

Effect of Ginger on the Histological Structure of Some Organs of Female Rats and Their Embryos during Pregnancy

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Abstract: In this study, males and females rats were treated with daily dose of ginger for a week, and then they were left to reproduce among each other. Pregnant females were divided into five groups; first one is the control group, the second group was treated with a daily dose of ginger from the first day to 21st of pregnancy, the third was treated with ginger during the first week of pregnancy (1-7), the fourth group was treated during the second week of pregnancy and finally the fifth one was treated with ginger from the 7th to 21st day. The histological investigation of liver and kidney from mothers and embryos of all treated groups showed that all treated groups did not influenced and nearly normal in their structure. While ginger increased the spleen functional efficiency in mothers and embryos in all treated groups. This was indicated by an increase in number of spermatozoa in testis and mature oocytes in ovary reflecting on the percentage of pregnancy occurrence and number of births. Also, embryonic distortions were not recorded and the body weight of embryos and mothers in all one-week treated groups was normal while it decreased in all two-weeks treated groups confirming ginger is efficient in lipid oxidation.

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1.Introduction:

Ginger has been used throughout the world as a therapeutic agent for centuries. The herb is increasingly used in Western society also, with one of the most common indications being pregnancy-induced nausea and vomiting (PNV).(Ding ,2013)

More than 85% of women suffered from pregnancy sickness during pregnancy and known drugs in this field carried the danger of embryonic distortions. Therefore women tended to use natural herbs for the pregnancy sickness treatment (Woolhouse, 2006).

Nearly 36% of pregnant women use medical herbs as ginger during different pregnancy periods by the rate 1.7 product per a woman, and 43% of them used it during lactation. In both cases, women used ginger without medical consultation or previous knowledge about its side effects (Nordeng and Havnen, 2004). Thus Marcus and Snodgrass (2005) confirmed that the level of quality and toxicity of ginger should be taken in consideration in treatment of pregnancy sickness, where there are not sufficient studies confirmed the level of safety to use herbal treatments.

Where Forster *et al.* (2006) confirmed that the data around the usage of medical herbs by women during pregnancy are still limited despite of little knowing of benefits and harms of these products. In their study, pregnant women at the week 36-38 were provided with herbal complementary; 36% were provided with at least one herbal complementary

during pregnancy, as mulberry (14%), ginger (12%) or chamomile (11%). They concluded that herbal complementary were used in a widely scale and it is necessary to test the safety of these complementary.

While Wilkinson (2000) mentioned that tea ginger had not toxic effects on mothers or embryos of rats and no morphological distortions in treated embryos were recorded. He also found that ginger increased the growth rate of the treated embryos and this is not associated with an increase in the placental size. However, he noticed a dose of 50 g/ liter that was used in the early stage of pregnancy resulted in a reduction in the embryos survivorship. Weidner and Sigwart (2001) used ginger extraction by oral doses of 100, 333, 1000 mg/kg to three groups of pregnant females rats from the 6th to the 15th day of the pregnancy. They dissected females at the 21st and examined embryos, and found that at all pregnancy stages there were no mortality or weight differences in embryos. The morphological and anatomy investigation showed that ginger had no any toxic effect that retarding growth or organization of embryos when it was used by a daily dose of 1000 mg/kg in the organs formation stage. Although, ginger has along history for using in different cases, it recently has attention to be used as a treatment and for armour. Barnes (2003) used ginger tea to treat pregnancy sickness in rats for a period exceeded 6-15 days of pregnancy. He used capsules of 250 mg of ginger fourth times daily for four days to treat pregnancy sickness in human. Results were

significantly better in the treated group with ginger than that treated by other herb. Also, one abortion case was recorded in ginger treated group comparing to three cases of abortion in treated group with medicines. Moreover, there were no distortions in embryos treated with ginger during different pregnancy periods or side effects. However, researcher referred that the safety of using ginger in treatment is not clear so he recommended to not use high doses where embryos were heavier in weight at the lower dose than the higher one. Portnoi *et al.* (2004) aimed in their study to test the degree of safety to use ginger as a treatment and its efficiency and effect on pregnancy sickness. They provided pregnant females with ginger in early stage of pregnancy and noticed that there was no difference between treated ginger embryos and those of the control group, except an increase in the weight of the treated embryos. Also there was one abortion case among 187 pregnant female and two cases of late delivery, thus ginger did not increase the rate of embryos distortion above the basic known rate (1-3%).

Labania (2005) described ginger as a seasonal plant grows in the tropical regions and its flowers are yellow, with rhizomes and long aerial stems. This plant belongs to Zingiberaceae and its scientific name is *Zingiber officinale*. It reproduces by rhizomes which are used as flavor and medicine. There are many commercial types of this plant, the most traditional one is the Jamaican type that is used in pharmacologic preparations. Ginger is considered one of 20 types that are the most sold medical herb in USA. He also mentioned that ginger has many uses to treat; sickness of pregnant women, sexual weakness, the involuntary urination in children, catch cold, and nervous tension. Ginger also enhances the skin blood circulation, repels mucus, reinforces kidney and liver, reinforces memory, diminishes joints pain and sweating to warm the body. It also reinforces heart, acts against vascular system diseases, prevents coagulation, is used in eye diseases, acts against inflammation, and fever, antioxidant, decreases cholesterol and treat alimentary canal diseases. Bryer (2005) advised to use ginger as effective treatment for the pregnancy sickness, he also defined the daily dose of different types of ginger where the known drugs have a medium effect during pregnancy by 80% but they have serious side effects on the embryos resulting in embryonic distortions. Chrubasik *et al.* (2005) added that ginger could be used to reduce joint and bone inflammations, and other pains. There was no doubt that ginger preparations as 6-gingerol zingiberene are antioxidants, anticancer, immune enhancer, antibacterial, antifever, lipid reducer and have effect

on the alimentary canal, heart, blood vessels. Boone and Shields (2005) found that different doses and forms of ginger were safe and effective to treat pregnancy sickness during the first and second periods of pregnancy. Betz *et al.* (2005) confirmed that a daily dose of 6 g of ginger could be used for pregnancy sickness treatment with few side effects as intestinal symptoms, sleeping and one abortion case from 136 women at the 12th week of the pregnancy. Recently, a study carried out on the effect of ginger to treat pregnancy sickness, it was found that ginger improved 77% of pregnant women after 7 days (Lania, 2005). Yemitan and Izegbu, (2006) tested ethanol extracted from ginger roots to resist the toxic effects of carbon tetrachloride on the rat liver. They found that the extracted oil from ginger roots was useful to prevent liver acute infection resulted from carbon tetrachloride exposure. In another study carried out by El-Hummdi (2006), it was found that a mixture of honey, black seed and ginger had a curial effect on the side pathological changes of anticoagulant (clexane) of the kidney of rats. Khalifa (2006) recommended using a mixture of ginger, honey, black seed with urine and milk of sheep to inhibit the toxic effect of the antidepressant drug (haloperidol) on the testicular structure of male rats. In another study, Khalifa (2007) proved the ability to use a mixture of honey, black seed and ginger to decrease the acute pathological histological changes in the intestinal region of albino mice treated with clexane.

Pieroni and Torry (2007) considered ginger to treat muscular, skeletal and digestive disturbance, while mint to treat digestive and respiratory problems and canella is effective in gastric diseases. Ghayur *et al.* (2007) also considered ginger as a universal food and used in treatment of intestinal disturbances. Ajith *et al.* (2007) suggest that the hepatoprotective effect of zingiber officinale against acetaminophen – induced acute toxicity is mediated either by prevent the decline of hepatic antioxidant status or due to its direct radical scavenging capacity. Tao *et al.* (2008) found that ginger are better in rat hepatocytes exposed to oxidative damage and definitive cytoprotective actions.

Amin *et al.* (2008) conclude that ginger has a protective and antioxidant effect against testicular damage and oxidative stress in cisplatin and testes appear normal morphology.

Ding *et al.* (2013) concluded that orally administered ginger to be significantly more effective than placebo in reducing the frequency of vomiting and intensity of nausea

Heitmann *et al.* (2013) result that. ginger during pregnancy does not seem to increase the risk of congenital malformations, stillbirth/perinatal death,

preterm birth, low birth weight, or low Apgar score. This finding is clinically important for health care professionals giving advice to pregnant women with NPV. Therefore, the present study is concerned in determining the safety level of ginger to be used as a treatment during pregnancy.

2. Material and Methods:

Material:

This study was carried out on 30 females and 15 males of albino mice as following:

1- A daily oral dose of 3 ml/kg of ginger was provided for males and females for a week. Ginger drink was prepared according to Zhuo *et al.* (2000).

2- Males and females were placed together for fertilization.

3- Pregnant females were divided into groups as follows:

First group was the control group and was provided with a dose of distilled water equivalent to ginger dose from the 1st to the 21st day of pregnancy.

Second group was provided with a daily concerned dose of ginger from the 1st to the 21st day of pregnancy.

Third group was provided with a daily concerned dose of ginger during the first week of pregnancy (from the 1st to the 7th day), and then females were left to the 21st day without any treatment.

Fourth group was provided with a daily concerned dose of ginger during the second week of the pregnancy (from the 7th to 14th day) then were left till delivery without treatment.

Fifth group were treated by ginger from 7th to 21st day of pregnancy and left to delivery.

Methods:

- Samples of testis and ovary were taken from some males and females of rat treated with ginger before fertilization.

- Females were weighed before and after pregnancy.
- Samples of liver and kidney from embryos of all groups were taken at delivery, weight of embryos were recorded and notes of number and shape were recorded.
- Samples of liver and kidney were taken from mothers of all groups.
- Samples were fixed in neutral formalin and the standard procedure of dehydration, clearing and wax embedding was followed. Sections were taken at 3-5 μ m and stained with hematoxylin, eosin and periodic Acid Schiff (Drury & Wallington, 1967).

3. Results and Discussion:

Changes in body weight:

It can be noticed from Table (1) a decrease in the body weight of mothers and embryos in the ginger treated group throughout the pregnancy till delivery (i.e. from 0 to 21st day) by the rate 170-180 for mothers and 4.3-4.9 for embryos. For the group treated with ginger for two weeks (7-21 day of pregnancy), the rate of body weight decrease was 170-180 for mothers and 5.4-5.7 for embryos. These agreed with the previous studies that ginger increased lipid oxidation (Chrubasik *et al.*, 2005) and with the study of Goyal and Kadnur (2006) who confirmed that ginger treatment decreased the body weight, blood glucose, insulin and lipid levels, this depended on the exposure period. The reduction in the weight of embryos may be due to the elevation in the embryos number where each female in all treated group gave 12 embryos without any morphological distortions in embryos. Also, the pregnancy percentage in all treated females was 100%. The present data are in accordance with those obtained by Wilkinson (2000).

Table 1. Mean changes in body and organs weight (g) of mothers and embryos.

Treated group	Mother weight		No. of embryos	Embryo weight		Liver weight		Kidney weight		Spleen weight	
	Beginning	End		Mother	Embryo	Mother	Embryo	Mother	Embryo	Mother	Embryo
Control	180	225	8	7.4	9.98	0.32	1.0	0.044	0.54	0.009	
Second group (0-21)	180	170	12	4.3	7.15	0.19	0.64	0.028	0.44	0.01	
Third group (0-7)	180	222	12	6.08	9.37	0.30	1.0	0.04	0.52	0.008	
Fourth group (7-14)	180	220	12	5.98	8.78	0.28	0.90	0.053	0.51	0.01	
Fifth group (7-21)	180	170	12	4.9	7.42	0.21	0.72	0.03	0.47	0.012	

For the two-weeks treated groups (from 7-14 days), the body weight increased by the rate of 180-220 and also from 0 to 7 days by the rate 180-222, and this is a normal pregnant increase for embryonic

formation. These weights were nearly similar to those recorded in the control group for mothers (180-225) and embryos (7.0-7.4). The weights of liver and kidney of both mothers and embryos were nearly

normal and this confirmed by Portnoi *et al.* (2004) who noticed that there was no difference between gingers treated embryos and the control group, except the increasing in the body weight of treated embryos. This also in agreement with the results obtained by Roberts *et al.* (2007) who found that the body weight decreased at the eighth week of pregnancy and concluded the ginger extraction was ineffective in body weight losing.

In all treated groups, the spleen weight was nearly similar to that of the control group, where it was 0.4-0.5 g for mothers and 0.01 g in embryos. This may be attributed to the absence of lipid in spleen and thus ginger did not affect on its weight.

Histological changes:

Kidney:

The histological structure of the kidney from mothers in all treated groups appeared normal in both cortex and medulla levels (Fig. 1). Most glomerulus were normal, both parietal and visceral epithelium appeared clearly, and distal and proximal tubules appeared normal in all regions of kidney. The edges of the cubic epithelial cells of the proximal tubules were obviously noticed by PAS stain as well as the collecting tubules and the ascending and descending limbs of Henle loop.

For the newly delivered embryos from a week ginger treated group, (Fig. 2) the kidney appeared

normal and resembled in its structure that of the control group; where the cortex was smaller than the medulla, smaller glomerulus, normal structure of cortex and medulla, less number of renal tubules, more interstitial connective tissue, and presence of mesoparenchymal cells. All these indicted the progressive formation of kidney. However, oedema was observed in the tissue and capsule was appeared as a thin narrow band around small kidney (Fig. 3).

Different developmental stages of glomerulus, distal and proximal tubules formation in the cortex were also observed. This indicates that kidney was not completely formed and still at the growth and formation stage at this age. It was also observed an increase in kidney growth with age, in kidney size, in the number of renal tubules, in cortex size to be in normal size and less interstitial tissue with increase the exposure period to ginger in both two- and three-weeks treated groups. These groups appeared to be more progressed in their growth than the control group of the same age.

The present results agree with those of El-Hummdi (2006) and Khalifa *et al.* (2008) which confirmed the high efficiency of ginger to reduce the side effects of esteretin and regaining the normal structure of the renal tissue.

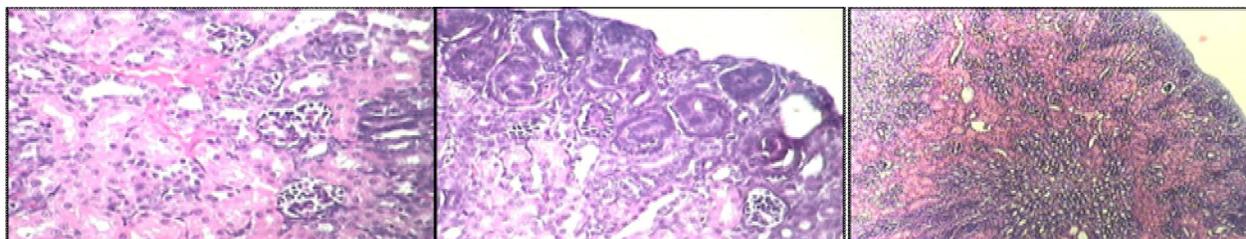


Fig. 1

Fig (1): Light micrographs of kidney from ginger treated mothers during gestation (0-21) showing the normal structure except bleeding

Fig. 2

Fig (2): Light micrographs of kidney from newly born rat treated with ginger during the first week of gestation (0-7) showing the similarity of tissue to the normal structure (H & E 10x).

Fig. 3

Fig (3): Light micrographs of kidney from newly born rat treated with ginger during the second and third periods of gestation (7-14) showing large kidney size and increased in the renal tubules number (H & E 100x).

Liver:

Normal liver structure appeared in mothers of all treated groups (Fig. 4), except blood filtration in some blood vessels. Hypatocytes appeared polygonal, large and arranged in the hepatic strands that extend from the central vein enclosing hepatic sinusoids. The portal spaces contain branch of artery and vein as well as bile ductules. Kupffer cells were observed to be normal and the glycogen granules were obviously stained with Pas inside the hepatocytes.

For treated newly delivered embryos (Fig. 5), liver was observed to be structurally normal unless its growth was incomplete at this age. For one-week ginger treated group, liver appeared normal except presence of filtration in some blood vessels, enlarged hepatic sinusoids that filled with stasis blood, and the hepatic stands were arranged, increased in their number and nearly in their final form.

At three-week treated group, portal spaces began to be formed, and hepatocytes increased in

their number. This was indicated by narrow hepatic sinusoids with a reduction in the rate of oedema. These changes were not observed in the same age in the control group which was similar in growth rate to two-week treated group. These observations support concept of Labania (2005) that ginger can be used to enhance liver and kidney, and agree with Nakazawa and Ohsawa (2002) who mentioned that hepatic enzymes of mice have an important role in 6-gingerol metabolism. Also the present results are in accordance with Khalifa *et al.* (2008) who recommended ginger to be used to reduce the serious effect of esteritin on the histological structure of albino mice liver, where liver was able to resume the normal structure.

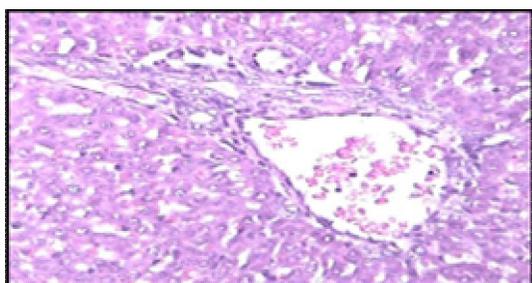


Fig (4): Light micrographs of liver of mothers treated with ginger during gestation (0-21) showing blood filtration and appearance of the tissue similar to the normal structure (H & E 10x).



Fig (5): Light micrographs of liver from newly born rat treated with ginger during gestation (0-21) showing that tissue did not affect and appeared normal (H & E 10x).

Spleen:

In mothers of all treated group, spleen appeared normal in structure (Fig. 6), surrounded by a capsule of connective tissue which extend as barriers to divide spleen into lobes and the red lobe appeared characterized from the white one. It was also observed that the red and white lobes were appeared darker indicating the elevation in the number of lymphatic cells. Increase in the number of spleen nodules and the size of white lobe were also recognized in comparison with the control group.

For the one-week ginger treated embryos (Fig. 7), the spleen did not completely formed at this stage where the barriers were not formed and the connective tissue spread inside spleen containing masses of lymphatic cells. These masses spread within the lymphatic tissue between the spleen sinusoids as a reticular connective tissue with oedema in the tissue. This structure was similar to that of the control group, despite the presence of more dense lymphatic cells in the treated group than those of the control one.

Concerning with two-weeks treated group. It was observed that the lymphatic cells were more than that of either control or one-week treated group.

For three0week treated group, there was an increase in the growth rate at the beginning of lymphatic nodules formation and white and red lobes differentiation. These results confirmed the ability of ginger to enhance the immune system and support data obtained by Chrubasik *et al.* (2005).



Fig (6): Light micrographs of spleen of mothers treated with ginger during the gestation (0-21) showing an increase in the numbers of splenic nodules and white lobe region (A)(H & E 40x).

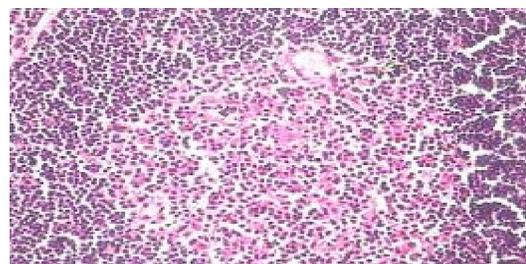


Fig (7): Light micrographs of spleen from rat at age 75day treated with ginger during the gestation (0-21) showing the unaffected tissue and an increase in the density of immune cells (H & E 100x).

Testis:

For all treated groups, testis appeared in its normal structure surrounded by fibrous capsule (tunica albuginea) followed by vascular capsule which interfere with intertubular connective tissue. Somniferous tubules increased in size and closed to each other resulting in reduction the intertubular

connective tissue. Shape of the tubules were varied from spherical to cylindrical or oval this due to their great length and bending, thus they appeared in sections at different levels (Fig. 8). Each tubule is composed of basement membrane on which spermatogonia rest on followed by primary spermatocytes then secondary spermatocytes and finally spermatids which differentiated to spermatozoa directed by their tails to Sertoli cells.

Also, in (Fig. 9) an obvious density of spermatocytes and spermatozoa comparing with the normal density indicating the ability of using ginger to increase the functional testis efficiency and in sexual weakness treatment as mentioned by Labania (2005). Moreover, Amin and Hamza (2006) confirmed that treatment by ginger extraction increased the activity of antioxidant enzymes and resumed the spermatozoa movement and significantly reversed to control group in treated mice with ginger and cisplatin drug that caused toxicity to the mice reproductive system.

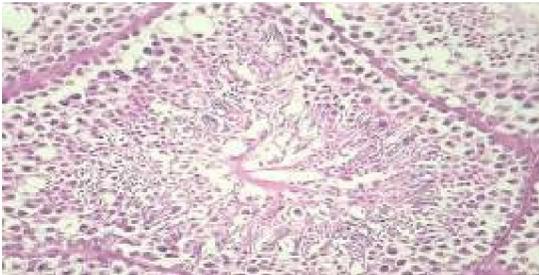


Fig (8): Light micrographs of testis from males treated with ginger for one week showing dense of Seminiferous tubules H & E 40x

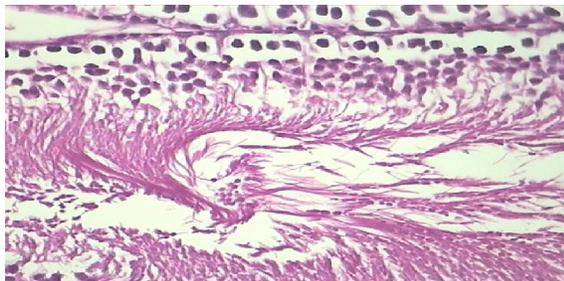


Fig (9): Light micrographs of testis from males treated with ginger for one week showing dense spermatocytes and spermatozoa comparing with normal case (H & E 100x).

Ovary:

Except appearance of edema and congestion in limited regions of the tissue, ovary appeared in all treated groups in normal structure (Fig. 10) where it covered by the germinal epithelium followed by a

dense connective tissue. Cortex represents the major part of the ovary and contains the growing follicles in different stages of development. These follicles represent the primary follicle that composed of primary oocyte surrounded by one layer of follicular cells that are present in a limited number. Sections are filled with secondary follicles which composed of one primary oocyte surrounded by several layers of follicular cells. These cells produced from the division of follicular cells. It was also observed a dense presence of mature follicles (Fig. 11) that contain one oocyte surrounded by discus proligerus, then the follicle is surrounded by the theca interna and externa. Follicular cells surrounded the central cavity which is filled with liquor folliculi (secreted by the follicular cells).

Some mature follicles appeared in the section stopping of growing after reaching maturity and an obvious presence of the corpus luteum in all stages (Fig. 12); either newly or retarding forms. The medium retarding stage contained small follicular cells with thick nuclei and large blood vessels. The late retarding stage represented by atrophic follicular cells with thick nuclei and fibrous lobe. With the retarding progressed, the connective tissue replaced the follicular cells after their atrophy forming the white luteum. This confirmed the ability of ginger to improve the functional efficiency of the ovary (Labania, 2005).

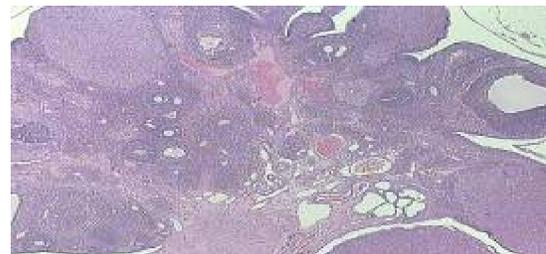


Fig (10): Light micrographs of ovary from females treated with ginger for one week showing dense growing and mature follicles compared with the normal case (H & E 10x).

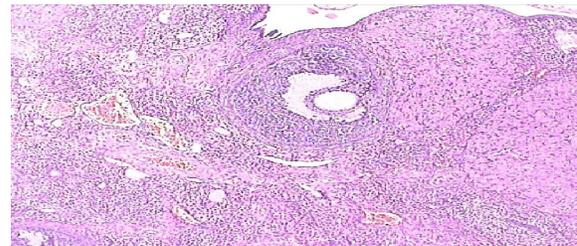


Fig (11): Light micrographs of ovary from females treated with ginger for one week showing mature follicles (H & E 40x).

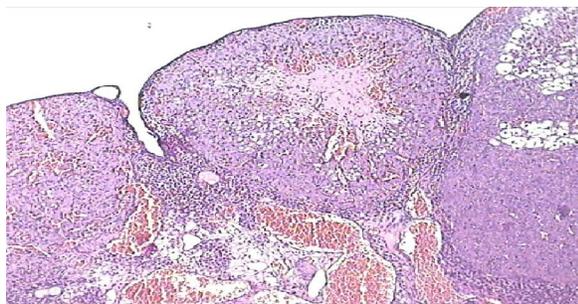


Fig (12): Light micrographs of ovary from females treated with ginger for one week showing corpus luteum (H & E 10x).

From these results, it could be concluded that:

- Treatment by ginger during all different pregnancy stages (division stage {0-7}, organs formation {7-14}, growth stage {7-21}, throughout pregnancy period {0-21}) did not cause damage effect on the histological structure of liver or kidney of both mothers and embryos; therefore it can be used safely during pregnancy.
- Ginger did not cause side or toxic effects stunting division, organs formation and growth in embryos, where there were not any recorded distortions either morphologically or histologically in treated embryos during different pregnancy periods.
- Ginger enhances the immune system and this was cleared from the histological structure of spleen from mothers and embryos.
- Ginger increased the growth rate in embryos over the normal rate by increasing the exposure period.
- It is advised to use ginger to treat the sexual weakness, enhance testis and ovary and increase the rate of formation of both male and female gametes, thus increase number of birth.
- The weights of mothers and embryos did not influence when they are treated with ginger for a week, and decreased when they were treated for two weeks confirming the ability of ginger to diminish lipids.

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