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#### Abstract

This study was executed in animal house of Education Faculty for girls -kufa university for 1-8-2020 to 1-11-2020 for detecting the effects of a nonsteroidal antiinflammatory drug (indomethacin) on fertility, some reproductive norms and histological changes of some organs of fetuses and newborns of administered albino rats before gestation, female and male albino white rats were used in this study with age rate (3months and 2.5 months) and weight rate(240 gm and 236 gm) respectively,the animal rats were divided into two groups:the first group was treated with normal saline and represented control group, the second group was treated with indomethacin drug before the pregnancy as following: The female and male rats were administered with indomethacin with concentration of 15 mg /kg of body weight for 30 days and 50 mg /kg of body weight for 60 days respectively, all experiment animals were administered orally one dose before mating by rat stomach tube before wiving, after that the animal rats were mated and left to the pregnancy, then some of the pregnant rats were dissected during 20 days period of the pregnancy, while the others renounced to the birth of study two groups. The results indicated that there was no influence on the fertility of male and female rats that were treated with indomethacin drug before pregnancy, pregnant female rats that were treated with indomethacin before pregnancy suffered from some cinical signs such as diarrhea, loss of appetite and lethargy during pregnancy, as the bleeding was observed during the birth in female rats compared with control group, the results recorded a significant reduce (P < 0.05) in numbers of gross and living fetuses for (20)days of pregnancy and nweborns after birth , while numbers of absorbed fetuses for (20)days of pregnancy and newborns after birth significantly increased (P <0.05) in treated animals with indomethacin before pregnancy compared with control group, as wall as the result of current study showed that a significant reducing (P <0.05) in the weight of body and lengths of body,tail and limbs of fetuses for (20)days of pregnancy and newborns after birth in treated group with indomethacin before pregnancy when compared with control group, and also the treatment with indomethacin caused patho-histological changes in livers and kidneys of fetuses for (20)days of pregnancy and newborns after birth compared with control group. We conclude of this study that indomethacin which is one of the nonsteroidal antiinflammatory drugs that was administered to animal rats before pregnancy may have a cumulative effect inside the body making its harmful effects extend to the fetuses during pregnancy and newborns after birth.

#### **INTRODUCTION**

Nonsteroidal antiinflammatory drugs(NSADs) are among the most used drugs in all countries of the world, some of them are often used even without a prescription to eliminate fever and relieve pain, NSADs include a large group of drugs such as naproxen, aspirin, paracetol, ibuprofen , ketoprofen ,indomethacin and others which although they differ in chemical composition but they have combined in therapeutic action which it performs mainly by inhibiting the **Kaywords:** indomethacin, nonsteriodal antiinflamatory drug, fertility, fetal norms, albino rats.

cyclooxygenase enzymes(cox) that produce prostaglandins (Driver *et al.*,2011), in addition to leukotrienes and thromboxines from arachodonic acid that presents in the membranes of all cells of the body which play important functional roles in sustaining various biological processes in the body, these prostaglandins were essential mediators in fever, pain and inflammation, therefore the inhibition the generation of these compounds by these drugs in addition to other mechanisms made them analgesic, antipyretic and anti-

#### inflammatory agents (Modi et al., 2012).

Indomethacin is a nonsteroidal and antiinflammatory drug that used in the treatment of several diseases such as inflammation of the vertebrae and joints, inflammation of the heart and tendons, gout, renal colic and diabetes insipidus (Sadeq and Jarbawi., 2017), in addition to use this drug during the pregnancy in women to reduce the level of fetal amniotic fluid when it is increased, delay childbirth and prolong pregnancy by stopping early labor (Namieta et al., 2000), recent studies indicated that indomethacin has potential antiviral activity like COVID-19 virus (Xu et al.,2020), but despite this, the use of these drugs especially indomethacin drug were accompanied by many negative side effects in various organs of the body, especially when used in high doses for a short period or for a long perio even if it is used within therapeutic doses, the most important repercussions were the injury of the stomach-intestinal tract with ulcers, perforation and bleeding which sometimes caused death in subjects treated with indomethacin (Sterwart et al., 1985), and it also affects the kidneys causing loss of urinary function in addition to its effect on the various functions of the male and female reproductive systems such as pregnancy and implantation, studies have also shown that exposure to indomethacin during pregnancy stimulates many harmful effects of the mother and dangerous of the fetuses at various stages of pregnancy(AL-Essawi ALjamali,2019).

#### MATERIALS AND METHODS

#### Laboratory animals

The study was executed in the laboratories of Education College for Girls of Kufa university, female and male rats *Rattus rattus* were used with age rate (3months and 2.5 months) and weight rate(240 gm and 236 gm) respectively, all animals were placed in special cages and under the same conditions in the of laboratory from the ventilation , humidity ,temperature and the lighting, the rats were given freely the food and water.

#### Drug

Capsules of indomethacin (Torge Medical Gmbh-Hamburg-Germany) which were used, each one contained 25 mg which brought from the pharmacy, the used concentrations in this study (15/ kg of body weight of female rats and 50 mg / kg of body weight of male rats) were prepared.

#### Animals adminstration

The female rats were administered with indomethacin drug with concentration 15 mg /kg of body weight for 30 days and the male rats were administered with indomethacin drug with concentration 50 mg /kg of body weight for 60 days, while the female and male rats of control group were administered with normal saline for same peroids respectively, all experiment animals were administered orally one dose by rat stomach tube before the mating.

#### Fertility test

For testing the fertility of both female and male rats after administering them with required concentrations of the indomethacin drug and for the specified periods, one female rat was placed with one male rat in the reproductive cage in the evening at (8 hour),then in the morning the female rats were tested to notice vaginal plug in the vagina of them or on the floorboard of cage, and for ensuring the mating between the female and male rats, vaginal smears were done and stained with blue methylene to see sperms in them, the day when sperm or vaginal plug were observed of female rats ,this day was the zero day of pregnancy,this process was repeated many times in this group and control group (Yaping *et al.*, 2006), the number of mated female rats and number of pregnant female rats were calculated, and then the pregnancy rate was extracted through the following equation:

Pregnancy rate = Number of pregnant females X100 Number of females married (Clegg *et al.*, 2001).

#### Autopsy of pregnant female rats

Some pregnant female rats in the two study groups were vivisected for a pregnancy period of 20 days by using diethylether to narcotize pregnant rats and abdominal cavity was opened and two uterine horns were eradicated from the body, then the uterine horns were opened by scissors and fetuses were obtained and washed and dried by distal water and filter papers respectively, the number of total fetuses in two horns of uterus (right and left) and numbers of living ,absobsed and dead fetuses were numerated, while the remaining animals of pregnant female rats were left to the birth,after the birth numbers of total and living, absobsed newborns and stillbirths were calculated ,then the weights and length of body,tail and limbs of the fetuses for 20 day of pregnancy and newborns after birth were recorded by the weight balance and measurement ribbon of length respectively.

# Histological sections civilizing of some organs of fetuses and newborns.

The fetuses for 20 days of pregnancy and newborns after birth were scramed by diethylether and dissected and abdominal cavity of them were opened and livers and kidneys were removed from the body, then these organs were put in formalin fixative solution with concentration (10%) for a (48) hours to prepare histological sections of them independent on Humason (1972) method, the sections were examined by using the light microscope and photographs were telephotographed by same microscope with a camera.

#### Statistical analysis

Results of study were absolved by T-test and the values represent mean  $\pm$  standered error (M  $\pm$  SE), least significant diffefence (L.S.D) was used for existing the significant diffefences between studying groups with propability level (P <0.05).

#### **RESULTS AND DISCUSSION**

# Studying the effect of indomethacin on clinical signs of pregnant female rats.

Pregnant rats treated with indomethacin before the pregnancy suffered from diarrhea, loss of appetite and lethargy during pregnancy, especially during the early stages of pregnancy and bleeding has also been observed during birth in female rats compared with control group, and because there are no adequate studies to explain these results, so the reasons may be due to the fact that nonsteroidal antiinflammatory drugs such as indomethacin which female rats were treated with it before pregnancy may have a cumulative effect in the body of pregnant animal rats leading to the harmful effects of them and their fetuses and which are reflected on the newborns later, studies have shown that this drug has direct effectiveness on the adrenergic-pituitaryhypothalamic system , as well as on the nervous system stimulating disturbances in the systems that control food intake and causing loss of appetite and lethargy (Morgan and

Clark, 1998), while the cause of diarrhea may be due to indomethacin inhibits the production of prostaglandins in the smooth muscles of the digestive system causing increased movement in them and inducing diarrhea in pregnant animals (Takeeuchi *et al.*, 2004), while the bleeding that occurred during birth in maternal rats may be back to the impact of remaining indomethacin drug in the body of pregnant animals when the rats were treated with it before pregnancy and continued its effect to the birth and induces the bleeding during birth by the ability of this drug on overlapping with the blood platelet functions platelets by inhibiting the activity of the enzymes responsible for platelets aggregation preventing their conglomeration and leading to bleeding during birth (Driver *et al.*,2011).

# Studying the effect of indomethacin on the fetility of female and male rats.

The results of our study demonstrated that there were no significant differences ((P > 0.05) in the fertility between the

group in which males and females were treated with indomethacin before pregnancy, as the percentage of pregnancy was (100%) in treated group and also in the control group (100%), as shown in the table (1), this result agreed with the results of some studies that did not show any clear effects on the fertility when indomethacin drug adminsteration with doses of (0.25,0. 5 mg / kg of body weight) of the mice and rats respectively for two consecutive generations (TGA, 2011), some studies indicated that prostaglandins play basic roles in regulating and controlling the different reproductive functions, therefore inhibition their synthesis by the indomethacin drug may inhibit the activity of cyclooxygenase enzymes that may **Table 1.** Effect of indomethacin on the fetility of female and male rats

reduce the production of these compounds causing some side effects in male and female reproductive functions, as prostaglandins especially prostaglandinE2 which were formed in the hypothalamus by cyclooxygenase enzymes that regulate the secretion of testicular hormones because these compounds represent intracellular intermediates for gonadotropin releasing hormones (GnRH) that affect sperm metabolism and vitality and then affect generally male reproductive function (Emea,2006), some studies did not show any significant effects on sperm concentration and sperm live ratio, reproductive organ weights and diameter of the seminalferous tubules in male rats treated with indomethacin at a dose of (25) mg / kg for a period of (14) days(Dawood ,1993), other studies have pointed to these drugs including indomethacin affect the female reproductive system by inhibiting the ovarian prostaglandins especially PGE2 and PGF2 $\alpha$  stimulating unruptured Luteinzed follicles syndrome and delaying the ovulation process by inhibiting the biosynthesis of the prostaglandins that control the function of the pituitary-hypothalamic-ovarian axis (Tsuboi et al., 2009), therefore when treated with indomethacin, it may inhibit the synthesis of prostaglandins but this inhibition may not completely, but it may cause reduction in reproductive efficiency within the concentration used in this study and did not cause loss of fertility for the animals treated with indomethacin drug.

Some studies have reported that the risk of indomethacin and other nonsteroidal antiinflammatory drugs in different reproductive systems depends on many factors such as the amount of active ingredient in the drug, the amount of dose, the number of times the drug was taken, the length of period the drug was administered and the age of the patient (Carol and Ricardo, 1987).

Table 1. Effect of indomethatin on the fermity of female and male fats.					
Crowns	Control group		Treated group		
Groups	female	male	female	male	
Number of female and male married	8	8	8	8	
Pregnancy percentage (%)	%100		%100		

# Studying numbers of gross, living, absorbed and dead of fetuses for (20) days of pregnancy and newborns after birth of administered rats with indomethacin before pregnancy.

Results of present study recorded that a significant reduced (P <0.05) in numbers of gross and living fetuses for (20) days of pregnancy and numbers of newborns after birth, while numbers of absorbed fetuses for (20)days of pregnancy and newborns after birth significantly increased (P <0.05) in treated animals with indomethacin before pregnancy compared with control group, whereas there were no significant differences (P >0.05) in numbers of dead fetuses for (20)days of pregnancy and newborns after birth between two groups ,as showen in (Tables 2,3) and (Figure 1,2,3,4) respectively, since there were no studies on the influence of indomethacin on the numbers of gross, live, absorbed and dead of fetuses and newborns of female rats that males and females were treated with this drug before pregnancy, therefore the results of this study may return to that nonsteroidal antiinflammatory drugs such as indomethacin that animals were treated with before pregnancy negatively affected many male and female reproductive processes before pregnancy as well as during pregnancy such as implantation and fetal development especially during the early stages of pregnancy which continues to affect the advanced stages of pregnancy, as some studies indicated that indomethacin inhibits the

efficacy of enzymes that were called cyclooxygenase enzymes (cox) that biologically create the prostaglandins that play essential roles in reproduction and pregnancy such as pre-implantation and embryo implantation processes that were as an inflammatory response and affect the vascular permeability of the inner uterine lining that stimulates implantation and the process of formation of duciuation during pregnancy, so when these drug inhibits the production of prostaglandins by inhibiting the activities of cox enzymes, this stimulates harmful impacts on the processes of implantation, growth and fetal development indicating that these compounds are a requirement for implantation of embryos as well as the preservation of these implanted fetuses and their subsequent growth and development (Antonucci et al., 2012), other studies showed that the reason for this results may be due to the ulcers in the digestive system such as the colon and its adhesion to epiplon and peritonitis increased the loss before implantation and reduced the processes of implantation of the embryos (Nikose et al., 2015), or the cause

of the result may back to free radicals especially the generated reactive species of oxygen by indomethacin drug and other nonsteroidal antiinflammatory drugs in the body stimulates oxidative stress causing the oxidative breakdown that induces the oxidation processes of fats in the vital cell membranes as well as the oxidation of other large molecules

such as DNA, proteins and carbohydrates in both the mother and fetus organ tissues and thus stimulating apoptosis of tissue cells and this causes implantation failure of the fetuses and fetal development and leads to the destruction and injury of cells and tissues in the fetuses especially during early stages of pregnancy and increased during the late stages of pregnancy and continued until after birth (Cuevas *et al.*,2017),or the reason of this results may be due to that the prostaglandins represent important vasodilators which improve vascular function and maintain blood flow that contains nutrients necessary for different organs, including reproductive, especially during pregnancy which enhances the various reproductive processes such as implantation and fetal growth in the uterine horns during the different stages of pregnancy which later is reflected positively on the newborns, therefore the inhibition of prostaglandins before pregnancy by indomethacin led to a decrease in the blood supply in the bodies of female rats and fetuses and thus a lack of the elements necessary for processes of implantation and growth of fetuses and their development and causing absorption of fetuses in the womb during pregnancy (Pountos *et al.*,2011).as in (Table 2,3)respectively.

Table 2. Studying numbers of gross, living, absorbed and dead of fetuses for (20) days of pregnancy of administered rats with indomethacin before pregnancy.

Norms	Number of fetuses					
Groups	Gross	Living	Absorbed	Dead		
Control group	$9.99 \pm 0.03$	$9 \cdot 9 \cdot 9 \pm 0 \cdot 0 \cdot 3$	$0  0 \ . \ 0 \ 0 \ \pm \ 0 \ . \ 0$	$0  0 \; . \; 0 \; 0 \; \pm \; 0 \; . \; 0$		
Treated group	$9.00 \pm 0.01$ *	$7.66 \pm 0.04$ *	$2 \cdot 8 \cdot 2 \pm 0 \cdot 0 \cdot 2 *$	$0  0 \; . \; 0 \; 0 \; \pm \; 0 \; . \; 0$		
LSD	0.37	1 . 0 5	0.64	$0  0 \; . \; 0 \; 0 \; \pm \; 0 \; . \; 0$		
Significant level	(P <0.05)					

Values: mean  $\pm$  standard error

\*: Implies a significant difference with control group.

L.S.D: Least Significant Difference.

 Table 3. Studying numbers of gross, living, absorbed and dead of newborns after birth of administered rats with indomethacin before pregnancy.

Norms	Number of newborns					
Groups	Gross	Living	Absorbed	Dead		
Control group	$10.54 \pm 0.03$	$1 \ 0 \ . \ 5 \ 4 \ \pm \ 0 \ . \ 0 \ 3$	$0  0 \ . \ 0 \ 0 \ \pm \ 0 \ . \ 0$	$0  0 \ . \ 0 \ 0 \ \pm \ 0 \ . \ 0$		
Treated group	$9.01 \pm 0.05$ *	$7 . 8 7 \pm 0 . 0 2 *$	$2.99 \pm 0.04$ *	$0  0 \ . \ 0 \ 0 \ \pm \ 0 \ . \ 0$		
LSD	0.95	1 . 4 0	0.71	$0  0 \ . \ 0 \ 0 \ \pm \ 0 \ . \ 0$		
Significant level	(P <0.05)					

Values: mean  $\pm$  standard error

\*: Implies a significant difference with control group.

LSD: Least Significant Difference.

#### Studying body weights and lengths of body, tail and limbs of fetuses for (20) days of pregnancy and newborns afte birth of administered rats with drug indomethacin before pregnancy.

The current study showed that a significant reduceing (P <0.05) in the weights of body and lengths of body,tail and limbs of fetuses for (20)days of pregnancy (Table 3) and newborns afte birth(Table 4) in group that administered rats with indomethacin drug before pregnancy when compared with control group, and because of the lack of sufficient researches to explain these results of the present study, therefore the causes may be due to that treatment of animals with indomethacin before pregnancy made the effect of this drug may has continued pregnancy especially during its early stages which was reflected in the postpartum and this drug may have a cumulative effect within the body of pregnant animals which subsequently affects the fetuses during the various stages of pregnancy, especially the early stages of it which may continue to affect the advanced stages of pregnancy and until after birth of newborns , as studies have shown that the basis of the action of nonsteroidal antiinflammatory drugs like indomethacin depends mainly on inhibition the biosynthesis of prostaglandins by the activity of cyclooxygenase (COX1 and COX2) in the cells of the body which are vital compounds that play main roles in different body functions generally and the reproductive functions in particular, such as growth and fetal development because they are factors that expand blood vessels and participate in regulating their vascular function and provide support for the endothelial cells in them which facilitates the supplying of nutrients and oxygen to different body tissues such as the uterus and thus fetuses that it contains by the

placenta, therefore decreasing or preventing the production of prostaglandins in the body by a nonsteroidal antiinflammatory drug such as indomethacin, this stimulates the vasoconstrictive effects causing reduced blood flow to the utero-placental circulation with the various nutrients that contains them which will be transferred less to the fetuses in the uterine horns and this stimulates harmful fetal impacts and malformations and delayeds fetal growth causing a decrease in the body weights of the fetuses during pregnancy, especially the early stages of it which continues to the end of pregnancy and after birth(Inagaki et al., 2020), or the results of this study can be explained stimulating oxidative stress as a result of the increase in the formation of free oxygen radicals in the uterine horns of pregnant animals and their fetuses when they crossed them from the mother's circulation system especially during the early stages of fetal development and continued to affect the newborns after birth, as the free

radicals that were generated by this drug stimulate toxic impacts of embryos through their interaction with fats in the fetal cell membranes and with other intracellular molecules such as proteins in the body's systems which leads to the programmed death of cells that leads to the breakdown of tissues in them and thus the failure of the development of the body's organs causing a reduction in weights fetuses and later newborns (Duhig *et al.*,2016),

And for the reduction in lengths of body, tail and limbs of fetuses and newborns, some studies have indicated that structural abnormalities are among the most important adverse impacts associated with nosteroidal antiinflammatory drugs use, especially indomethacin drug

on fetuses during pregnancy and newborns whose mothers were treated during pregnancy(Shahin *et al.*, 2011), as for the reason of the decrease in the lengths of the body, tail and limbs of the fetuses and newborns may be due to in addition to the previously mentioned reasons that caused the decrease in the weights of the fetuses and newborns as well as that this accumulated inside the body of treated female rats before pregnancy which has the ability to inhibit the early stages in the process of new bone formation in the body because it is controlled different arachidoinic acid metabolites, especially prostaglandin compounds such as PGE2 which activates the link (NF-kB) RANKL which is a factor that stimulates osteoblasts that were inhibited by indomethacin as a result to inhibit it the synthesis of PGE2 causing a lack of bone formation (Kusanag *et al.*, 1997), or the reason of this result may be due to the ability of indomethacin to inhibit osteoblasts resulting in the resorption of the formed bone or failure to form new bones, or the drug prevents deposition the calcium in skeletal elements in the body of fetus and newborn because indomethacin activate and differentiate osteoclasts that cause resorption as a result of inhibition of transmission of the bone-phosphorylated factor NF-kB. (Karakawa *et al.*, 2009).

**Table 4.** Studying body weights and lengths of body, tail and limbs of fetuses for (20) days of pregnancy of administered rats with drug before pregnancy.

Norms	Body weight and body, tail and limbs lengths of fetuses					
Groups	body weight(gm)	body length (cm)	Tail length (cm)	Forehand limb length (cm)	backhand limb length (cm)	
Control group	$7.32 \pm 0.05$	$4.59 \pm 0.01$	$1.75\pm\ 0.02$	$1.50\pm0.05$	$2.10 \pm 0.03$	
Treated group	6.01±0.03*	$4.00 \pm 0.02$ *	$1.25 \pm 0.04 *$	$1.00 \pm 0.03$ *	$1.52 \pm 0.01$ *	
LSD	0.85	1 . 2 9	0.10	0.14	0.31	
Significant level			(P < 0.05)			

Values- mean  $\pm$  standard error

\*- Implies a significant difference with control group.

LSD-Least Significant Difference.

Table 5. Studying body weight and lengths of body, tail and limbs of newborns after birth of administered rats with drug before gestation.

	Body weight and body, tail and limbs lengths of newborns				
Norms Groups	body weight(gm)	body length (cm)	Tail length (cm)	Forehand limb length (cm)	backhand limb length (cm)
Control group	$7 \cdot 3 \cdot 9 \pm 0 \cdot 0 \cdot 2$	$4.60 \pm 0.01$	$1.77 \pm 0.01$	$1.52\pm0.01$	$2.12 \pm 0.05$
Treated group	$6 . 0 9 \pm 0 . 0 1 *$	$4.05\pm0.05$ *	1.27 ± 0.05 *	$1.04 \pm 0.02$ *	$1.57 \pm 0.04$ *
LSD	0.73	1.00	0.12	0.15	0.20
Significant level			(P < 0.05)		

Values- mean  $\pm$  standard error

\*- Implies a significant difference with control group.

LSD- Least Significant Difference.

Studying histological influences on some organs of fetuses for (20) days of pregnancy and newborns afte birth of administered rats with drug before pregnancy.

The pathohistological study of the kidney and liver sections of fetuses for a pregnancy period of 20 days and those newborns after birth showed pathological changes in histological structure of kidneys which showed different pathological changes in cortex and medulla of kidney such asshrinking of glomulus, expansion of glomular capsule and renal tubule, fibrosi and necrosis of interstitial tissue, separation of endothelium aqnd bleeding of renal tubule respectively in fetuses for 20 days of pregnancy as shown in figures(6,7,12,13,14) respectively ,while these effects have increased severity in the kidneys of newborns after birt as in (9,10,16,17,18) respectively, figures whereas the pathological effects of livers were loss of histomorphology of general architecture form, Sinsoids Widening degeneration and necrosis of hepatic tissue, necrosis and degeneration of hepatic vein , necrosis of hepatic cells, expansion and damage wall of hepatic vein in fetuses for 20 days of pregnancy, as shown in figures (20,21,22,23,24,25) and in newborns after birth increased histomorphology of general architecture loss of form, expantion and bleeding of hepatic vein , increased degeneration and necrosis of hepatic tissue, as in figures (27,28,29,30,31) in the group which animal rats were treated with indomethacin before pregnancy compared with control group as in figures (5,8,11,15,19,26) respectively, and due to the lack of studies which explain the effect of this drug and other nonsteroidal antiinflammatory drugs on the

various pathological changes in the kidneys and livers of fetuses and newborns of pregnant animals and mothers who were given indomethacin before pregnancy, so the reasons for these effects in these organs may be due to drug accumulation in the body of treated animals before pregnancy has continued to affect pregnancy and after birth, stimulating the pathological changes in these organs of fetuses and newborns, studies have indicated the ability of this drug and other anti-inflammatory and non-steroidal drugs to inhibit the activity of COX enzymes responsible for the production of prostaglandins that are vasodilators in body tissues causing decrease blood flow to them, and thus reducing access of nutrients and oxygen to these organs of fetuses and newborns and causing histological changes in them, prostaglandins among the compounds created by the different organs of the fetus, such as the kidneys and the livers during fetal life and they play roles in the growth and development of these organs during pregnancy and their maturation after birth, so the suppression of prostaglandins during pregnancy, especially the early stages, may lead to hypoplasia in addition to the occurrence of pathological changes in the formed tissues in fetal organs in the uterine life which was later reflected on the newborns after birth(Klein and Scott, 1984), or the cause of this result may be return to the oxidative stress caused by indomethacin that stimulates free radicals of oxygen in the kidneys and livers during the various stages of pregnancy, as these free radicals attack fats in cell membranes and other large molecules in the renal and hepatic cells such as DNA and protein molecules causing oxidative breakdown and damage of the

developed renal and hepatic tissues of fetuses and newborns,

thus reducing their lengths(Maqbool et al., 2018).



Figure 1. Female rat for 20 days of pregnancy of control group notice: Number of fetuses in left uterine horn



Figure 2. Female rat for 20 days of pregnancy of treated group with indomethacin before pregnancy notice: Number of fetuses in left uterine horn (LUH) and right uterine horn (RUH), Fetus (F), Placenta(T), Absoebed fetus(AF).



Figure 3. Normal newborn after birth of control group.

Figure 4. Abnormal (small and short) newborn after birth of treated rats' group with indomethacin before pregnancy.

Figure 5. Histological section of rat embryo kidney cortex tissue of control group for (20) days of pregnancy signifies that: - Normal glomulus(GL), Glomular capsule( GC), Renal tubule (RT), interstitial tissue (IT) .(H.E- 100 X).

Figure 6. Histological section of rat embryo kidney cortex tissue of treated group for (20) days of pregnancy signifies that: -



Shrinking of glomulus(GLS), Expansion of glomular capsule( RCE), Expansion of renal tubule (TE), Interstitial tissue necrosis (IN) .(H.E- 100 X).

Figure 7. Histological section of rat embryo kidney cortex tissue of treated group for (20) days of pregnancy signifies that: - Shrinking of glomulus(GLS), Expansion of glomular capsule( RCE), Interstitial tissue necrosis (IN), Expansion and bleeding of renal tubule (TB), Fibrosis of Interstitial tissue (IF). (H.E- 100 X).

Figure 8. Histological section of rat newborn kidney cortex tissue of control group signifies that: - Normal Glomulus (GL), Glomular





capsule (GC), Renal tubule (RT), Interstitial tissue (IT). (H.E- 100 X).

Figure 9. Histological section of rat newborn kidney cortex tissue of treated group signifies that: - Shrinking of glomulus(GLS), Separation of endothelium of renal tubule (TS), Interstitial tissue necrosis (IN), Expansion and bleeding of renal tubule (TB), Degeneration of interstitial tissue(ID), Necrosis of renal tubule (TN) .(H.E- 100 X).



**Figure 10.** Histological section of rat newborn kidney cortex tissue of treated group signifies that :- Shrinking of glomulus(GLS), Expansion of glomular capsule( RCE), Expansion and necrosis of renal tubule (TE) Interstitial tissue necrosis (IN). (HE-100 X).

Figure 11. Histological section of rat embryo kidneymedulla tissue of control group for pregnancy (20) days signifies that: -Normal



renal tubule (T), Interstitial tissue (IT). (H.E- 100 X).

Effect Study A Nonsteroidal Antiinflammatory Drug (Indomethacin) on Fertility, Some Reproductive Norms and Histological Changes of Fetuses and Newborns of Administered Albino Rats Before Pregnancy



**Figure 12.** Histological section of rat embryo kidney medulla tissue of treated group for pregnancy (20) days signifies that: - Necrosis of renal tubules (TN), Bleeding of renal tubules (TB), Separation of endothelium of renal tubes (TS), Interstitial tissue fibrosis (IF). (H.E- 100 X).



Figure 13. Histological section of rat embryo kidney medulla tissue of treated group for pregnancy (20) days signifies that: -Necrosis of renal tubules (TN), Atrophy of renal tubules (TA), Bleeding of renal tubes (TB), Fibrosis of interstitial tissue (IF), Necrosis of interstitial tissue (IF), Necrosis of interstitial tissue (IN). (H.E- 100 X).



Figure 14. Histological section of rat embryo kidney medulla tissue of treated group for pregnancy (20) days signifies that: -Necrosis of renal tubules (TN), Atrophy of some renal tubules (TA), Separation and bleeding of renal tubes (TS), Fibrosis of interstitial tissue (IF). (H.E- 100 X).

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Figure 15. Histological section of rat newborn kidney medulla tissue of control group signifies that: -normal renal tubule (RT), Interstitial tissue (IT). (H.E- 100 X).

Figure 16. Histological section of rat newborn kidney medulla tissue of control group signifies that: Necrosis of renal tubules (TN),



Atrophy of renal tubule (TA), Separation of endothelium of renal tubes (TS), Bleeding of renal tubes (TB), Fibrosis interstitial tissue (IF). (H.E- 100 X).

Figure 17. Histological section of rat newborn kidney medulla tissue of treated group signifies that: -Necrosis of renal tubules (TN),



Separation of endothelium of renal tubes (TS), Bleeding of renal tubes (TB), Necrosis of interstitial tissue (IN), Fibrosis interstitial tissue (IF). (H.E- 100 X).

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Figure 18. Histological section of rat newborn kidney medulla tissue of treated group signifies that: -Necrosis of renal tubules (TN), Separation of endothelium of renal tubes (TS), Bleeding of renal tubes (TB), Necrosis of interstitial tissue (IN). (H.E- 100 X).



**Figure 19.** Histological section of rat embyro liver tissue of control group for (20) days pregnancy signifies that: - Normal histomorphology of general architecture form: -Central Vein (V), Sinusoids(D), Hepatic Cell (H). (H. E- 100 X).



**Figure 20.** Histological section of rat embyro liver tissue of treated group for (20) days pregnancy signifies that: - Loss of histomorphology of general architecture form (AR), Sinsoids Widening (P), Necrosis of hepatic tissue (O), Degeneration of hepatic tissue (G). (H.E- 100 X).



Figure 21. Histological section of rat embyro liver tissue of treated for (20) days pregnancy signifies that: - Degeneration of hepatic vein (VG), Sinsoids Widening (P), Necrosis of hepatic cells (OH), Degeneration of hepatic tissue (G). (H. E- 100 X).



Figure 22. Histological section of rat embyro liver tissue of treated group for (20) days pregnancy signifies that: - Degeneration of hepatic tissue (G), Necrosis of hepatic tissue (O), Necrosis of hepatic cells (OH). (H. E- 100 X).



Figure 23. Histological section of rat embyro liver tissue of treated group for (20) days pregnancy signifies that: - Degeneration of hepatic tissue (G), Necrosis of hepatic cells (OH), Sinsoids Widening (P). (H. E- 100 X).

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Figure 24. Histological section of rat embyro liver tissue of treated group for (20) days pregnancy signifies that: - Expantion of hepatic vein (VE), Degeneration of hepatic vein wall (DW), Bleeding and blood ciotting(BC), Necrosis of hepatic cells (OH).(H. E - 100 X).



Figure 25. Histological section of rat embyro liver tissue of treated group for (20) days pregnancy signifies that: - Expansion and damage wall of hepatic vein (VDE), Necrosis of hepatic tissue (O), Sinsoids widening (P), Expansion and bleeding of hepatic vein (VEB). (H.E- 100 X).



Figure 26. Histological section of rat newborn after birth liver tissue of control group signifies that: - Normal histomorphology of general architecture form: -Central vein (V), Sinusoids(D), Hepatic Cell (H). (H.E- 100 X).

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Figure 27. Histological section of rat newborn after birth liver tissue of treated group signifies that: - Loss of histomorphology of general architecture form (AR), Increased expansion and bleeding of hepatic vein (VEB), Degeneration of hepatic tissue (G), Necrosis of hepatic tissue (O). (H.E- 100 X).



**Figure 28.** Histological section of rat newborn after birth liver tissue of treated group signifies that: - Bleeding and separation of endothelium of vein (GB), Degeneration of hepatic tissue (G), Necrosis of hepatic tissue (O), Degeneration of hepatic vein (VG), Necrosis of hepatic cells (OH). (H.E- 100 X).



Figure 29. Histological section of rat newborn after birth liver tissue of treated group signifies that: - Increased degeneration of hepatic tissue (G), severe necrosis of hepatic tissue (O), Increased sinsoids widening (P). (H.E- 100 X).

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Figure 30. Histological section of rat newborn after birth liver tissue of treated group signifies that: - Loss of histomorphology of general architecture form (AR), Degeneration of hepatic tissue (G), Necrosis of hepatic tissue (O), Degeneration of hepatic vein (VG), Damage of hepatic tissue (DT) Necrosis of hepatic cells (OH). (H.E- 100 X).



Figure 31. Histological section of rat newborn after birth liver tissue of treated group signifies that: - Necrosis of hepatic tissue (O), Seprartion of endothelium of hepatic vein (SP), Necrosis of hepatic cells (OH), Increased expantiom and bleeding of hepatic vein (VE). (H.E- 100 X).

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