# Toxic effects of cadmium chloride on pregnancy, kidneys, and livers of newly born albino rats.

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**Abstract:**
Cadmium is an environmentally toxic metal, and epidemiological studies have confirmed that exposure to it originates from various environmental sources. Study investigates the effect of cadmium chloride on uterus in rats and newborn livers and kidneys. Twenty female rats, aged 6–8 weeks and weighing 200–250 g, were divided into two groups. Group A received distilled water, while Group B received oral $CdCl_2$ at a dose of 40 mg/kg/day via gastric gavage, five times per week. The first day after birth, the kidneys and livers of the newborns were collected, while the non-pregnant rats were sacrificed after 35 days to collect the uterus for routine histological examination. Histopathological examination of newborn kidneys revealed mild granular degeneration and a little necrosis of lining cells of renal tubules while livers showed a similar histological feature to control group. The uterus revealed marked hyperplasia of the endometrial epithelium with noticeable multiple glandular cyst formations and marked mitotic figures of the glandular lining cells, along with many tissue macrophages laden with hemosiderin. The study showed that exposure to oral $CdCl_2$ affected female rats; approximately 80% of the cases were non-pregnant. Meanwhile, 20% of the pregnant females showed a decrease in the number of newborns. Examination of the newborns' kidneys showed several changes, while the livers were similar to those of the control group.
**Key words:** Cadmium., endometrial hyperplasia., hemosiderin., renal tubules necrosis.

# التأثير السمي لكلوريد الكادميوم على الحمل,الكبد والكلى لدى حديثي الولادة في الجرذان البيضاء

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**الخلاصة:**
الكادميوم معدن سام بيئيًا، وقد أكدت الدراسات الوبائية التعرض له يكون من مصادر بيئية مختلفة. هدفت الدراسة إلى دراسة تأثير كلوريد الكادميوم على الرحم لدى الفئران، وعلى الكبد والكلى لدى حديثي الولادة. قُسِّمت عشرون أنثى فأر، تراوحت أعمارهن بين 6 و8 أسابيع، ووزنهن بين 200 و250 غرامًا، إلى مجموعتين . تلقت المجموعة (أ) ماءً مقطرًا، بينما تلقت المجموعة (ب) كلوريد الكادميوم فمويًا بجرعة 40 ملغ/كغ/يوم عن طريق التغذية الأنبوبية المعدية خمس مرات أسبوعيًا. في اليوم الأول من الولادة، جُمعت كلى وكبد المواليد الجدد، بينما استاصل رحم الفئران غير الحوامل بعد 35 يومًا لإجراء فحص نسيجي روتيني . أظهر الفحص النسيجي المرضي لكلى حديثي الولادة تنكسًا حبيبيًا خفيفًا ونخرًا طفيفًا في الخلايا المبطنة للأنابيب الكلوية، بينما أظهرت الكبد سمة نسيجية مشابهة للمجموعة الضابطة. كشف الرحم عن فرط تنسج ملحوظ في ظهارة بطانة الرحم، مع تكوّن أكياس غدية متعددة ملحوظة في الغدة الرحمية، وأنماط انقسامية ملحوظة في الخلايا المبطنة للغدة الرحمية، مع وجود العديد من الخلايا البلعمية النسيجية المحملة بالهيموسيديرين . أظهرت الدراسة أن التعرض للإعطاء الفموي ل كلوريد الكادميوم أثر على إناث الفئران، حيث كانت حوالي 80% من الحالات غير حوامل. في حين انخفض عدد المواليد الجدد بنسبة 20% لدى الإناث الحوامل. أظهر فحص كلى المواليد الجدد عدة تغيرات، بينما كانت الكبد مماثلة للمجموعة الضابطة.
**الكلمات المفتاحية:** الكادميوم، فرط تنسج بطانة الرحم، الهيموسيديرين، تنخر الأنابيب الكلوية .

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**Introduction**

Cadmium (Cd) is an environmentally toxic heavy metal. its epidemiological investigations show that Cd exposure is confirmed by both environmental and occupational sources, as a different way through which cadmium is released into the environment; through the air, water and through the soil (Genchi et al.,2020). Occupational exposure takes place because Cd is used in the steel industry and in manufacturing plastics or batteries and pigments (Nawrot et al.,2010). General population's primary route of exposure to cadmium daily dose comes from contaminated food or water sources (Nordberg et al.,2018). Moreover, tobacco leaves carry higher concentrations of cadmium than they are found in the soil, thus making smoking the main non-occupational sources (Järup & Akesson.,2009).

The reproductive system is one of the most sensitive systems to the effects of toxins, and in particular, Cadmium has been found to have serious impacts on the reproductive systems (Alaee et al., 2014). Cadmium may affect both the health of potential experimental animals and humans and affect the morphological, functional characteristics of the reproductive tract (Maretta et al., 2022). It has a toxic impact on male and female fertility, disrupts hormones each production and synthesis, decreases pregnancy likelihood or its quality even at low concentrations (Kumar et al.2019).

It has been found to induce many embryonic malformations depending on the developmental stage and the dose used. Craniocerebral, neurological, cardiovascular, gastrointestinal, genitourinary, and limb malformations have been reported in placentals (Nwar-Mohamed et al.,2009).

**Aim of the study:** To investigate the effect of cadmium chloride on the uterus of adult female rats and on the livers and kidneys of their newborn fetuses.

**Materials and Methods:**

**Animal care and breeding:**

The study was performed on albino rats (Rattus rattus). Ten healthy males and twenty females were obtained from the animal house of Iraqi Center for Cancer Research and medical genetics / Al-Mustansiriyah University. Their ages ranged between (6-8) weeks and weight between (200-250gm). The rats were maintenance at temperature (21±4 ºC) with photo periods 12hrs.Light /12hrs.Dark and the care is taken from sterilized and cleaned the cages. The dry food pellets and water were providing *ad libitum* ( Al-Nailey & Majeed.,2009 ) , the sexually mature females were isolated in the estrus phase and entered male rats in cages. One rat male for two females in each cage and males stayed for 10 days in cages. The pregnant females were sacrificed on the first day after birth; the kidneys, livers, and uterus were collected . While the non-pregnant female was sacrificed at 35 days of engaging and took their uterus .

**Experimental design & treatment:**

Twenty healthy female rats were divided equally into two groups: Group A (control) received distilled water, and Group (B) was used as an experimental group which administrated oral cadmium chloride (CdCl2, Jenin office, Germany) at a dose of 40 mg/kg/day via gastric gavage for five times week. In rats and mice, the acute oral LD50 of cadmium was estimated to be 100-300 mg/kg/bw (Faroon et al.,2008) and the dosing started from first day of entering males .Cadmium chloride powder is purchased from janin office(Country of manufacture: Germany)which located at Bab al-Mu'adham, Baghdad ,as 5gm under supervention of National Center of Hematology, Mustansiriyah University.

**Preparation of cadmium chloride solution:**

Five grams of cadmium chloride powder is dissolved in one liter of distilled water. We dosed rats with concentration 40 mg/kg/day depending on the weights and acute oral LD50 of cadmium was estimated to be 100-300 mg/kg/bw, in rats and mice. 2 ml of cadmium chloride solution is given to females via gastric gavage for five days a week at morning in eight o'clock .

**Histological preparations:**

Non -pregnant female rats were sacrificed after 30 days by decapitation under ether anesthesia for the excised uterus from the female reproductive system to histological examination, while the kidneys and livers of newborns were removed on the first day after birth. The samples were immediately washed and placed in 10% formaldehyde for 24 hours for routine

histological preparation and (H&E) staining (Suvarna et al.,2013). The sections were examined under a light microscope at magnification x (4,10,40).

**Results & Discussion:**

The current study showed that no pregnancy occurred in most female rats, from total number of administered group (B) only two became pregnant. In addition to that, the number of newborns of pregnant females was decreased, as one gave birth to one newborn and the second gave birth-to two, one of whom died at once after birth as (table-2). This is attributed to the toxic effect of cadmium. pregnancy did not occur in most experimental animals; we studied the uterus histologically to figure out the absence of pregnancy.

**Histopathological Change of the Uterus:**

The histopathological figures of the uterus in control group revealed normal appearance of the endometrial surface epithelium with normal uterine glands and normal myometrium (Fig-1 A, B). While in treated group revealed marked hyperplasia of endometrial epithelium with marked multiple glandular cysts formation of uterine gland and marked mitotic figures of glandular lining cells of uterine gland with many tissue macrophages laden hemosiderin (Fig-1 C, D).

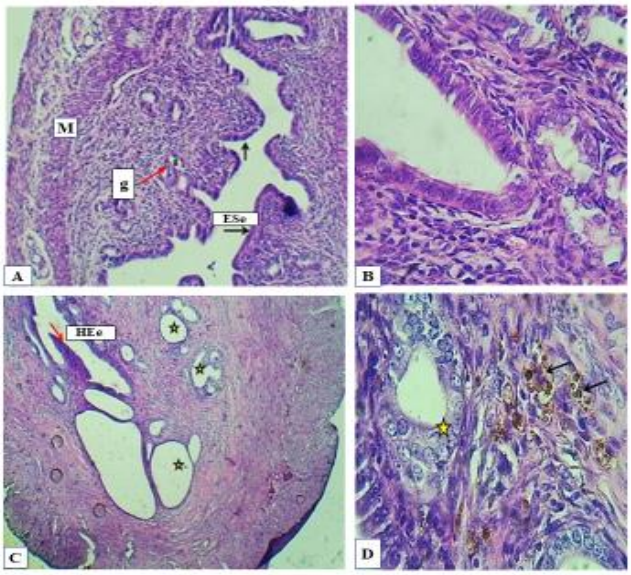


**Figure-1: A&B:** section of uterus (control group) shows normal endometrial surface epithelium (black Arrows ESe), with normal uterine gland (g) & myometrium (M). **C&D:** section of uterus (treated group): **C** shows: marked multiple glandular cysts of uterine gland (Asterisk), hyperplasia of endometrial epithelium (red Arrows HEe). **D.** showed marked mitotic figures of glandular lining cells of uterine gland (Asterisk) with many macrophages laden homoserine particle (Black arrows). H&E stain. A&C 100X, B&D 400x.

**Table 1:** Reveals the differential between Mean number of pregnancy control group and treated group administration cdcl2.

| group | mean | Std. deviation between group | P ≤ 0.001 |
|---|---|---|---|
| control | 2.00 | 0.51299 | |
| treated | 9.00 | | |

**Histopathological Change in Newborn kidney**

The histopathological figures of the kidney of newly born in treated group was revealed a mild granular degeneration with little necrosis of the lining cells of renal tubules with normal appearance glomerular cells, normal appearance of renal capsule, normal lining cells of all types of renal tubules and glomerular cytoarchetecture (Fig-2 C, D). While, in the control group normal appearance of renal capsule, normal lining cells of all types of renal tubules and glomerular cytoarchetecture (Fig-2 A, B).

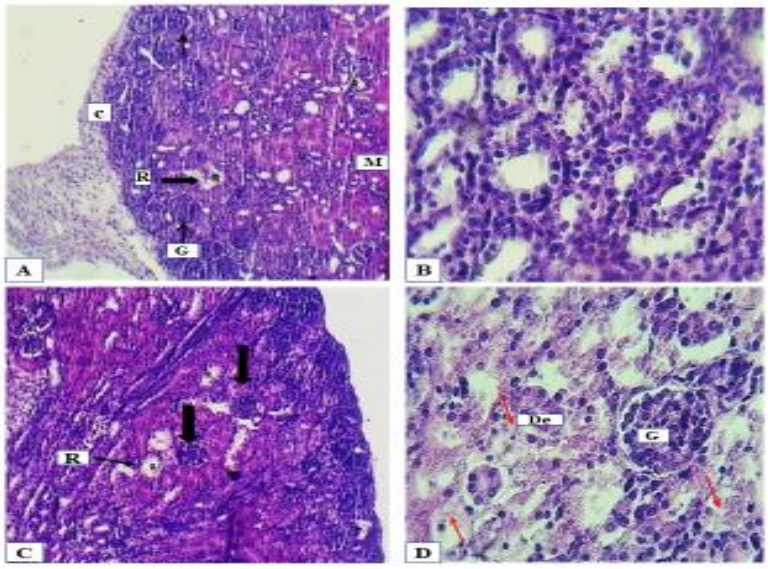


**Figure-2: A&B:** section of kidney (newborn-control), **A** shows normal appearance of renal capsule (C,) renal tubules (R), glomeruli (Arrows G) & renal medulla (M). **B**: shows normal appearance of proliferating cells of renal tubules. **C&D:** section of kidney (newborn-treated group) **C** shows normal lining cells of all types of renal tubules (R). **D** shows: mild granular degeneration with little necrosis of lining cells of renal tubules (red arrows De). and normal glomerular cells (G) H&E stains. A 100x, B,C &D 400X.

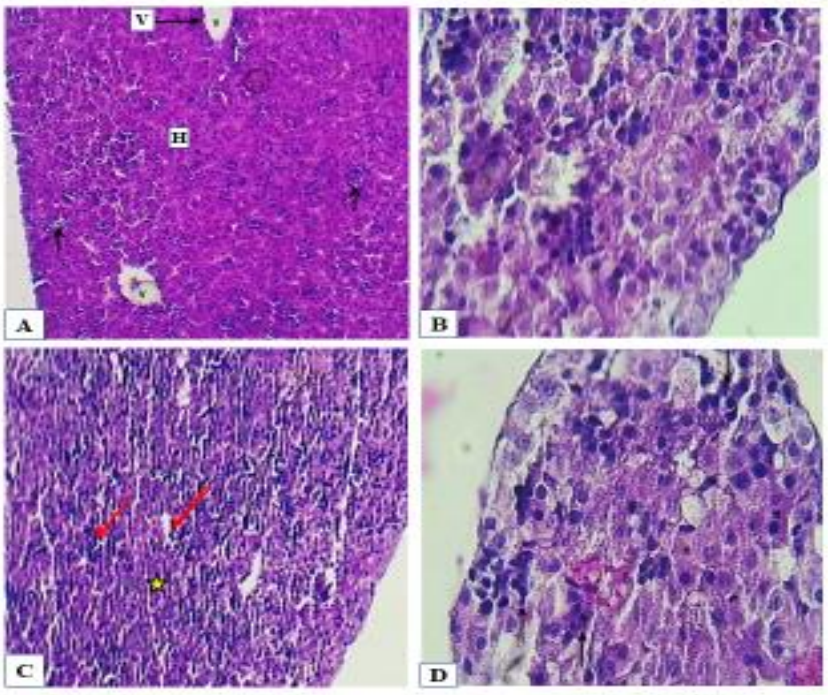


**Figure-3: A&B:** Section of hepatic lobule (newborn-control): shows normal appearance of central vein (V) normal arrangement of hepatic cords (H) and sinusoid that filled with hemopoietic tissue (black Arrows). **C&D:** Section of hepatic lobule (newborn-treated group) shows normal arrangement of hepatic cords (asterisk) and sinusoid that filled with hemopoietic tissue (red Arrows). H&E stain: A,B,C& D 100x.

**Histopathological Change in Liver of Newborn**

The histopathological figures of the liver in control group revealed normal appearance of the central veins, normal arrangement of the hepatic cords and sinusoids that were filled with hemopoietic tissue (Fig-3 A&B).and the histopathological figures of experimental group showed the liver were similar those of control (Fig-3 C&D).

**Table 2:** Reveals the differential between Mean number of newborn control group and treated group their mother's administration cdcl2.

| **groups** | **mean± Std. deviation** | **P ≤ 0.003** |
|---|---|---|
| control | 5.5000 ± 0.52705 | |
| treated | 1.5000 ± 0.52705 | |

The current study was targeted the effect of cadmium on the females (uterus) as a daily routine exposure (as five day a week), when cadmium administered to females rats was noted that the small number of pregnant women occurred, as two pregnancies occurred out of 10 females (table-1), as well as the small number of births to pregnant mothers, as one of them gave birth to one newborn and the other gave birth to two newborns, one of whom died immediately after birth. Therefore, a histological examination of liver and kidneys of newborns as most vital organs was performed and female uterus was performed to decide the reason that pregnancy did not occur as many studies have investigated.

The reproductive system of female is particularly susceptible to being harmed by cadmium, it has specifically effect on uterus, People are exposed to cadmium directly and

inhalation of the same through cigarette smoking or consumption of food and water contaminated by cadmium. The effects of cadmium on female reproduction include interference with steroidogenesis, retardation of puberty and/or menarche, pregnancy loss, menstrual cycle and reproductive hormone disorders and low birth weights and premature birth (Olaolu.,2018). Cadmium is consider female reproductive toxins ,this might be a direct effect on uterus or a modulation on the hypothalamic-pituitary-gonadal hormones, which can either suppress or raise several critical metabolic reactions known to make it an endocrine disrupt (Diamanti-Kandarakis, et al.2009 ; Tchounwou,et al.2018), numbers of researches suggests that environmental contact with this metal may be one of agents caused the disorders that affect the female reproductive system, infertility, premature puberty, polycystic ovary syndrome (Rull et al.,2020 ; Chen X et al ., 2017 ; Lee, et al.2020 ; Eriksen et al ., 2014). Shamelashvili & Shatorna agree with our study found Cadmium have negatively affected development of embryos, through decreased number of rat embryos an average of 22%. Parallelly, embryonic mortality rises 4.8 folds on the 13th day of the embryo development and 3.8 folds on 19th day. Hence, according to the data obtained, cadmium compounds are quite embryo toxic and raise the embryonic death of rats in several times (Shamelashvili & Shatorna ., 2021)

In our study histological examination of uterus for non- pregnant female rats administered with cadmium revealed marked hyperplasia of endometrial epithelium with marked multiple glandular cysts formation of the uterine gland and revealed marked mitotic figures of glandular lining cells of the uterine gland with numerous tissue macrophages laden hemosiderin this agree with authors found Estrogen stimulates uterus hyperplasia and cadmium acts on an estrogen dependent pathway (Rzymski,et al.2014 ;Yang et al., 2022). Cadmium is showed related to increased estrogen, it deposits in human endometrial tissue, and its concentration is higher in smoker female (Jackson,et al.2011).

Estrogen stimulates Hyperplasia or proliferative endometrial glandular epithelium and relative insufficiency of progesterone (Nees et al ., 2022). Additionally, cadmium has potent estrogen and androgen mimicry because cadmium can bind to estrogen and androgen receptors(Manna et al ., 2016 ). Like estradiol, cadmium exposure can induce a very rapid activation of extracellular signal-regulate kinase 2 (ERK1/2) and protein kinase B (AKT)(Zhang, et al 2008). Cadmium also reduces the production secretion of progesterone through down regulation of StAR, a protein essential in cholesterol transport across the mitochondria and by inhibiting the cytochrome P450 cholesterol side-chain enzyme P450scc(Takiguchi &Yoshihara ., 2006). Endometrial hyperplasia is mostly associated with ovulation disorders thus, 71.0% of these patients with primary infertility were seen (An et al .,2024).

patients suffering endometrial hyperplasia (EH), often have abnormal uterine bleeding (AUB), which may generate a high level of heme production (Ruan, et al .,2022) . There can be high levels of heme release in the uterus of any female patient with abnormal uterine bleeding, as heme is generated from the post-lysis of hemoglobin in the bloodstream and is believed to cause many sorts of oxidative damage and inflammatory (Martins & Knapp.,2008). In pathological states, the body's capability to metabolize heme becomes overwhelmed and heme accumulates to toxic levels inside the body and imparts damage, disease and heme may interfere with the activity of a variety of immune cells, including macrophages, as well as recruit and activate immunologic cells (Liu et al ., 2019 ).

The present study appeared that the kidney shows mild granular degeneration with little necrosis of the lining cells of renal tubules with normal appearance glomerular cells, while the histopathological examination of the liver appeared like the control. This agree with authors found Cadmium toxicity is regulated by metallothioneins (MT),the Cd–MT complex is formed chiefly in the liver and is released into the circulation more slowly over a period and then transport steps: the kidneys (Curtis *et al* .,2009 ; Simonescu *et al* ., 2020 ).Degeneration , desquamation in the lining epithelium of proximal convoluted tubules noted and these finding could be explained as; Cd induced nephrotoxicity through the following steps; The

formation of the complex between the cadmium ion and protein-metallothionein. (Cd-Mt), which is produced in liver and distributed into blood stream. It was removed by the renal glomeruli and accumulated within the proximal convoluted tubular cells, this led to tissue deterioration and progressive destruction of the function of the organ (El-Refaiy& Eissa .2013 ). As well as cadmium exposure caused a suppression on the activities of antioxidant enzymes and the elevation of the level of malondialdehydes (MDA) and reactive oxygen species (ROS). This oxidative stress was caused by the imbalance between the formation of ROS and the ability of antioxidant enzymes to break them down (Birben et al., 2012).

Metallothioneins , are stored in hepatocytes in the form of Cd-MT complexes, therefore act as antidote preventing toxic Cd ions from damaging the cell and majority of these complexes are accumulated in the liver although small concentrations of these complexes may dissolve in the blood passing in the tubular fluid. In lysosomes of renal tubular cells the complex of Cd-MT is decomposed to amino acids and free Cd ions , these released ions stimulate the production of other MT proteins in kidneys where these complexes are found; the stability of these Cd-complexes is not high and these complexes dissociate to Cd-ions and free metallothioneins (Saboli´c et al .,2010) .

**Conclusion**

The present study appeared that exposure to oral Cadmium chloride administration effected on female rats for most cases, approximately 80% of cases was revealed no pregnancy and histological examination for uterus of these female rats administered of cadmium revealed marked hyperplasia of endometrial epithelium with clear multiple glandular cysts formation of the uterine gland; and revealed marked mitotic figures of glandular lining cells of the uterine gland with numerous tissue macrophages laden hemosiderin. Meanwhile the 20% of pregnant female rat noticed decrease in number of newborns and histological examination for kidneys of newborns show granular degeneration with little necrosis of the lining cells of renal tubules, while the livers revealed a normal appearance of the central veins, normal arrangement of the hepatic cords and sinusoids that filled with hemopoietic tissue like control.

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