Histopathological Studies on the Effect of 4-Tert- Octylphenol on the Neonatals from Treated Pregnant Female Rats after Their Delivery and Maturation

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ABSTRACT

The present study was under taken to examine the effect of 4-tert- Octylphenol (40mg/kg and 80 mg/kg) on female rat from the first day post natal until weaning. At the lower dose (40 mg/kg), the histological study of liver of embryos showed expanded of blood vessels and rupture of epithelial layer of portal veins while the higher dose (80 mg/kg) led disordered liver architecture represented by disassociation of hepatocytes which filled by fat vacuoles with extracellular fat infiltration. Also, the lower dose resulted in separation in the lining epithelium of proximal tubules of kidney with decayed parietal and visceral epithelium of glomerulus, while the second dose induced serious effect in proximal and distal convoluted tubules in beside the collecting tubules. This dose also affected glomerules found in the cortex that appeared smaller in size than the medulla. On the other hand, at maturity, the exposure to low dose of octylphenol led to proliferation of the lining and secretory epithelium of the uterus and a reduction in the number of the uterine glands. Whereas, exposure to high dose resulted in complete absence of the corpus luteum and different stages of ovulation.

Mating between mature females treated with high dose of octylphenol during the lactation and normal males, led to pregnancy failure, while low dose reduced the number and weight of embryos dramatically.

These results indicated that exposure to octylphenol from post natal to weaning caused histological alterations in liver, kidney, uterus and ovary in female rat and consequently affected on their fertility.

KEY WORDS: Octylphenol -rat-liver-kidney-ovary-uterus-lactation-weaning-post natal- high dose- low dose.

INTRODUCTION

The present study aimed to investigate the histopathological studies of liver, kidney, uterus, and ovary of neonatal female rat after their exposure to octylphenol from postnatal to weaning.

It is well known that the normal functions of all body systems are controlled by the endocrine system, and any disturbance in its functions especially the critical periods as development, gestation and lactation led to serious and prolonged damages on these systems (Nagao *et al*., 2001). Therefore, chemicals resemble functionally the sex hormones (particularly estrogens) are very important because of their interference with estrogen receptors and their direct influence on the hormone synthesis. These chemicals influenced on the relation between hypothalamus and pituitary gland as well as the relation between gonads and hormonal secretion and metabolism.

Alkyl phenol ethoxylates are considered as non-ionic synthetic chemicals and have the ability to decrease the surface tension. These chemicals are used 40 years ago in the detergents, paints, plastic, textile and colloids industries (Nimrod and Benson, 1996). About 300,000 tons of these chemicals are produced annually all over the world and octylphenol represents 20% of them (Naylor, 1992).

Human may exposed to octylphenol through polluted water, sewage used as fertilizers or food to plants or aquatic animals and materials used in packing foods and drugs. These chemicals have estrogenic activity and are responsible on the gametes reduction in human during the last 40 years, where their effects on the genital duct formation in both male and female appear in the embryonic stages (Gotz *et al.*, 2001). Shape *et al*. (1995) found rupture in the genital duct, reduction in the sperm number and distortion of sperms in mammals. They also observed that exposing female rat to one dose of nonoxynol-g (N- g) led to a rupture of vaginal epithelium and acute inflammations in the vagina and uterus neck, this could be attributed to its ability to diffuse through cellular membranes (Tryphonas and Buttar, 1982),they also recorded an embryonic toxicity when female rat exposed to a dose of 50 mg/L nonoxynol-g (N- g) during the first week of gestation where a decrease in the number of the absorption positions was observed. The decrease in the reproductive efficiency was attributed to reduction in the membrane normality of the receptor epithelium of the embryo. Soto *et al.* (1991) found in female rats exposed to 50 mg/kg of nonylphenol an enhancement of the mitotic division in the epithelium of the uterus.

Lee and Lee (1996) showed that peritoneal injection of 1mg/kg of nonylphenol resulted in uterus growth in immature females similarly the normal estrogen 17-E2. While exposure of newly born rat to nonylphenol led to

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a decrease in the size of testis and secondary genital organs as well as a reduction in the sperm number and an estrogenic effect on the female genital duct of female (Boockfor and Blake, 1997).

DeJager *et al.* (1999 and 2001) noticed that rats exposed to nonylphenol (P.NP) during gestation and lactation disturbed the weight of body and testis during the embryonic stage, as well as after birth and weaning (till 10 weeks age). They also noticed a significant decrease in the diameter of seminiferous tubules and germinal epithelium, in addition to a body weight decrease, toxic marks on the epidydmus, male gametes and the number of sperms.

Nagao *et al*. (2001) showed disturbance in the reproductive system and efficiency when nonylphenol (NP) was injected subcutaneously in young newly born rats from the first to the fifth day after delivery. This disturbance represented by a significant delay in the sexual maturity and deceasing in the weight of the body and prostate. They also proved that octylphenol induced a disturbance in the balance of the endocrine glands and may interfere with the normal reproduction in the terrestrial, aquatic and human life.

Katsuda *et al.* (2000b) mentioned that octylphenol inhibited the gland formation the uterus in female rats when newly born exposed to octylphenol. They also added that environmental and functional exposure to these synthetic chemicals is responsible for the serious effects on the genital duct in various living organisms including man. There was no ovum in the oviduct in the treated rats while at 10 weeks by the rate 13.1±0.8 ovum in the control group. They also added that these chemicals led to absence of follicles, and corpus luteum with changes in the lining epithelium of the uterus. Certa *et al*. (1996) observed that treated rats by high dose of Octylphenol (OP) resulted in its accumulation in many tissues as liver, kidney and muscles, Daidoji *et al.* (2006) mentioned that nonylphenol inhibit the endocrine glands where it continuously occurred in the liver of rats after toxicity removing in the form of glucuronide.

Zaroogian *et al.* (2001) studied the effect of octylphenol on the development of gonads, liver and kidney in the case of sexual immature fish and found a decrease in the testis size and histopathological changes in the liver, kidney and testis. Moreover, Willoughby *et al.* (2005) demonstrated that many synthetic chemicals as Octylphenol (OP) inhibit the activity of the endocrine glands and have a critical effect on the development of the genital system as they are able to bind with estrogen receptors. They also noticed that in the treated group with Octylphenol (OP) during the early period after delivery (from 0 to 10 days) inhibited ovulation in a significant number of female rats with reduced ovary weight and relatively high weight of uterus. Histological investigation showed a reduction in the corpus luteum and an increase in the growing follicles, while ovulation was normal in the control group.

Hafez *et al*. (2008) showed cytological, pathological, histological, histochemical and ultra structural changes in the male genital duct of embryos and newly born from mothers treated by either low or high doses. These changes were continued till maturity. Takahashi *et al* .(2008)concluded that dinitrophenol (DNP)has general and reproductive/developmental toxicity, but not teratogenicity. Bian *et al.* (2006) recorded that treatment by OP decreased the weight and size of testis, epidydmus, and prostate as well as distortion of the spermatozoa and Sertoli cells with a reduction in the rate of spermatogenesis, all these changes influenced the fertility.

MATERIALS AND METHODS

Method of Experiment: Mature females albino white rats, about 200mg in weight were placed for one night with mature males for mating and fertilization. After mating confirmation by vaginal smear, pregnant females were divided into three groups; the first untreated group is the control one, the second group was treated by oral dose of 40 mg/kg of 4-tert-octylphenol while the third one was treated by 80 mg/kg 4-tert-octylphenol (Boockfor and Blake, 1997). The treatment of mother‘s rats was continued during lactation till weaning. Infants were left till maturity then mating was allowed between treated Infants females with normal males to investigate the effect of 4-tert-octylphenol on fertility. Weights of control and treated groups at the beginning and the end of the treatment was recorded and then weekly after treatment till maturation. Cotton seed oil was used as a solvent of Octylphenol (OP).

Samples of liver and kidney from infants at the weaning age treated with both doses were taken. Samples of uterus and ovary from infants of treated females at maturity were also taken. All specimens were placed in formalin and the standard procedure of dehydration, clearing and wax embedding was followed. Histological sections were done and stained with Hematoxylin and Eosin (Drury and Wallington, 1967). Sections from each tissue were compared with those of the control group.

RESULTS AND DISCUSSIONS

i. Histological investigation of liver and kidney at the weaning age:

1-Kidney:

The histological sections from treated group by 40 mg/kg showed normal size of cortex in ratio with the

medulla in comparison with control group (Fig. 1). , partial decaying of parietal and visceral epithelium of most glomerulus, dilation of the capsular space and reduction in the blood capillaries. Sections also showed some normal glomerulus whereas most proximal convoluted tubules were appeared swollen with disassociation of the lining cells and rupture of the brush border. It was also observed decaying of some lining cells with scattered nuclei on the basement membrane of the tubule. While the distal convoluted tubules did not seriously affect as some of them appeared nearly in normal form and others appeared with disassociated lining epithelium, decayed cellular membranes, cytoplasmic vacuoles, pale staining and large spaces in the interstitial connective tissue due to decaying of the renal tubules. It was obvious that the collecting tubules did not seriously affect (Fig. 2).

In addition to the previous changes, others were also observed when a dose of 80 mg/kg was used, as expansion of the nutrient blood vessels, congestion and Oedema in the tissue, atrophied glomerulus, expansion of blood capillaries as a result of spaces formation between the their mesonchymal cells and smaller cortex size comparing with medulla. Also, the proximal and distal convoluted tubules as well as the collecting tubules were affected by increasing the dose as their lining epithelium decayed (Figs. 3, 4). (Ohshima *et al*., 2005) contributed these changes to the inhibitory effect of 4-tert-octylphenol on the kidney chromosomes of type 2 where embryos and infants obtained this compound through placenta and milk (Hafez *et al*., 2008).

2- Liver:

At lower dose, a dilation and widening of blood sinusoids, especially in the portal area, with blood accumulation and rupture of lining epithelium of some portal vessels. Except the previous changes, liver appeared structurally normal in comparison with control group (Fig. 5). ; arranged hepatic strands, characterized portal area by a branch of portal vein and hepatic artery, proliferated bile ductules and more Kupffer and lining cells between hepatocytes (Fig. 6).

On the other hand, at a dose of 80 mg/kg, previous changes at the lower dose were observed beside other histological changes. These changes were oedema in the tissue, decaying of some portal and central veins, disassociation of hepatic strands, and appearance of fat vacuoles inside and outside the hepatocytes with an obvious increase in Kupffer cells, phagocytes and lymphocytes. It was also observed that the number of bile ductules decreased with deformed structure (Figs. 7, 8). These results are in agreement with those obtained by Zaroogian *et al*. (2001), and this may be due to the inhibitory effect of OP on the liver chromosome of type 1 as it is well known the ability of alimentary canal in absorption of these estrogens (Ohshima *et al*.,2005).

Lee and Lee (1996) explained these changes that nonoxynol affect on the enzymatic activity of hepatic chromosomes (CYPIA, EROD) and their genotype in the rat where Matsumoto *et al.* (2002) mentioned that exposure of pregnant female rats to OP decreased the hepatic enzymatic activity to about the half in the embryos due to their effects on the hepatic chromosome.

ii. -Histological investigation at maturity:

1- Uterus: in comparison with control group (Fig. 9)

The histological investigation of the uterus sections at the first dose showed inhibition in the formation of the uterine gland, small gland size, and proliferation of the lining columnar epithelium of uterus and secretory epithelium, and an increase in the number of phago-follicles. It was also observed a proliferation of the internal epithelium of glands resulting in their extension and presence in the lining epithelium of the uterus. This may be due to proliferation of tissue and squamous epithelial cells (Figs. 10, 11). At the second dose, beside the previous changes, other changes were recorded represented by rupture of the uterine epithelium, decreasing in the uterine glands although uterus passes by the fast growing phase during the first two weeks of delivery. The uterine glands are formed for the first time at the 9^{th} day, complete their formation at 10-14th day after delivery and increase in their number with age. A disassociation of the apparent lining glandular cells and their pale staining were also observed. Investigation also showed dilation and widening of blood vessels and capillaries with oedema appearance, smaller muscular layer in comparison to the internal region of the uterus and an increasing in the uterus weight (Figs. 12, 13).

These observation are in accordance with Katsuda *et al*., 2000b; Willoughby *et al* ., 2005 who attributed these changes to the effect of OP on the endocrine glands and their ability to bind with estrogen receptor as the genital duct is considered as the last fate of environmental pollutants effects (Aydogan and Barlas, 2006). It is well known that OP dissolves in lipids and accumulates biologically in the stored fats in the body. Therefore during gestation and lactation, the precipitated fats are used and pass to embryos and infants affecting on the sexual growth as they pass easily through the plasmic membrane of cells (Sharpe *et al.*, 1995).

Tryphonas and Buttar (1982) and Matsumoto *et al.* (2002) said that exposure to nonylphenol and octylphenol is very danger on the reproductive organs in the embryos and newly born rats. This opinion is agreed with Yoshida *et al*. (2002) who injected newly born

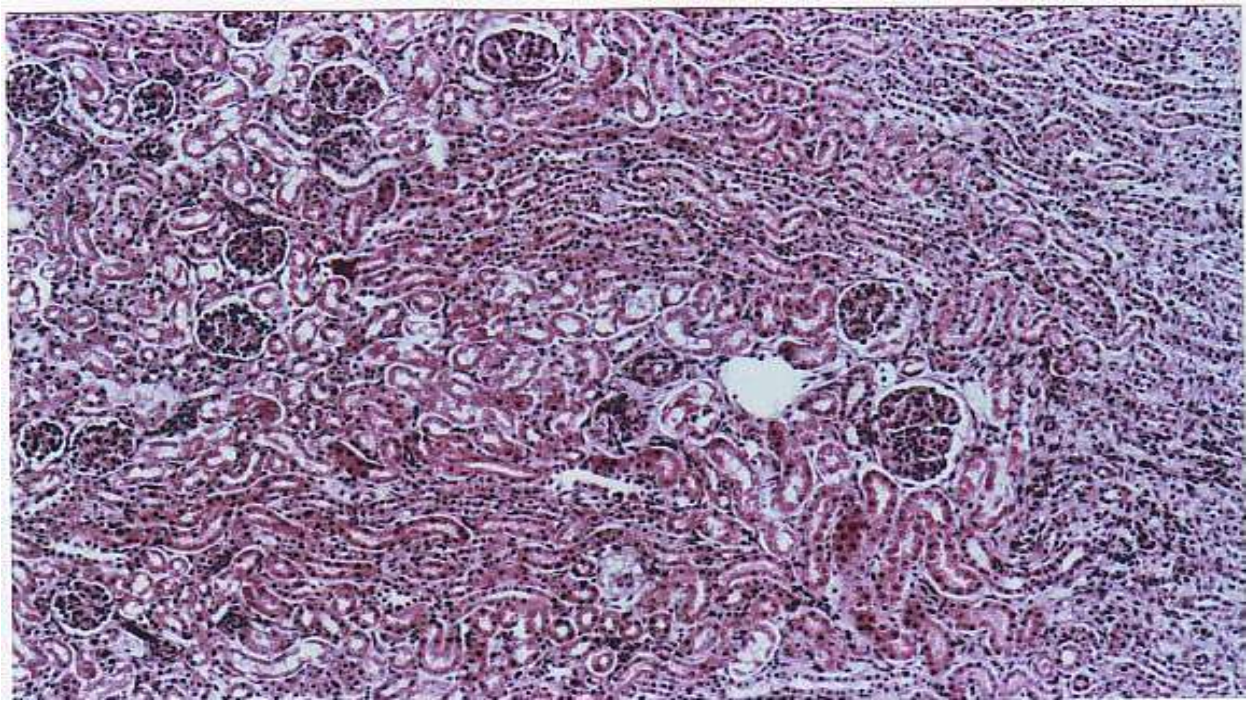

Fig1. Light micrographs of kidney from 21 days age rat from delivery IN CONTROL GROUP (H & E 40x)

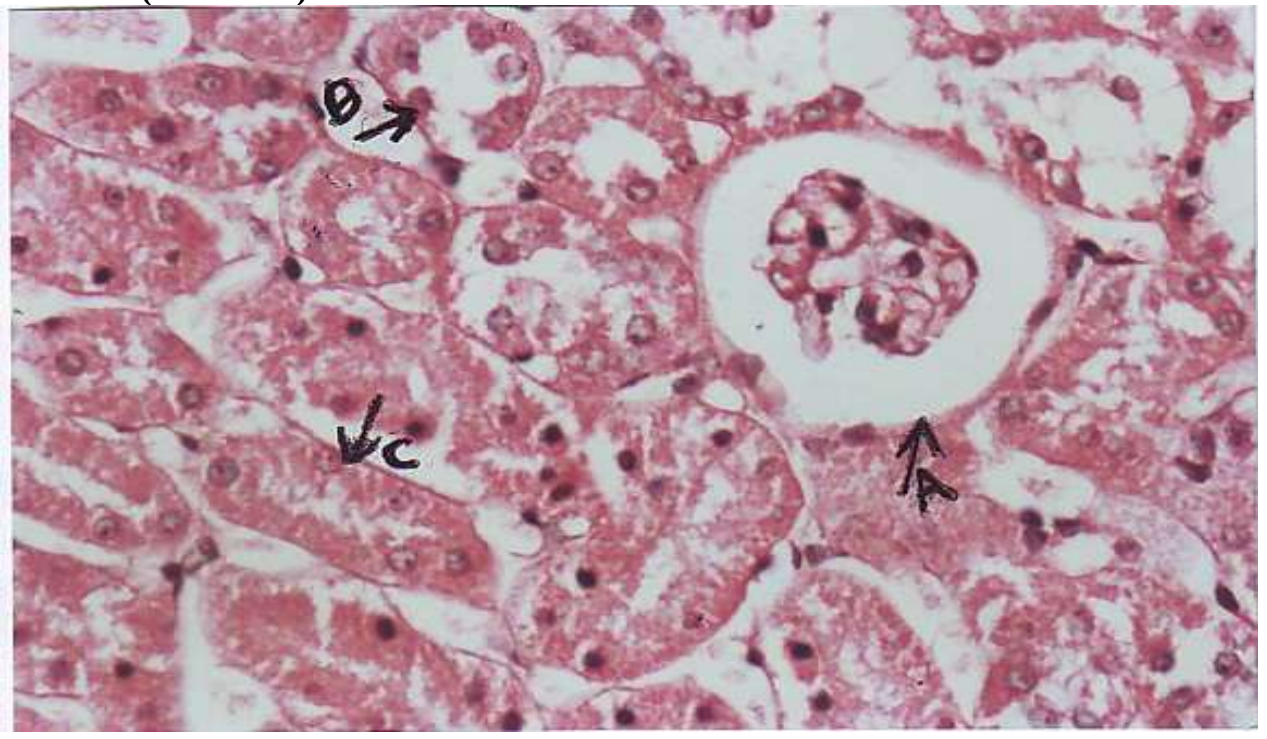

Fig 2. Light micrographs of kidney from 21 days age rat from delivery at low dose treated group showing shrinking glomerulus (A) and decaying the proximal (B) and distal (C) convoluted tubule epithelium (H & E 100x)

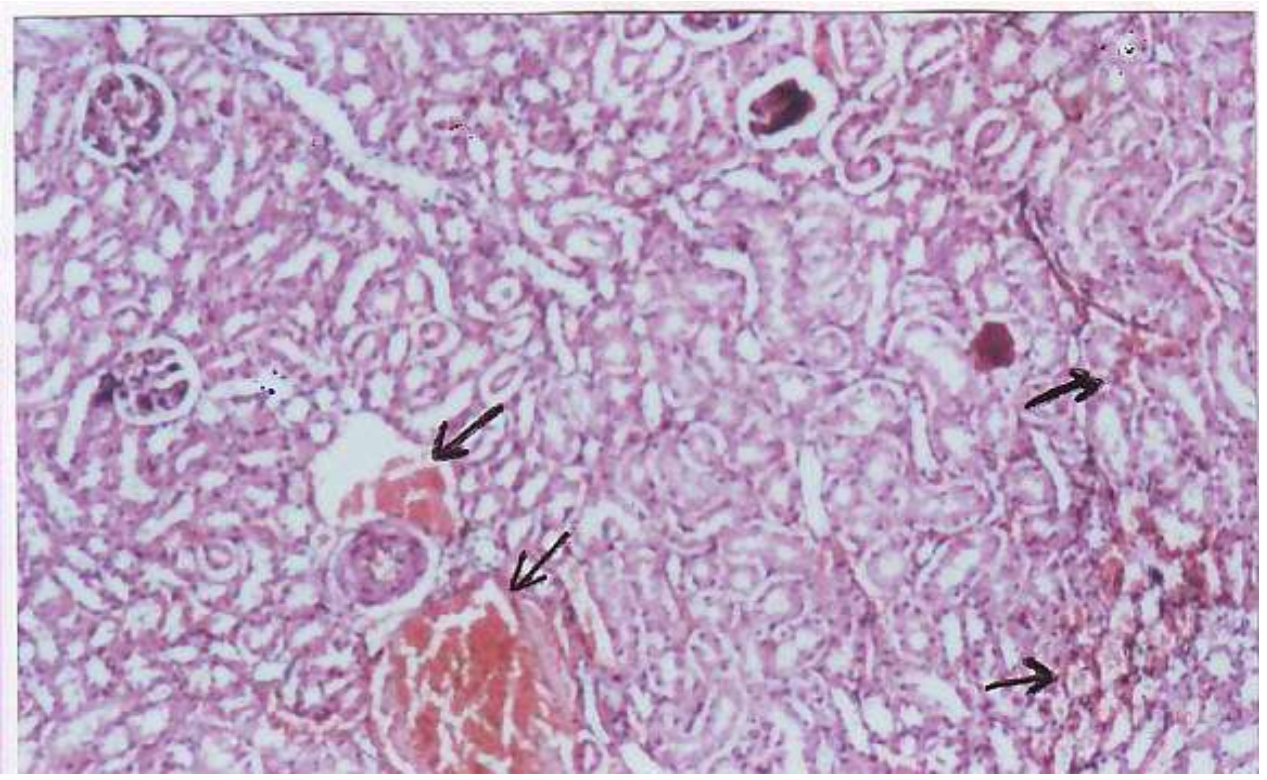

Fig 3. Light micrographs of kidney from 21 days age rat from delivery at high dose treated group showing expansion and oedema of the blood vessels (H & E 40x)

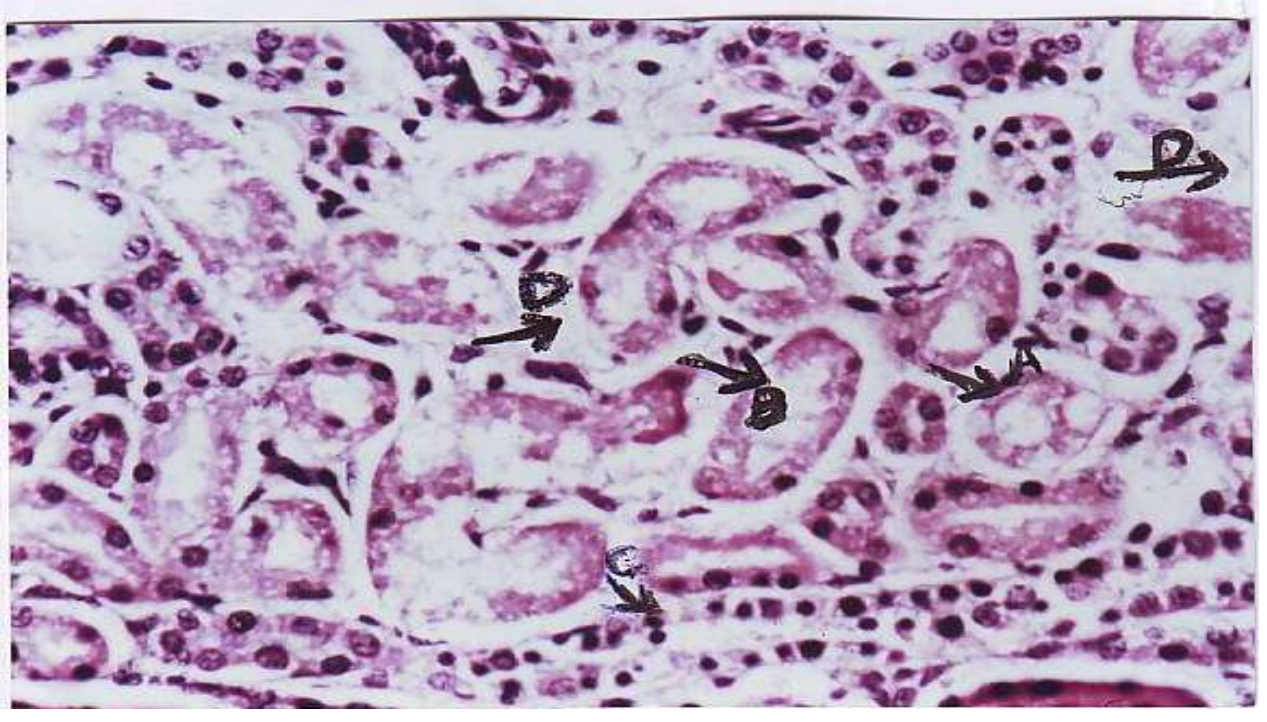

Fig 4. Light micrographs of kidney from 21 days age rat from delivery at high dose treated group showing decaying of the proximal (A) and distal (B) convoluted tubules and collecting tubules (C) as well as appearance of vacuoles in the interstitial tissue (D) (100x H & E)

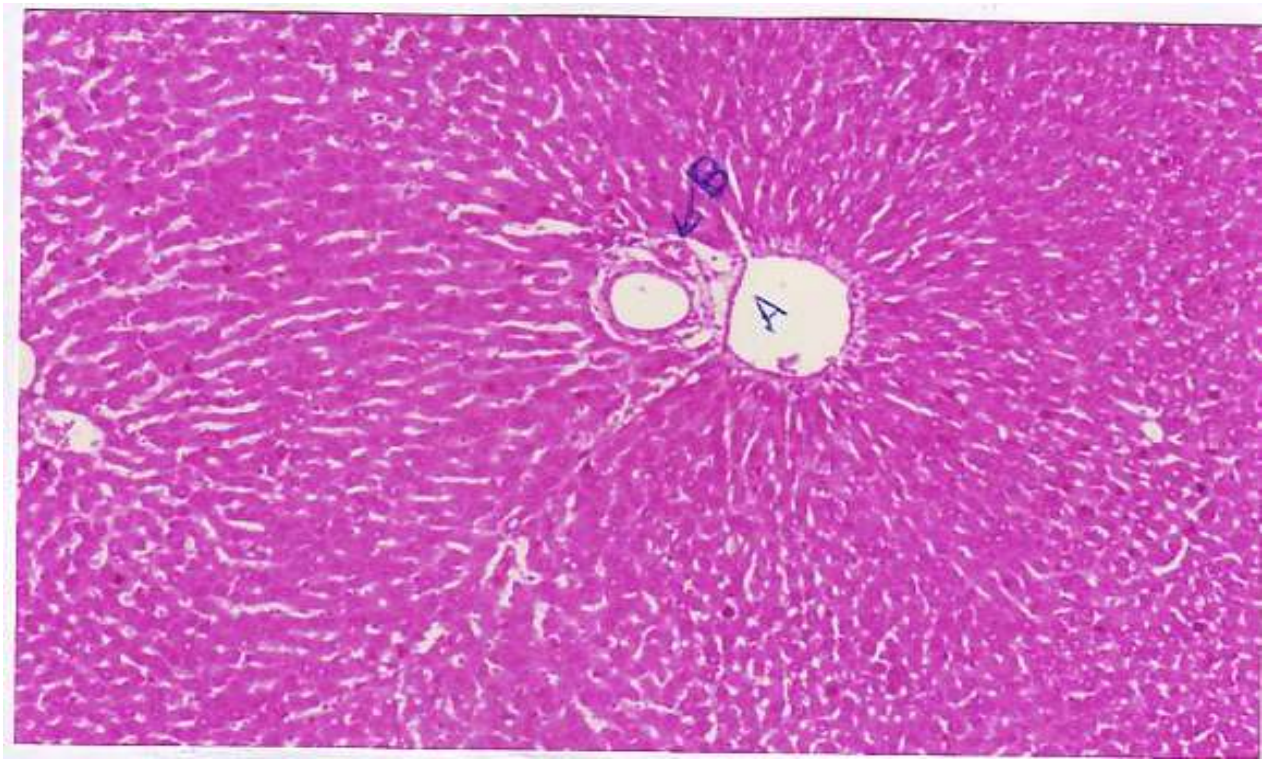

Fig 5. Light micrographs of liver section from 21 days age rat from delivery IN CONTROL GROUP showing portal vessels (A) bile ductules (B) (H & E 40x)

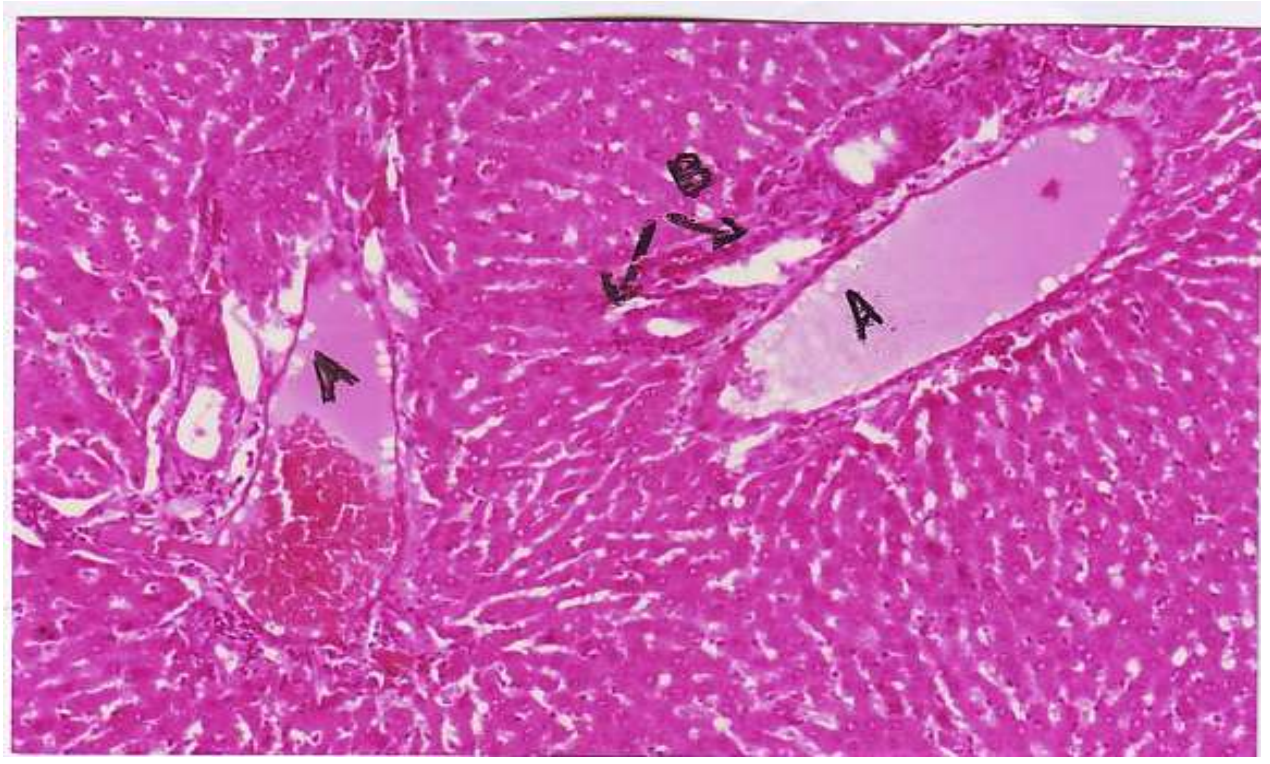

Fig 6. Light micrographs of liver section from 21 days age rat from delivery at low dose treated group showing expansion of portal vessels with odeama (A) and bile ductile proliferation (B) (H & E 40x)

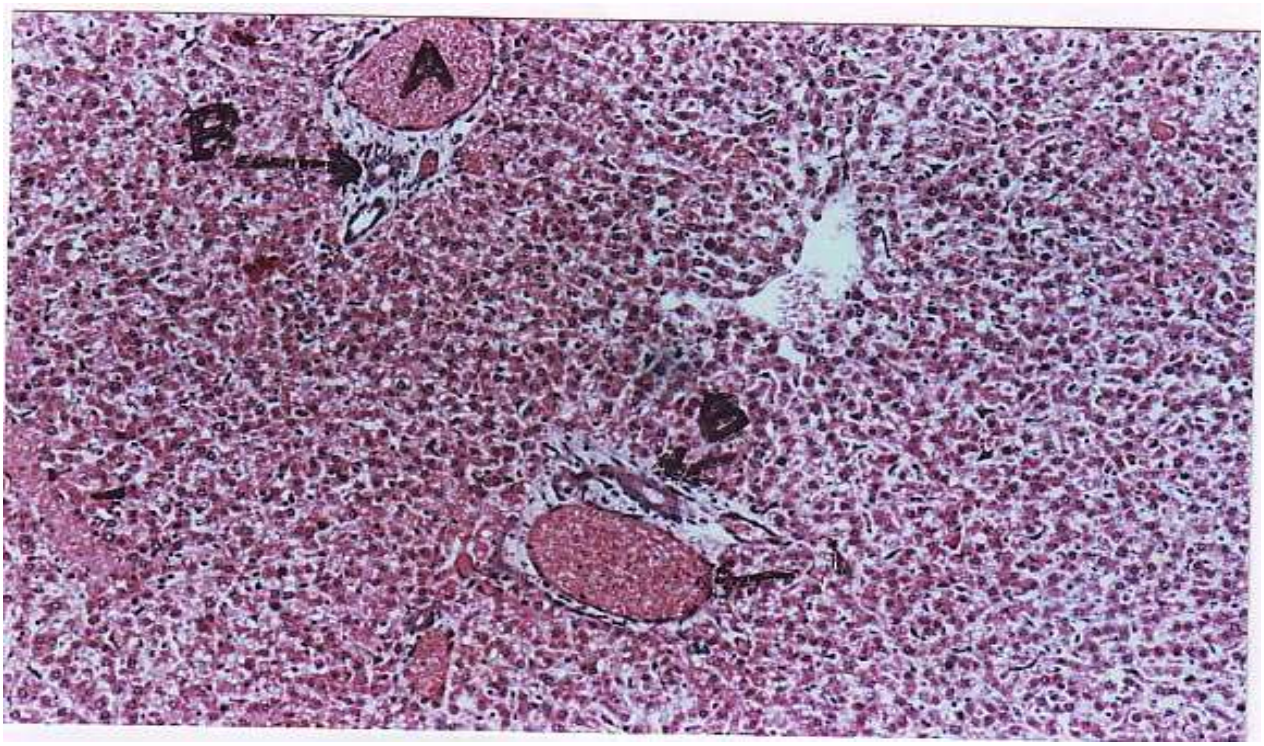

Fig7. Light micrographs of liver section from 21 days age rat from delivery at high dose treated group showing congestion and odeama iside tissue (A) deformed bile ductules (B) (H & E 40x)

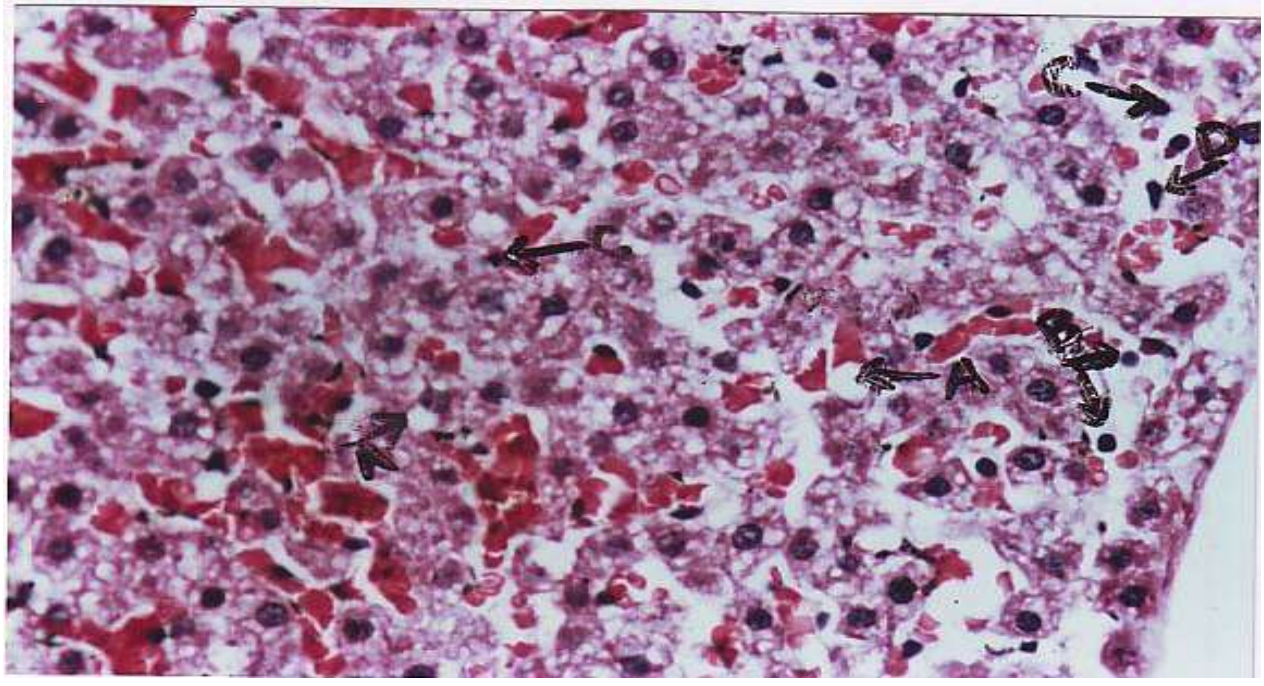

Fig 8. Light micrographs of liver section from 21 days age rat from delivery at high dose treated group showing intra- and extracellular fat vacuoles (A) lymphocytes (B), Kuppfer cells (C) and lining cells (D) (H & E 100x)

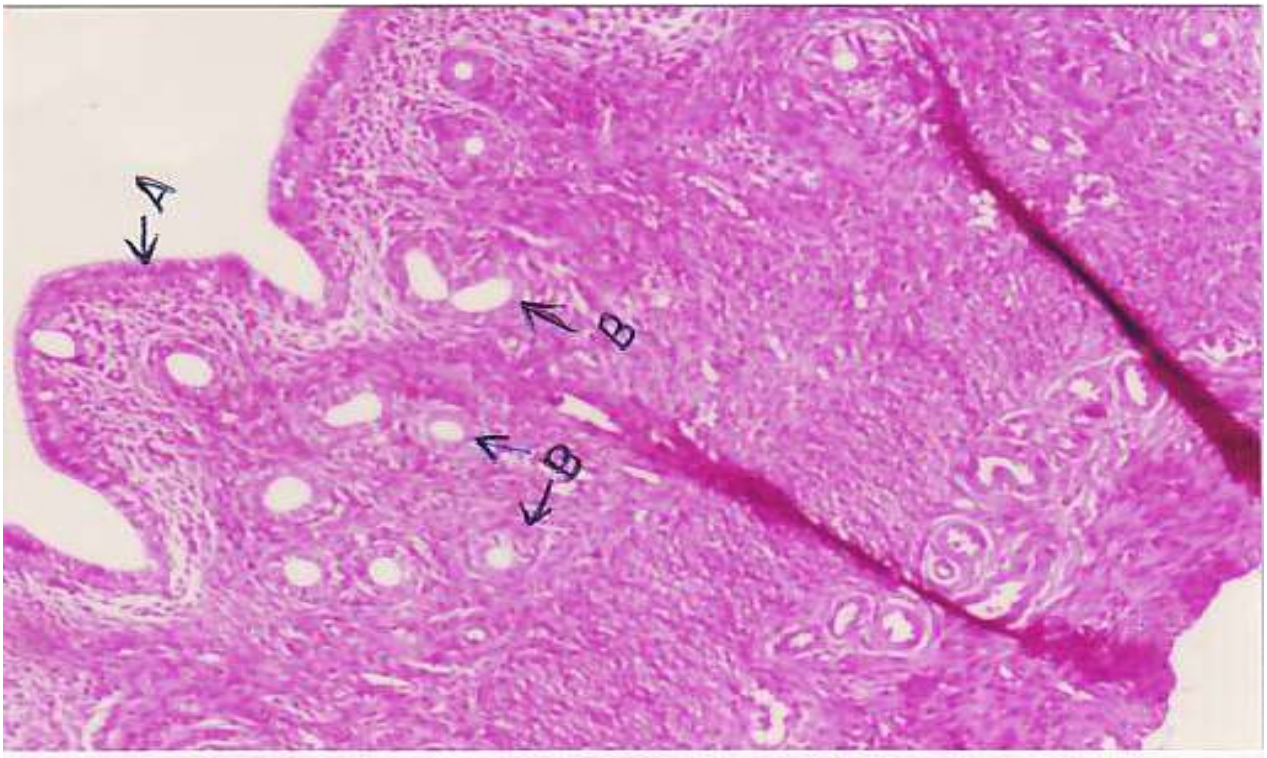

Fig 9. Light micrographs of uterus section from 21 days age rat from delivery IN CONTROL GROUP showing uterine epithelium (A), uterine glands (B) (H & E 100x)

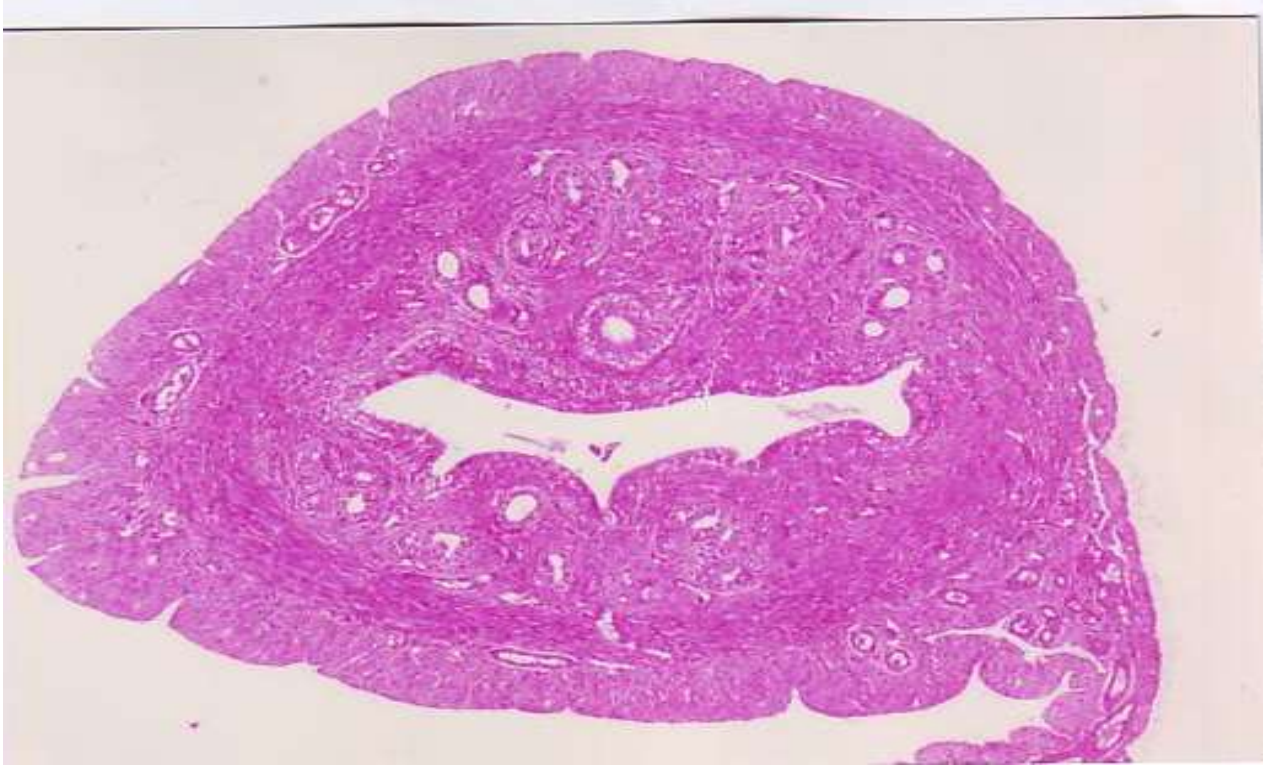

Fig10. Light micrographs of uterus section from 21 days age rat from delivery at low dose treated group (H & E 40x)

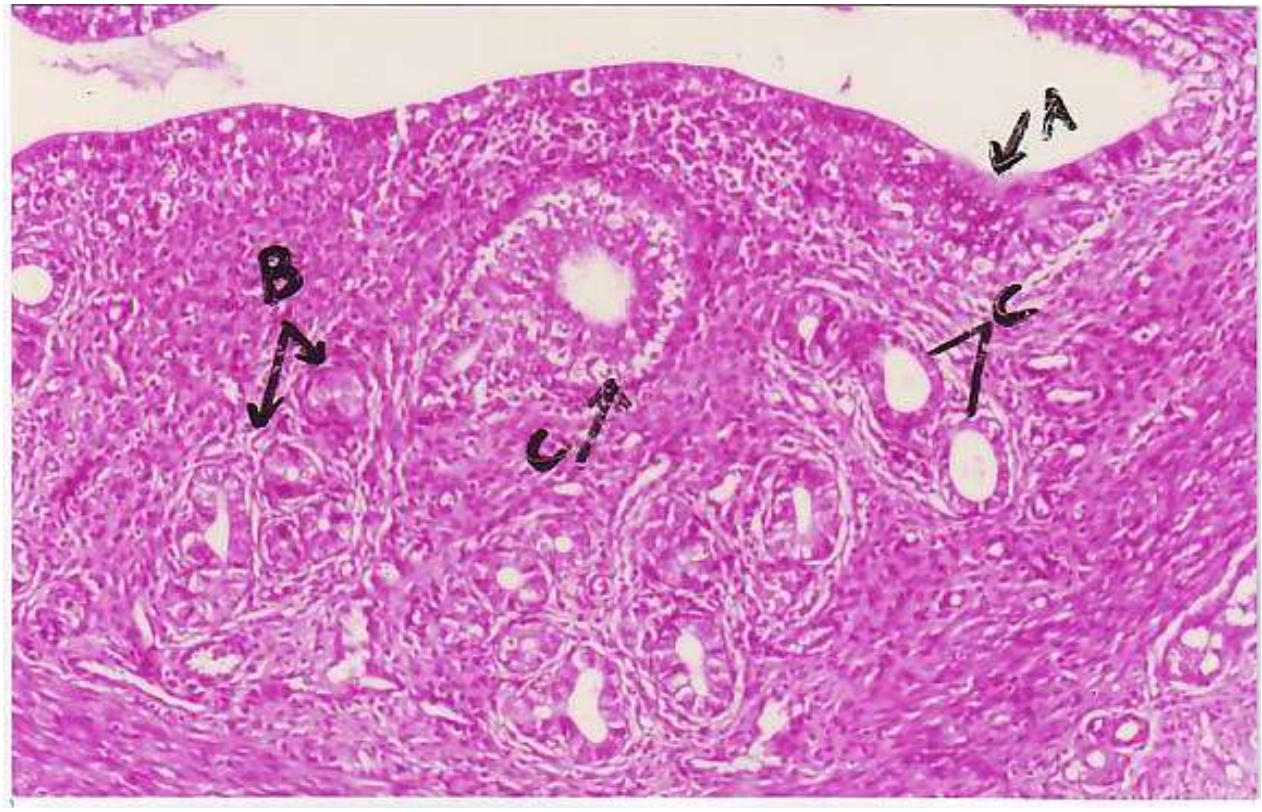

Fig11. Light micrographs of uterus section from 21 days age rat from delivery at low dose treated group showing proliferation of lining epithelium of the uterus (A), proliferation of secretory epithelium (B) and deformed uterine glands (C) (H & E 100x)

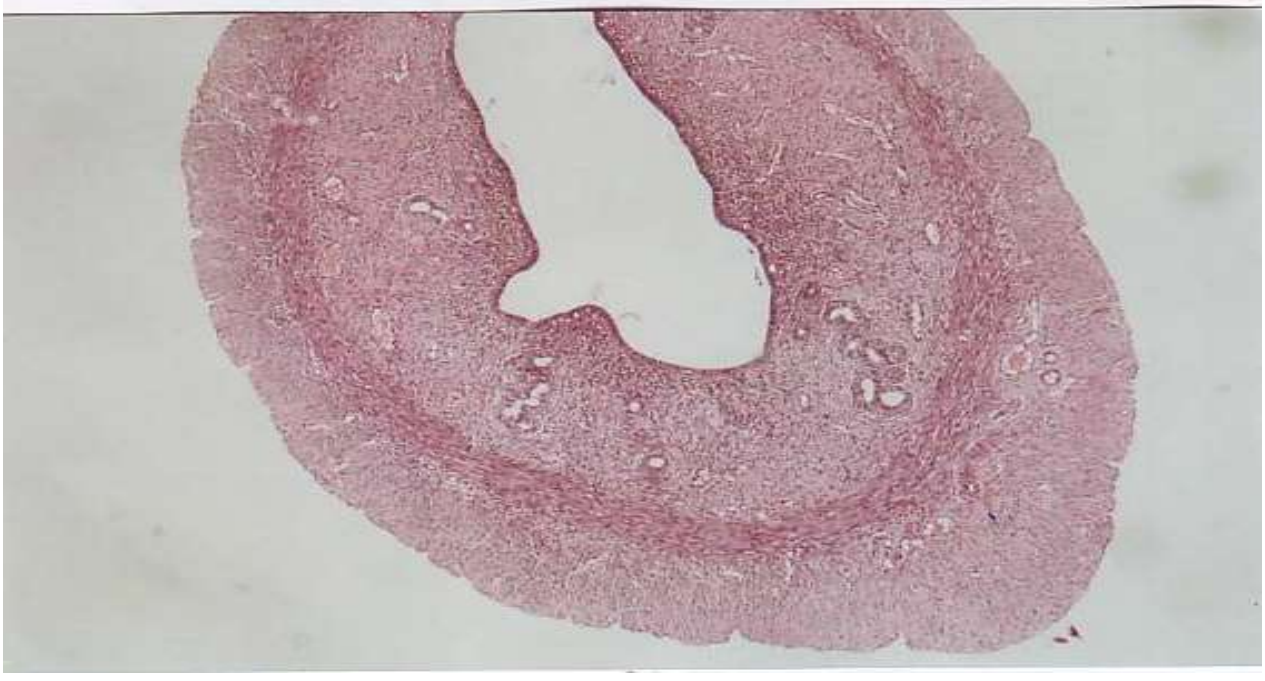

Fig 12. Light micrographs of uterus section from 21 days age rat from delivery at high dose treated group (H & E 40x)

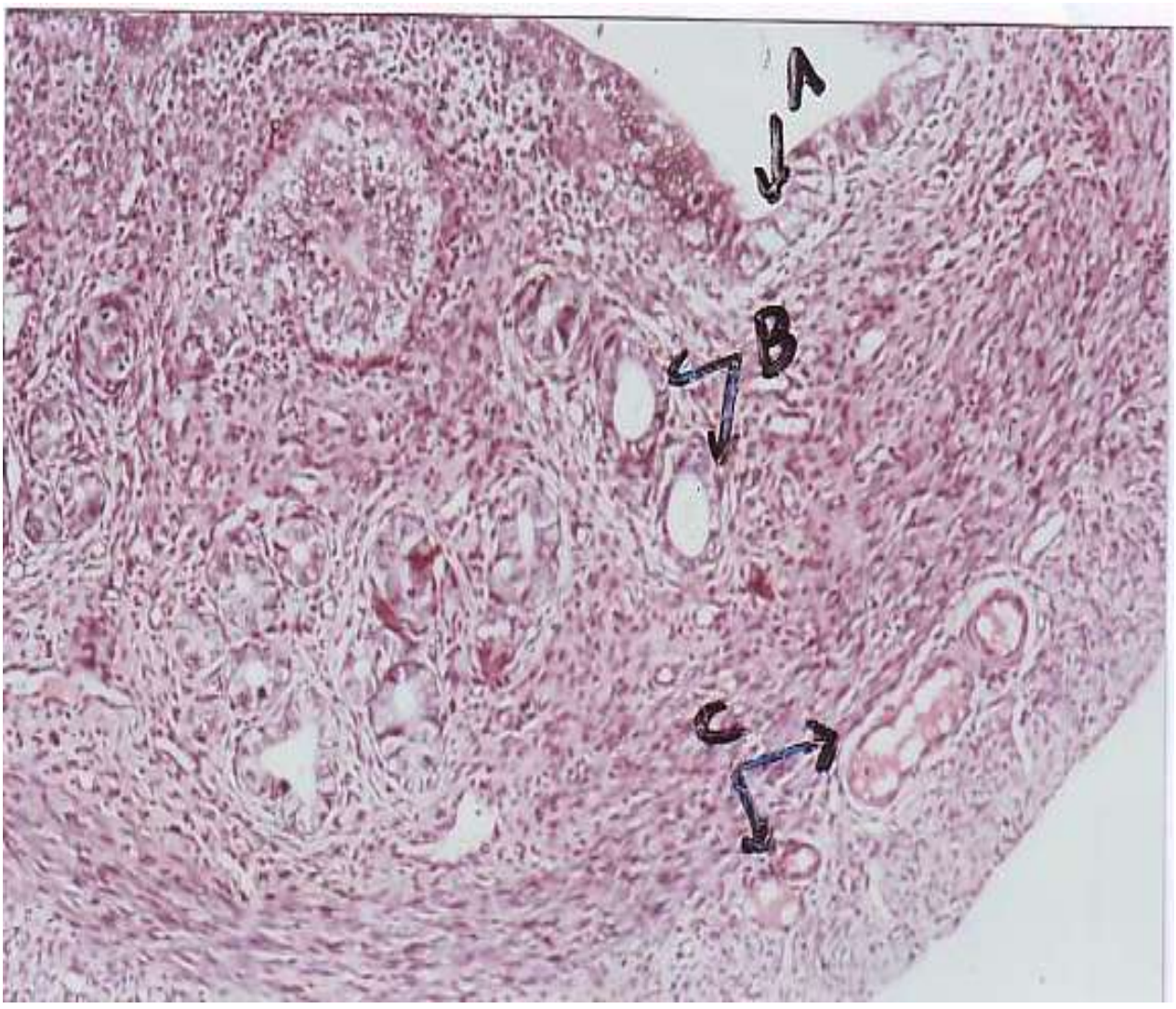

Fig 13. Light micrographs of uterus section from 21 days age rat from delivery at low dose treated group showing rupture of uterine epithelium (A), acute reduction in uterine glands (B) and expansion of blood vessels with oedema (C) (H & E 100x)

rats with OP from the first to the 15th of delivery and found that at 28 days age after delivery, the germinal epithelium proliferated and the uterine gland formation is inhibited which formed at the 14th day after delivery. Hong *et al.* (2004) confirmed that exposure to alkylphenol retarded the organization formation of uterus in newly born females as these chemicals pass easily through placenta during pregnancy when mothers exposed to them. Thus these chemicals affect on the structure and activity of the reproductive organs of embryos.

2- Ovary: in comparison with control group (Fig. 14)

It was noticed that at the first dose, the number of primary and mature follicles and ova decreased with proliferated fibers, congestion and oedama within the tissue and corpus luteum decaying (Fig. 15). While normal ovulation was observed in the control group and many corpus luteum was also recorded. These changes continued till maturation confirming the ability of 4-tert-octylphenol in disturbance of the endocrine system (Katsuda *et al*., 2000b).

The second dose influenced on the ovary weight with complete absence of the corpus luteum and ovulation (Fig. 16). This result agrees with that obtained by Willoughby *et al*. (2005) who pointed that treatment with 4-tert-octylphenol during the early period after delivery significantly inhibited ovulation, decreased the ovary weight, increased the uterus weight, decreased the corpus luteum number and increased the number of prenatal and atretic follicles. Ohshima *et al*. (2005)

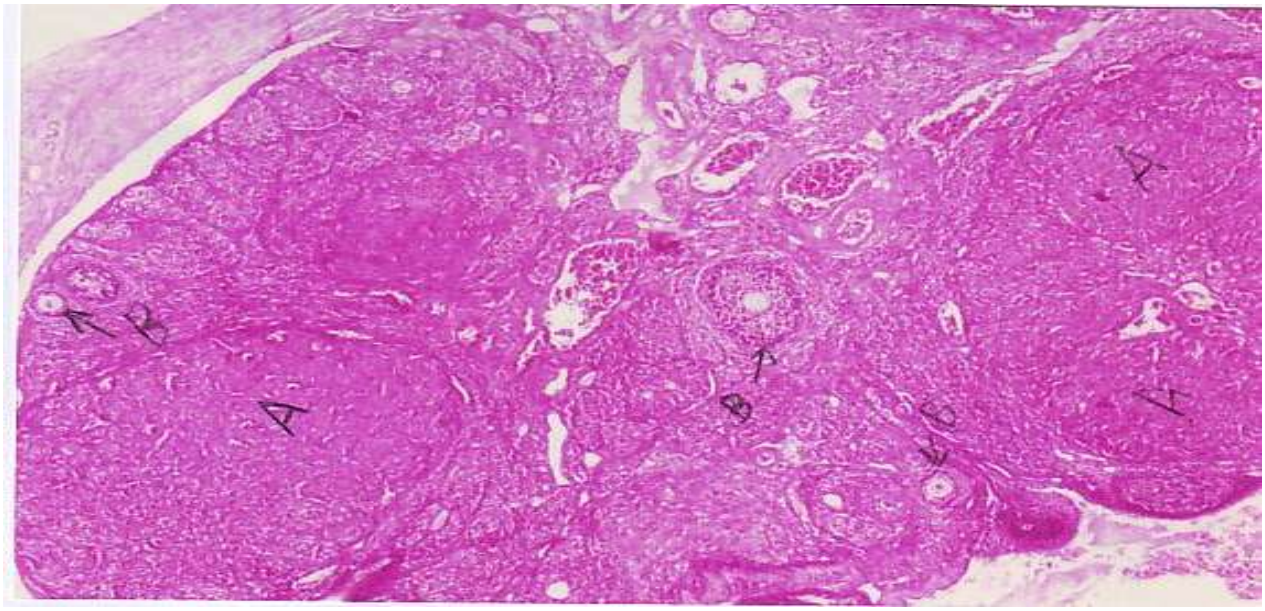

Fig14. Light micrographs of ovary section from 21 days age rat from delivery IN CONTROL GROUP showing corpus luteum (A) primary and mature follicles (B) (H & E 100x)

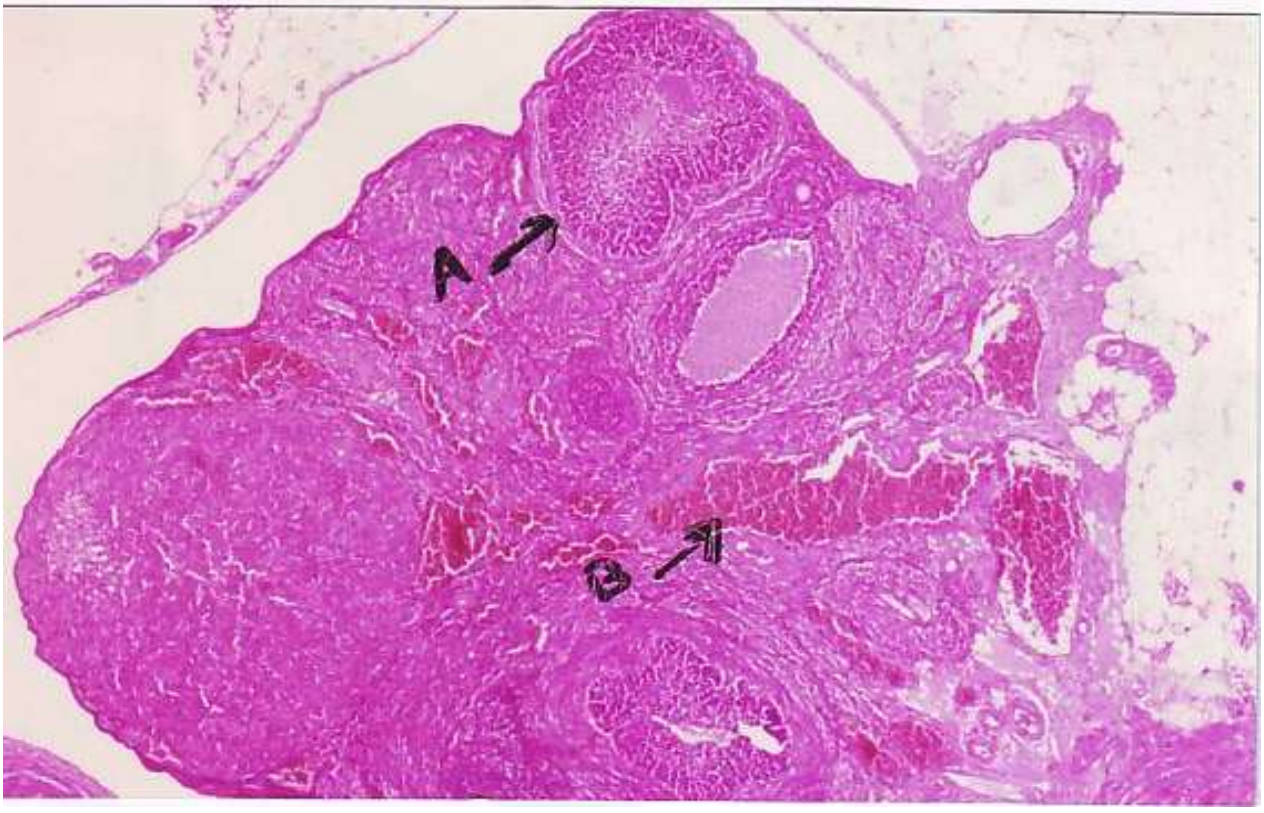

Fig15. Light micrographs of ovary section from 21 days age rat from delivery at low dose treated group showing fibrosis of corpus luteum (A) and odeama in the tissue (B) (H & E 40x)

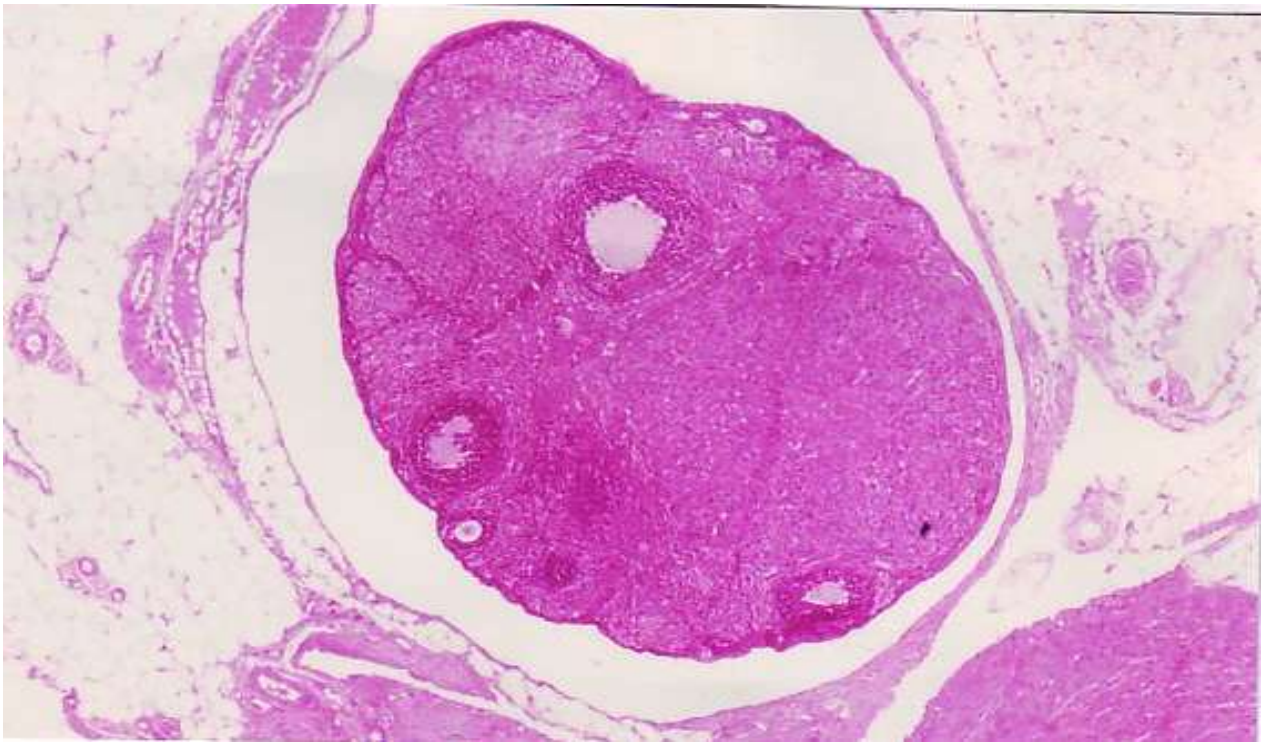

Fig16. Light micrographs of ovary section from 14 days age rat from delivery at high dose treated group (H & E 40x)

contributed this change to the ability of 4-tert-octylphenol to inhibit ovary chromosomes of type 2 and Nagao *et al.* (2001) added that treated newly born rats with OP inhibited permanently gametes formation and caused genital glands atrophy. This indicated that OP acted as estrogens that they inhibit gonad growth in males and females. Herath *et al.* (2001) also said that

exposure of newly born females to high dose of OP interrupt the sexual hormonal cycle and affect on the maturity. Furuta *et al*. (2006) cleared that exposure to Op increased significantly the rate of LH (follicle-stimulating hormone) secretion and this through its effect on the anterior lobe of the pituitary gland. While, Myllymaki *et al*. (2005) said that the effect of OP in the childhood is temporary and can be inverted.

iii. Fertility:

Mating between females exposed to 4-tert-octylphenol from delivery to the weaning, were left till maturation with untreated males resulted in pregnancy by the ratio 1 pregnant female to 3 not pregnant. Also the number and weight of the new born embryos were lower than normal where number of new born embryos was 4, 5, 6, while no pregnancy occurred at the higher dose. This may be contributed to the damage occurred in the lining epithelium of the uterus that received embryos and absence of ovulation (Tryphonas and Buttar, 1986).

The present results are in accordance with those of Willoughby *et al.* (2005) and Dejager *et al.* (1999) who noticed that exposure to these toxics during embryonic stage resulted in abnormal effects on the reproduction of young males. These abnormalities represented by decreasing in spermatozoa number and increasing the opportunity of testis disappearing, affected on the fertility. Also Hafez *et al.* (2008) confirmed that treatment by OP influenced the histological structure of testis, epidydmis and vesicular seminalis and inhibited spermatogenesis.

iv. Body weight:

The body weight of newly born infants of the control group at the first week of delivery ranged between 16 to 20 g with an average of 17.95 g. The same weight rate was recorded at the lower dose but decreased to 15 g at the higher dose.

At the second week after delivery, the body weight ranged from 31 to 35 g in the control group and nearly the same for the treated group with the lower dose, 30-38 g. The body weight was obviously decreased in the treated group with higher dose recording 25-30 g.

At the weaning age, the body weight of the control group was about 65-85 g and for low dose treated group was 52-85 g whereas it recorded 49-60 g for higher dose group. Recording body weight from weaning to maturity

showed that for the low dose treated group, it decreased to 180-190 g comparing to the control group 220-253 g and dramatically decreased in the higher dose treated group to 120-180 g (Table 1).

These obtained results are in agreement with those obtained by Dejager *et al.* (1999, 2001) who confirmed that nonylphenol usage decreased the body weight as it inhibited the estrogenic compound that anti-entrogenic of food consumption. Thus the rate of gaining weight decreased through affecting on the appetite and disturbing secretion and controlling growth hormone (Boockfor and Blake, 1997).

Nagao *et al.* (2001) added that treatment of males and females of newly born rats from the first to the 5th day by estrogenic substances decreased the body weight throughout the life. **v. Number of embryos and infants during gestation and lactation periods:**

Table (2) showed that there was insignificant (P>0.05) decrease in the number and size of rats newly born from pregnant females treated with low and high dose of OP in comparison with the control group. It was also observed that there were no morphological or behavioral changes on the newly born rats during lactation to maturation. Table (3) showed that the number of young rats died during lactation was about 17.31 and 24.71 % from mothers treated with low and high doses respectively compared with 7.29% for the control group. There was not mortality in the young rates after weaning and removing the treated mothers till maturation. These results are in accordance with Hafez *et al.* (2008) who recorded that OP decreased the number and body weight of newly born rats from treated mothers comparing with the control group.

Thus, it can be concluded that treatment with 4-tert-octylphenol during gestation and the early period after delivery affect on the development and function of the reproductive system resulting in histological damages of liver and kidney with increasing dose.

Table1. Body weights (g) of infants from delivery to maturation in the control and treated groups with 4-tert-octylphenol

Age of infants (week)	Control group	Range Mean ±S.D	Low dose treated group	Range Mean ±S.D	High dose treated group	Range Mean ±S.D
1	16-20	17.95± 1.75	16-20	132.85±61.6	15-20	120.1±67.3
2	31-35	22.88± 7.6	30-38	126.6±64.2	25-30	114.9±68.8
4	65-85	35.56±22.9	52-85	148.6±61.01	49-90	115.5±67.4
6	85-100	108.46±2.84	65-100	140.89±60.6	61-108	141.26±55.08
8	105-124	109.8±20.9	78-118	139.1±59.3	70-120	111.26±66.49
10	125-130	113.3±20.9	108-138	138.6±57.86	105-130	115.5±60.5
12	140-146	117.4±2.03	132-150	139.0 ±56.4	100-145	112.0±64.7
14	180-185	121.05±2.4	152-168	122.0±67.01	105-165	113.0±64.0
16	220-253	1144.07±49.8	180-190	143.4±55.22	120-180	115.063.9

Table2. Number and body weight (g) of new born at the end of gestation in control and treated groups

Groups		Embryos number	Pregnant mothers number	Body weight (g)
Control	Range	9-15	10	8-13
	Mean ±S.D.	10.55±0.77		10.40±0.50
Low dose	Range	8-11	10	8-12
	Mean ±S.D.	9.78±0.86		9.60±1.14
High dose	Range	7-11	10	6-12
	Mean ±S.D.	8.53±1.58		8.04±1.74

Table3. Mortality percentage of young rats during lactation in the control and treated groups

Groups	Number	Mortality	
		Number	Percentage
Control	96	7	7.29
Low dose	88	18	17.308
High dose	85	21	24.706

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الملخص العربي

دراسات نسيجية مرضية على تأثير4-tert-octylphenol على مواليد إناث الفئران الحوامل المعاملة بعد الولادة وعند البلوغ

سميرة عمر أبوبكر بالبيد

تم في هذا البحث تعريض المواليد بعد الولادة وحتى الفطام بإعطاء الأمهات جرعتين من 4-tert-octylphenol مقدارها 40ملجم/كجم,80ملجم/كجم وبالفحص النسيجي لقطاعات الكبد للمواليد عند الفطام كان هناك تمدد واتساع للأوعية الدموية وتمزق للطلائية المبطنة للأوعية البابية عند الجرعة المنخفضة (40ملجم/كجم) أما عند الجرعة العالية (80ملجم/كجم) فقد حدث اختلال في التنظيم التركيبي للكبد تمثل في تفكك الخلايا الكبدية وامتلائها بالفجوات الدهنية مع زيادة ارتشاح الدهن خارج الخلايا ,.بينما أظهرت الكلية انفصال للطلائية المبطنة للأنيبيبات القريبة وتحلل الطلائية الجدارية والحشوية لبعض الكبيبات وذلك عند الجرعة(40ملجم/كجم) في حين أدت الجرعة (80ملجم/كجم) إلى التواء للأنيبيبات البعيدة والقريبة والجامعة مع حدوث تجمع لها

وكذلك تأثرت الكبيبات في منطقة القشرة التي بدت اصغر حجما من النخاع.

أما عند البلوغ احدث استخدام االفينولات المقلونة تكاثر للطلائية البطانية والإفرازية للرحم وتناقص عدد الغدد الرحمية عند الجرعة المنخفضة وغياب كامل للجسم الأصفر وقلة وانعدام البويضات في المبيض عند الجرعة العالية.

وعند عمل التزاوج بين الإناث البالغة المعاملة خلال فترة الرضاعة مع ذكور سليمة فشلت الإناث في الحمل عند الجرعة العالية وكان هناك تناقص ملحوظ في عدد ووزن المواليد عند الجرعة المنخفضة.

هذه النتائج أكدت أن التعرض للفينولات المقلونة من بعد الولادة وحتى الفطام تؤثر على التركيب النسيجي للكبد والكلية والرحم والمبيض لإناث الجرذان وبالتالي أثرت على خصوبتها.