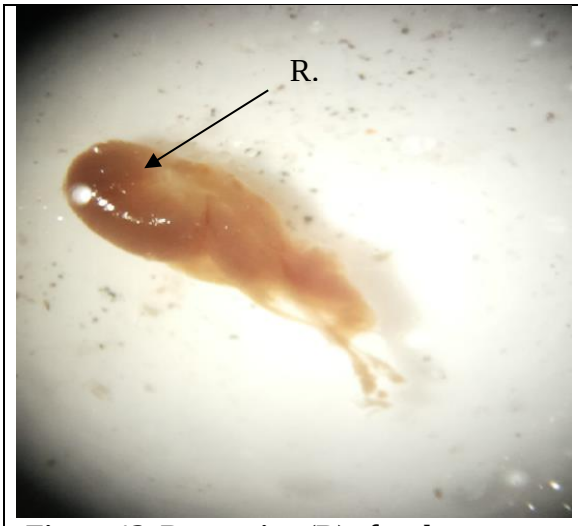

Figure 12. Resorption (R) of embryo mouse treated with OTA (4mg/kg). 160X

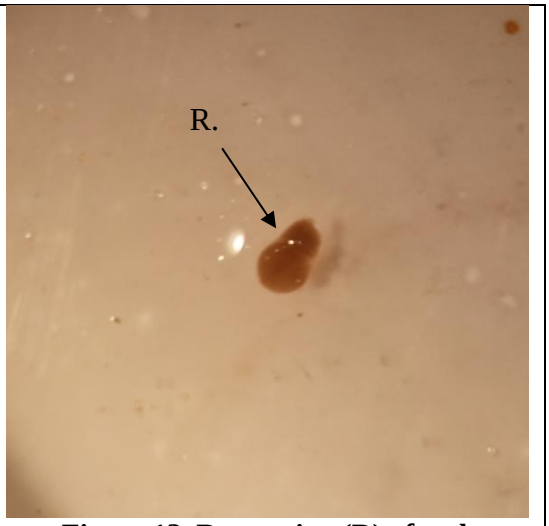

Figure 13. Resorption (R) of embryo mouse treated with OTA (4mg/kg). 60X

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تأثير الاوكراتوكسين -A في أجنة الفأر

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الخلاصة:

تضمنت الدراسة، تحديد التشوهات الحاصلة من الاوكراتوكسين –A (OTA) في أجنة الفأر. عشرون أنثى من الفئران البيض السويسرية (*Mus musculus*) البالغة ، قسمت على أربع مجموعات وبواقع 5 اناث لكل مجموعة ، وضعت الذكور مع الإناث بنسبة ذكر واحد مع انثيين في كل قفص، تم التأكد من حصول التزاوج بمشاهدة السدادة المهبلية (Vaginal plug) في الصباح الباكر التالي، وعُدّ يوم التزاوج هو اليوم صفر من الحمل والذي يليه اليوم الأول من الحمل. أختيرت ثلاث تراكيز تحت مميتة من الاوكراتوكسين-A ، 1mg/kg ، 2mg/kgو4mg/kg. جرعت الحيوانات مل لكل 10 gm من وزن الجسم لكل تركيز من مادة الاوكراتوكيين -A مرة واحدة في اليوم وللمدة من7-14 من الحمل. جرعت السيطرة الماء المقطر. شرحت الفئران الحوامل، وأستؤصلت أرحامها وأستخرجت منها الاجنة للتعرف على تأثيرات الاوكراتوكسين-A المشوهة لها. درست عدد من المعايير، منها التغيرات في وزن الجسم الحي للفئران الحوامل قبل التزاوج وبعد انتهاء مدة التجربة، أوزان وأطوال الاجنة، ودراسة التشوهات في أجنة الامهات المعاملة بالاوكراتوكسين-A ولمختلف التراكيز.

أشارت الدراسة الى عدم وجود فروق معنوية في معدل وزن الجسم للفئران الحوامل المجرعة بالتركيز 1mg/kg، مقارنة بمجموعة السيطرة، كما لوحظ أنخفاضا معنويا ($p<0.01$) في معدل وزن الجسم في الفئران الحوامل المجرعة بالاوكراتوكسين وللتركيزين 2mg/kg و 4mg/kg. تبين وجود أنخفاضا معنويا ($p<0.01$) في معدل وزن الجسم للأجنة لكلا المجموعتين من الامهات المجرعة بالاوكراتوكسين –A وللتركيزين 1mg/kgو 2mg/kg، مقارنة بأوزان الأجنة لمجموعة السيطرة. أما بالنسبة لأجنة المجموعة المجرعة بالتركيز 4mg/kg، فلاً يمكن تسجيلها كونها أجنة مرتشفة resorption في ارحام أمهاتها. أظهرت النتائج وجود فرق معنوي في معدل طول جسم الاحنة لكلا المجموعتين من الأمهات المعاملة بالتركيزين 1mg/kg و 2mg/kg من الاوكراتوكسين، مقارنة بأجنة مجموعة السيطرة. أظهرت النتائج العديد من التشوهات، بسبب المعاملات في المجاميع المعاملة، مقارنة بأجنة الفئران السيطرة، ظهرت التشوهات في الأجنة المعاملة بالاوكراتوكسين-A وللتركيزين 1mg/kg و2mg/kg منها الذنب المفقود أنعدام العيون، انشقاق الشفة ،أختراج الدماغ، والشوكة المشقوقة، تقوس الجذع وأختزال الاصابع . يمكن الاستنتاج ان للاوكراتوكسين –A تأثيرا سلبيا في الاجنة المعاملة أمهاتها به .

الكلمات المفتاحية: السموم الفطرية، Ochratoxin-A، تشوهات جنينية .