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Micromorphological Study of The Corpus Luteum of The Rabbit During Pregnancy

Moussa M.H.G., El-Sakhawi M.A., El-Saba A.A. and Tony A.M.*
Department of Cytology and Histology, Faculty of Veterinary Medicine,
Cairo University. *PhD student Histology

Abstract

The micromorphological characteristics of growth and regression of rabbit corpora lutea were investigated by light and scanning electron microscopy during pregnancy. In the latter, the corpus luteum (CL) of rabbit ovary gradually increased in diameter and reached its maximum size at the mid of gestation period (14 days post mating). It slightly decreased in size around the end of pregnancy. This increase and decrease in the size of the corpus luteum was accompanied by an increase and decrease in the size of lutein cells. The fibrous boundary between the CL and the surrounding interstitial gland cells was vanished at the later stages of regression, allowing the two cell types to intermingle. During the structural regression of the CL the mean number of the lutein cells was markedly and significantly decreased while the mean number of the interstitial gland cells was significantly increased. Macrophages and other connective tissue cells, except fibroblasts, were not prominent during regression indicating that these cells in the rabbit, unlike other species, may not play an important role in luteolysis.

Keywords: Rabbit,Doe, Ovary, Corpus luteum, Pregnancy, Post-partum, Luteolysis, Luteinization

Introduction

Corpora lutea (CL) are progesterone-secreting ovarian tissue which develops from follicles after ovulation to regulate early pregnancy and mammary gland development **(Niswender and Nett, 1994)**. In the rabbit, estradiol secreted by the follicles is essential for CL maintenance **(Keyes and Nalbandov, 1967; Holt et al., 1975)**. In some primates, the presence of active CL inhibits folliculogenesis**(Koering, 1974a; Baird et aI., 1975)**. When progesterone levels decrease during luteolysis in rabbit, ovulation can occur **(Hammond and Marshall, 1925)**. Degeneration of the rabbit CL takes place following parturition and can be induced experimentally by either estrogen deprivation **(Miller and Keyes, 1975)** or by **$PGF_2\alpha$**administration **(Koering and Kirton, 1973; Keyes and Bullock, 1974)**. Growth and regression of rabbit CL results primarily from changes in volume and not in number of individual lutein cells **(Zheng, Redmer and Reynolds, 1994 and Dharmarajan, 1988)**. The morphological persistence of the CL beyond functional activity may be relevant to the development of both follicles and interstitial gland tissue which is abundant in the mature rabbit ovary **(Koering and Kirton, 1973 and Mori and Matsumoto, 1973)**. Another aspect to be considered in the luteolytic process is the role of the macrophages and vasculature. This can be examined by use of a morphological tracer such as colloidal carbon to locate phagocytic cells in various organs **(Wislocki, 1924)**. **Zheng, Redmer and Reynolds (1994)** have suggested that programmed cell death or apoptosis may be responsible in bovine CL cell regression.

This study was undertaken to determine the micro morphological characters of growth and regression of the CL during pregnancy.

Materials and Methods

Twenty one New Zealand White adult healthy female rabbits (6-9/phase) were the source of CL. They aged 14 to 20 weeks and weighing 2.2 to 3.5 Kg. and were obtained from a local farm (Physiology lab) of Faculty of Veterinary Medicine - Cairo University. Rabbits were individually housed in separate cages with daily illumination of 16 hours of light and allowed free access to water and rations. The day of mating of the does with the fertile bucks

was called 0 Day of gestation. Animals were sacrificed by an over dose of pentobarbital sodium (100 mg/ Kg body weight).The ovaries were removed from 3 does in each of the following stages during pregnancy (Table -1). The ovaries were prepared for:

Light microscopy (LM): Ovaries were fixed in Bouin's fluid, dehydrated in ethanol, embedded in paraffin, sectioned and stained with H&E, Toluidine blue, Osmium tetroxide.

Stage of Pregnancy	Samples collection day			No. of Does used
Early	3rd Day		7th Day	6
Mid	14th Day		18th Day	6
Late	21st Day	25th Day	28th Day	9

Table -1: Selected days for samples collection.

Results

Early pregnancy:

At the **3rd day** post-mating, gross examination of the rabbit ovary revealed several antral follicles and corpora lutea bulging from the ovarian surface **(Fig.1)**. With SEM the CL was seen protruding out of the outer surface of the ovary and appeared surrounded by fibrous capsule **(Fig. 2a&b)**. This indicated that lutinization process in rabbit started just after ovulation by the transformation of the pre-ovulatory follicles into corpus luteum.

Histologically, the ovary was covered with an epithelium, usually of simple cuboidal cells **(Fig. 3a&b)**. The outer cortex was occupied with different types and various sized-follicles. Corpora lutea

were seen embedded in the ovarian stroma **(Fig. 4)**.

By the **7th day** post-mating, the CL became more apparent and occupied a great area of the ovarian cortex as pregnancy advance **(Fig.5)**. One to three developing corpora lutea were observed in the examined ovarian sections. Each CL was surrounded by fibrous capsule housing numerous spindle-shaped fibroblast cells. The capsule separated the developing CL from the adjacent interstitial gland cells **(Fig. 6)**. It was formed of lamellated fibrous tissue rich in small blood vessels and lymphatics. Elastic tissue was sparse and occurred only in the wall of the blood vessels **(Fig.7a&b)**. This early stage of pregnancy was characterized by the differentiation of the granulosa cells to form the lutein cells. It was also characterized by the presence of massive network of blood capillaries and small vessels scattered in the scanty amount of the interstitial connective tissue between the lutein cells **(Fig.8a&b)**. With higher magnification, the newly formed CL consisted of abundant large polyhedral or oval lutein cells. Their nuclei were mostly eccentric, stained basophilic and showed obvious nucleolus. The cytoplasm was loaded with numerous lipid droplets of different sizes. Three forms of lipid droplets could be distinguished in the cytoplasm of the large lutein cells: They were mostly appeared as large clusters of very fine droplets along the periphery of the cell **(Fig.9a)**. The lipid also appeared as moderate circular droplets of uniform size forming large aggregations in the cytoplasm **(Fig.9b)**. They usually pushed the nucleus eccentrically. The third type of lipid inclusions seen in the lutein cells was in the form of irregular patches. They appeared large so that only one patch occupy a large space in the cytoplas **(Fig. 9c)**.

It was obvious that, the lipid droplets in the peripheral cytoplasm of the lutein cells were more intensely stained with osmium tetroxide than those in the interior region due to the weak penetration of the osmium tetroxide solution **(Fig.10)**.

Mid-pregnancy:

The **14th day** post-matting was the peak of luteal activity and the stage of hypertrophy. The CL became fully developed, much larger and reached its maximum size. It was formed of a large highly vascularized cellular mass surrounded by fibrous capsule **(Fig. 11)**. The CL was characterized by an increase in the size of the lutein cells as a result of increasing in the amount of cell organelles and lipid droplets **(Fig.12)**. Accumulation of lipid droplets in the luteal cells likely is important for energy storage and steroidogenesis in the highly metabolically active CL. The large lutein cells showed abundant pale eosinophilic cytoplasm with the

lipid droplets which appeared vacuolated as a consequence of their leaching out during dehydration.

Numerous blood capillaries were seen in the CL at this stage to form a rich vascular network that occupying the fine slits between the lutein cells.As a result, the large lutein cells became permeated by tiny irregular capillary spaces lined by endothelial cells. RBCs were scattered in these newly formed capillaries. As pregnancy advance, the capillary spaces between the lutein cells became more marked than before **(Fig.13).** Tiny spaces were seen separating the capillary basal lamina from the basal lamina surrounding the lutein cells. The nuclei of the vascular endothelium appeared small flattened.

The morphometric measurements of the CL at this stage of pregnancy revealed that the CL was markedly increased in size than in the previous stage. The mean diameter of the CL was significantly increased to become about 0.055 mm. The large lutein cells significantly increased in size than before. Their mean diameter was 1µm. While the mean diameter of the interstitial gland cells was about 0.040 µm. The mean number of the large lutein cells /HPF was about 0.58 cells. Whereas the mean number of the interstitial gland cells was about 1.02 cells.

At **day 18th**of pregnancy, the CL slightly decreased in size compared with that of the day 14th. It still inhabiting a distinct area of the ovarian cortex. The luteal cells also decreased in size and became irregular in shape. In some sections the collagen fibers surrounding the CL were ill-distinct and eventually disappeared making it difficult to distinguish between the regressing luteal cells and the adjacent interstitial gland cells.

In osmium tetroxide stained preparations, the cytoplasm of the lutein cells contained relatively few fine black lipid droplets **(Fig.14)** except in the areas representing the site of the nuclei which appeared pale or unstained.

Late-pregnancy:

At **day 21st** of pregnancy, the CL still inhabited a distinct area of the ovarian cortex (Fig.15). It was greatly decreased in size and appeared less vascularized. Many lutein cells showed clear signs of regression. They decrease in size, with an increase of uniform sized lipid droplets (Fig.16). Their nuclear membrane became irregular and the cytoplasm showed vacuoles and condensation (Fig.17).These regressing lutein cells were usually seen scattered in most parts of the CL (Fig.18). The capillary spaces seen before in-between the lutein cells became less pronounced than before. Intercellular fibrous tissue was mostly seen in the areas near the center of the CL (Fig.19).

At **day 25th** and towards the end of pregnancy, the CL was formed of less vascularized fibrous net and many regressed lutein cells. Most of these lutein cells were obviously decrease in size and exhibited clear signs of apoptosis indicated by pyknotic nuclei, ill-distinct cell boundaries, and condensed cytoplasm. Moreover, the capillary spaces in-between the lutein cells became less pronounced than before. The tiny spaces, which separating the basal lamina of the capillaries from the basal lamina surrounding the lutein cells, became more conspicuous and wide (Fig.20).

As pregnancy advanced, most of the apoptotic lutein cells disappeared and were replaced by newly formed collagenic fibers and fibroblast cells. particularly in the central region of the CL(Fig.21). The density of this fibrous tissue between the lutein cells was increased due to the gradual invasion of the collagen fibres and the fibroblasts. As regression advances the intercellular collagen was increased. No macrophage cells could be observed in the examined sections. Some parts of the same CL presented a more fibrosed stroma. This indicated that the involution of the CL was a gradual process that begun at the center of the CL from which it extended to the other parts.

It has been found that the examined corpus luteum remained morphologically active nearly until the end of pregnancy. Moreover, The luteal cells during pregnancy showed abundant lipid droplets which were indicative of active steroidogenesis.

At **day 28th** of pregnancy, clear signs of structural regression or luteolysis were found. The CL was significantly decreased in size than before **(Fig. 22).** In H&E preparations the cytoplasm of the regressed lutein

cells became more vacuolated than before due to the increase of lipid droplets (**Fig.23**). Some of these lipid droplets were coalesced to form large lipid vacuoles. The pericapillary spaces, permeating the lutein cells were enlarged and became more prominent than before due to shrinkage of the lutein cells and increased the amount of intercellular collagenic fibers.

Many of the peripheral parts of the CL were completely disappeared and replaced by the interstitial gland cells. At higher magnification the cytoplasm of the regressed lutein cells appeared faint with coalesced lipid droplets or vacuoles. It possessed relatively abundant fine osmiophilic lipid droplets (**Fig. 24**). Most of the nuclei of the lutein cells showed deformities and signs of karyolysis. The nuclear membrane was lost in most of the cells.

The interstitial gland cells, lying adjacent to the CL, were easily distinguished from the luteal cells of the regressing CL by their smaller size and uniform-sized lipid droplets. They were usually separated from the CL by a less distinct fibrous boundary which gradually disappeared, allowing the luteal cells to intermingle with the interstitial gland cells.

Discussion

In the rabbit during early gestation 3rd -7th days, the corpus luteum is partly activated and usually enlarges due to cell hypertrophy. It reaches its maximum activity by the day 14th – 18th of mid-pregnancy. In late-pregnancy 21st - 25th day, the corpus luteum undergoes a transient regression. Shortly before parturition at 28th day, the CL is reactivated by retaining its usual appearance. Similar findings were described by (**LeMaireet al., 1970; Treloaret al., 1972** and **Gulyas 1974**).

In this study the luteal tissue is formed only of the granulosa derived lutein cells. They are large cells with acidophilic cytoplasm and a vesicular eccentric nucleus with a prominent nucleolus.The transformation of the granulosa cells into lutein cells is accomplished by hypertrophy of the cell, the accumulation of lipids and by increase in the cell size. However, an increase in the cell number does not usually take place. **However, Blanchette (1966)** described that in rabbit the luteal cells arise mainly from the granulosa cells, supplemented by differentiation of the surrounding theca and stromal cells.**Enders** and **Lyons (1964)** mentioned the same finding in rat.In other species, a second, smaller cell type arising from the theca and the stroma becomes part of the corpus luteum (theca lutein cells) (**Koering, 1969; Mossman** and **Duke, 1973**).

According to **Corner Jr. (1956)** and **Baird et al., (1975)** the theca lutein cells become a prominent part of the corpus luteum in the primate.

Gulyaset al., (1976) mentioned that at the 3rd day of pregnancy the granulosa lutein cells accumulate lipid droplets until about day 13 of gestation which subsequently decline concomitantly with an increase in number of dense bodies or lysosomes. In the 25-day old corpus luteum the lutein cells become devoid of lipid droplets (**Koering et al., 1973a**). At this time the capacity of the corpus luteum to secrete progesterone is diminished (**Stouffer et al., 1976**).

According to (**Green et al., 1967; Crisp et al., 1970; Gulyas et al., 1976**) prior to parturition at 28th day the cellular components of the corpus luteum appear again morphologically capable of synthesizing steroids.Lipid droplets reappear and together with sER comprise most of the cytoplasm. rER and Golgi complexes are also abundant. Vesicles in close relation to Golgi cisternae are seen. **Adams** and **Hertig (1969)** and **Koeringet al., (1973)**describe large mitochondria and lipid droplets in the large lutein cells. These findings lead to the suggestion that the lutein cells may act as storage sites for cholesterol and cholesterol esters (**Fienberg** and **Cohen, 1966**) and for progesterone (**Koering et al., 1973**).

Signs of regression start to appear soon after the corpus luteum has formed: 10-12 days post-ovulation in the rhesus monkey (**Koering, 1969**), in human (**Corner Jr., 1956**) and in sheep (**Deane et al., 1966**). The lutein cells shrink in size show clumping of chromatin, karyorhexis and vacuolization of the cytoplasm becomes marked. The involution of the granulosa lutein cell is characterized by large

lipid filled vacuoles, which eventually occupy most of the cytoplasm (**Lennep** and **Madden, 1965**).

The luteal cells during the early stages of regression show the basic characteristics of degeneration in the rabbit (**Koering** and **Kirton, 1973; Koering, 1974b**). The cells decrease in size, possibly as a result of a decrease in cytoplasmic organelles.

In the examined rabbits, close to term, the corpus luteum usually shows signs of luteolysis, i.e. shrinkage of lutein cells. However, the formation of autophagic vacuoles indicative of advanced stages of luteolysis was not found in the corpus luteum at term. The same finding was mentioned by **Gulyas etal., (1976)** in rhesus monkey.

Koering (1974b) described that the luteolytic process in the rabbit is more gradual and complex process. The effect of ovulation and lactation on CL regression was investigated by **Breed** and **Hilliard, (1970)** and **Foxcroft and Hasnain, (1973)**. Their findings support a previous observation that CL at Day 12 after pseudopregnancy resembled the CL on Day 12 of lactation. More variation could often be seen among CL in the same ovary (**Hammond and Marshall, 1925**).

In the present study, cells similar to interstitial gland cells are scattered within the regressing CL. In some areas a distinction between the original regressing luteal cells and the interstitial gland cells is practically impossible to detect under the light microscope. This finding suggests that either (1) luteal cells are converting to interstitial gland cells or (2) some of the interstitial cells are differentiating into interstitial gland cells. It is also possible that (3) the interstitial gland cells are migrating into the regressing CL. Further support can be given to each of these 3 possibilities (**Saunders, 1966**) or because they may be capable of reversible differentiation (**Gurdon and Woodland, 1970**). It is also known that in many species the CL is composed of cells derived not only from granulosa cells but also from cells located in the theca interna (**Mossman** and **Duke, 1973**). This has not been observed for the rabbit in the present study. However, the theca cells could be the ones that now resemble the interstitial gland cells but were not seen previously as they were in an undifferentiated state. This was further supported by data which revealed that much of the interstitial gland tissue in the rabbit is of theca interna origin (**Davies** and **Broadus, 1968; Mori** and **Matsumoto, 1973**). Another possible explanation is that interstitial gland cells move into the regressing CL as the fibrous tissue boundary disappears (**Mossman** and **Duke, 1973**).This hypophysis resembles the suggestion of the result of the present study.

In agreement with **Cohen et al., (1977)**in rabbit,a gradual invasion of collagen fibres and fibroblasts occurs. As regression advances the intercellular collagen increases. Moreover, invasion of connective tissue increases during late pregnancy.However, in rat, mice and hamster the corpora lutea disappear without leaving any scars.

Some CL maintains their separation from the adjacent interstitial gland cells by a fibrous tissue band housing blood vessels. The breakdown of this band is likely due to collagenase which can be formed by the mesenchymal cells located in the area (**Gross, 1974**).

The current study identified the fibroblasts in the center of the CL as the lutein cells begin to shrink and become increasingly vacuolated. Similar finding was described by (**Han et al., 1977**).

Macrophages take an active part in the atrophy of various tissues (**Helminen, 1975**) including the involuting mammary gland (**Helminenand Ericsson, 1968**).In uterine endometrium macrophages engulfed extracellular materials as regression progressed(**Padykulaand Campbell, 1976**).

In order to investigate the possible involvement of macrophages in luteolysis, **Koering** and **Thor (1978)** used carbon particles as a tracer to assist in the location of these cells. In the present study neither macrophages nor other cells except the fibroblasts were identified in the regressing CL of rabbit. This result agree with the findings of **Koering (1974b)** during the stages of regression of the CL in the rabbit.This is contrary to what was reported in the guinea pig (**Paavola, 1977**) and in rat (**Dott, 1969**) that

macrophages were abundant during luteolysis.This suggesting that a species difference may exist.

However, during CL degeneration in the rabbit, cellular activity has been observed. This activity is attributed to the presence of fibroblast-like cells and endothelial cells (**Han et al., 1977**). It is quite possible that some of that activity is due to the presence of the interstitial gland-like cells seen in the present study

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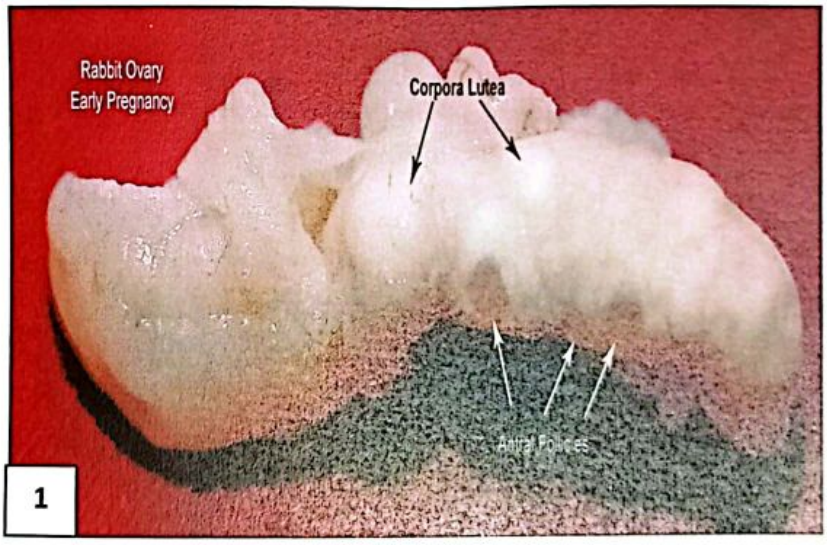

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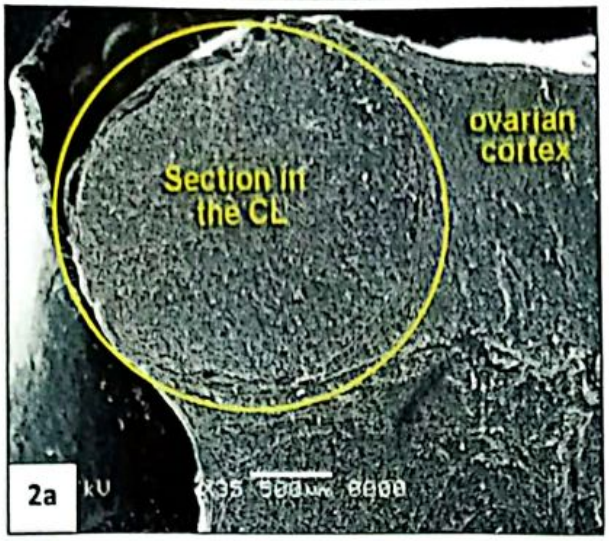

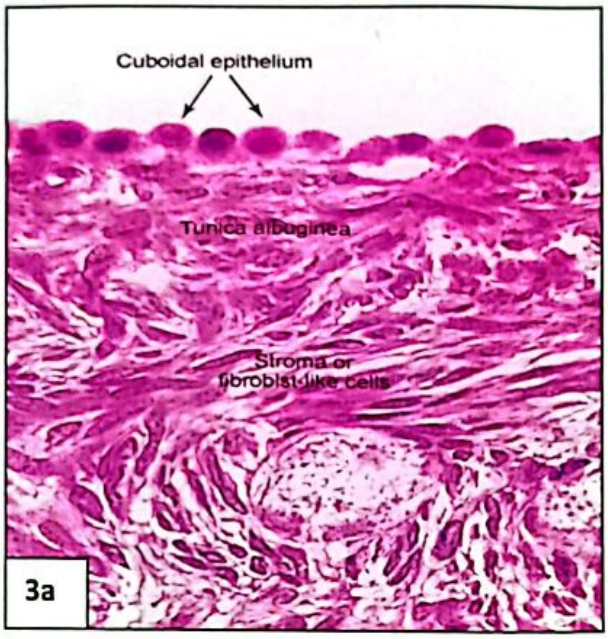

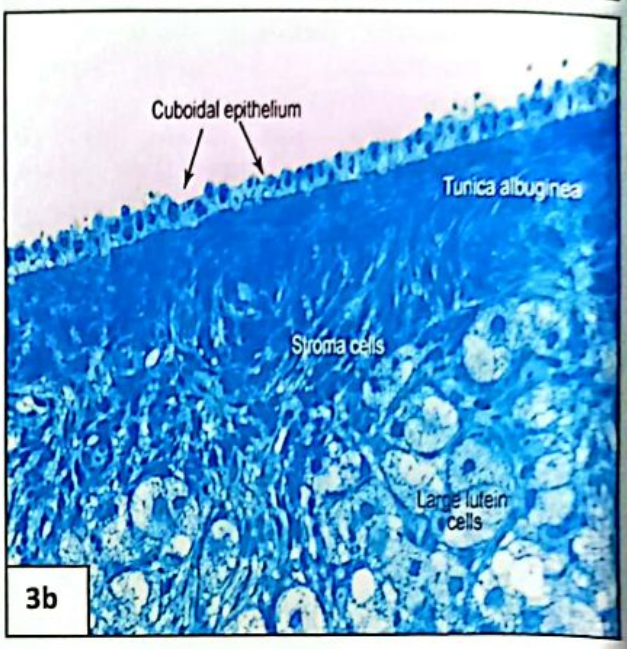

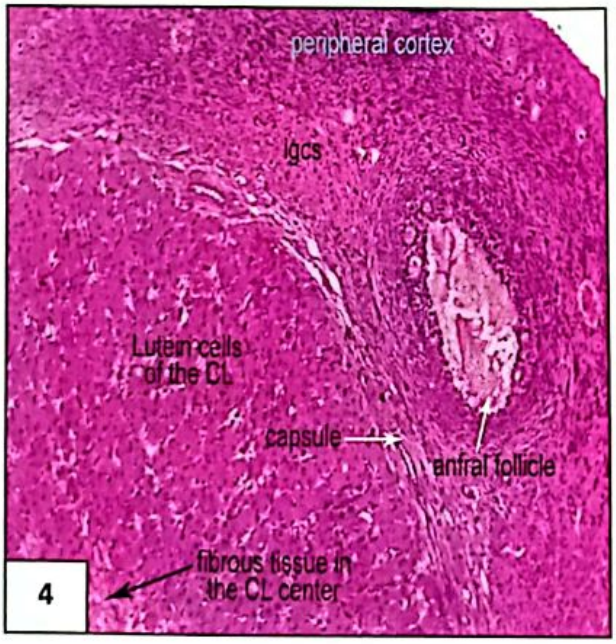

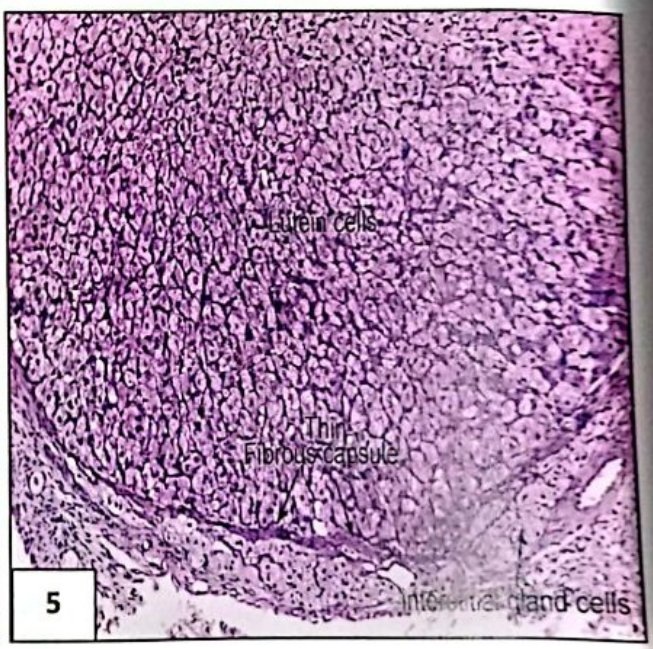

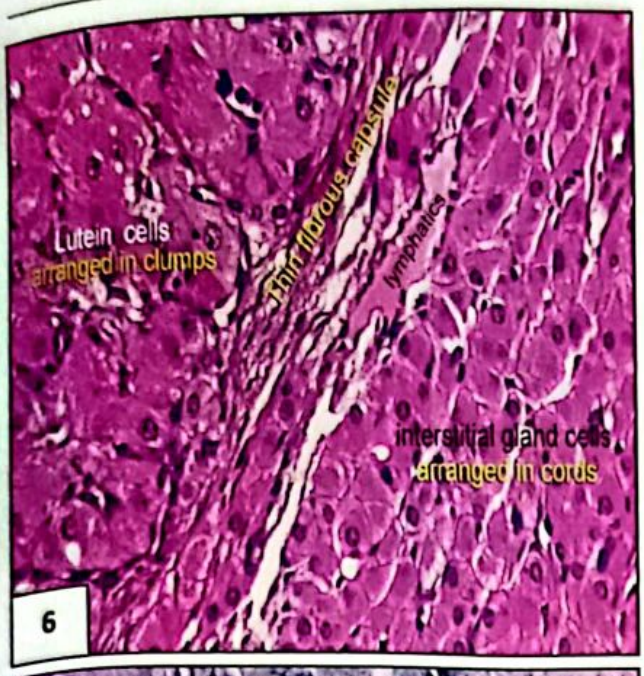

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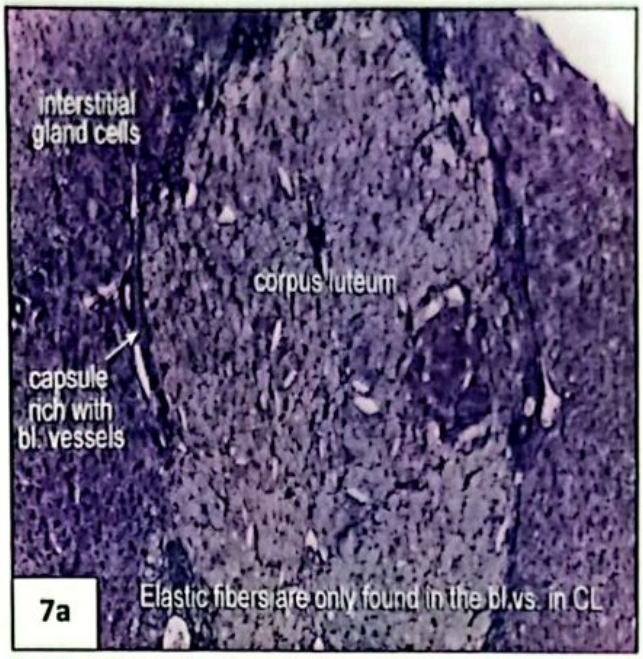

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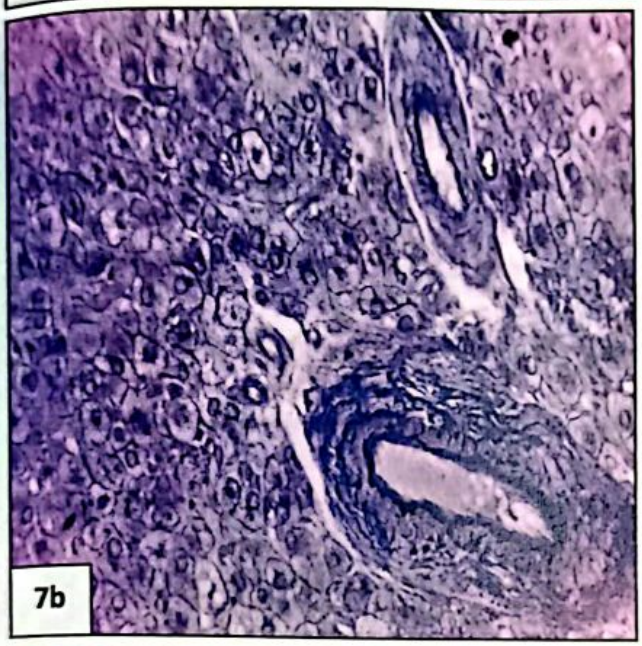
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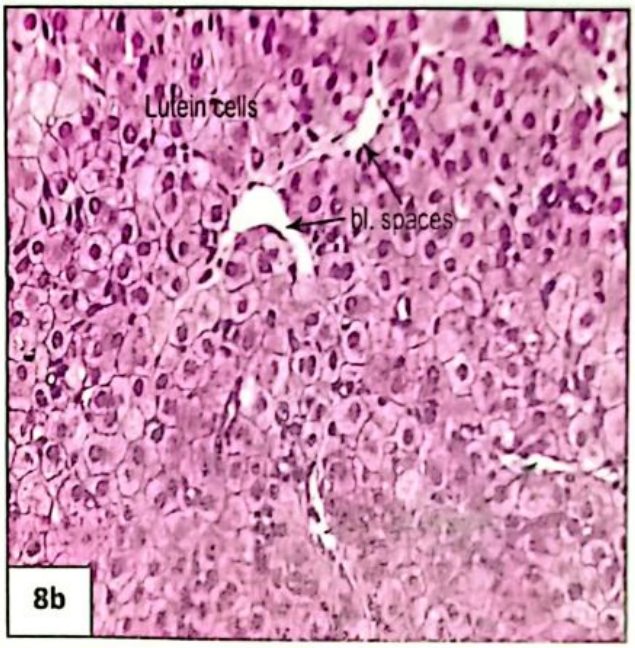

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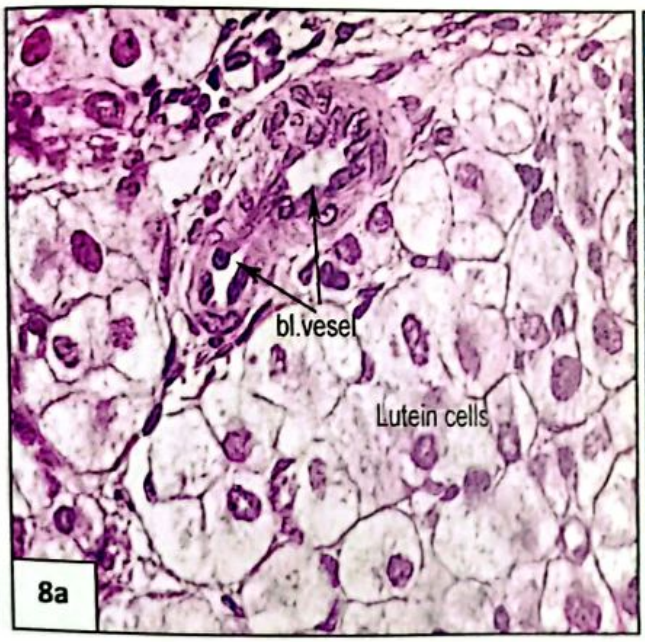

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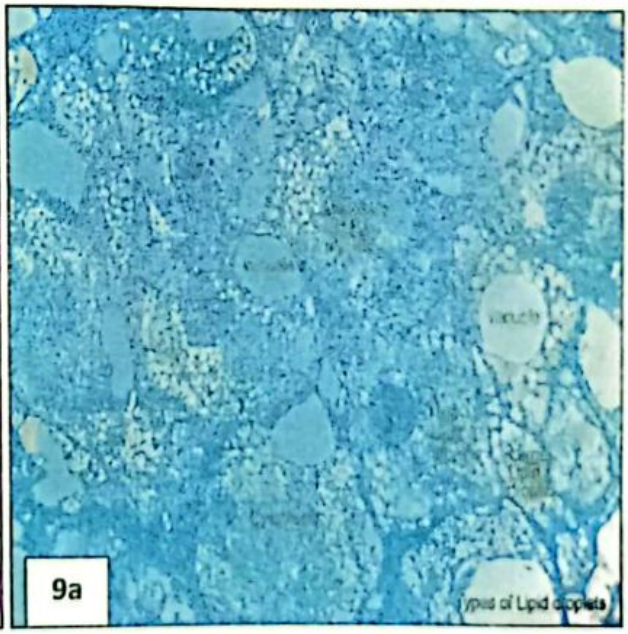
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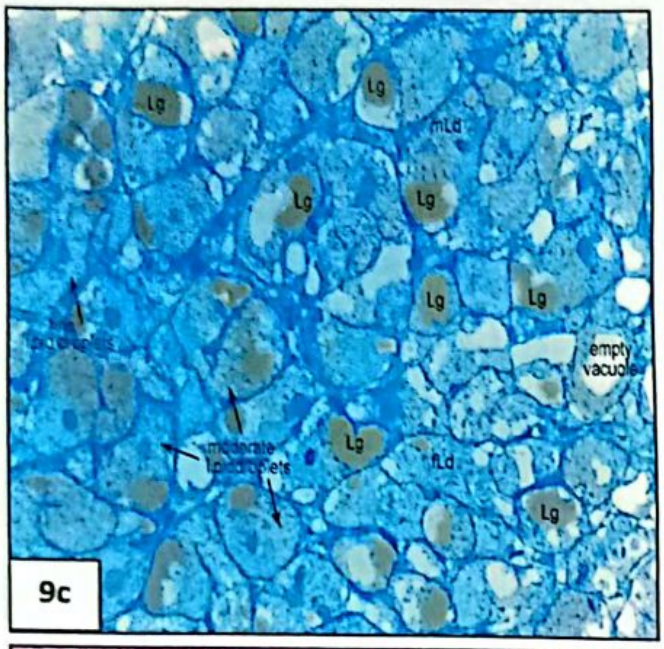

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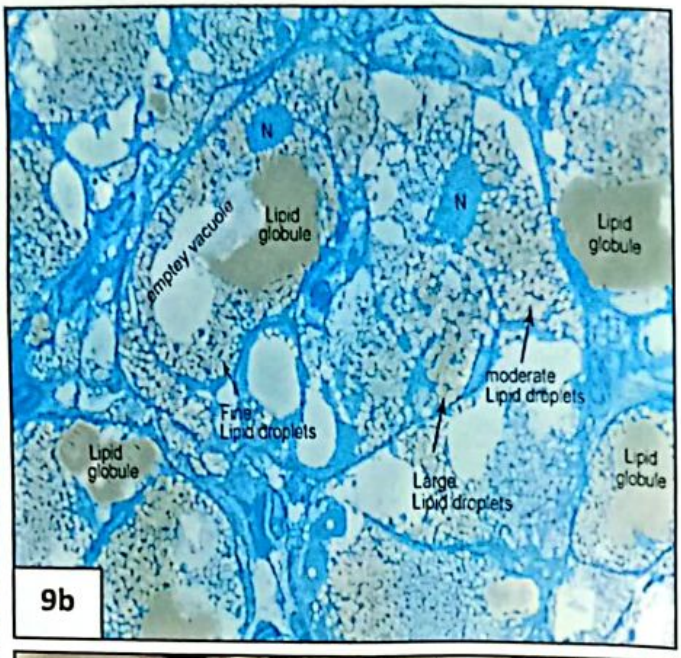

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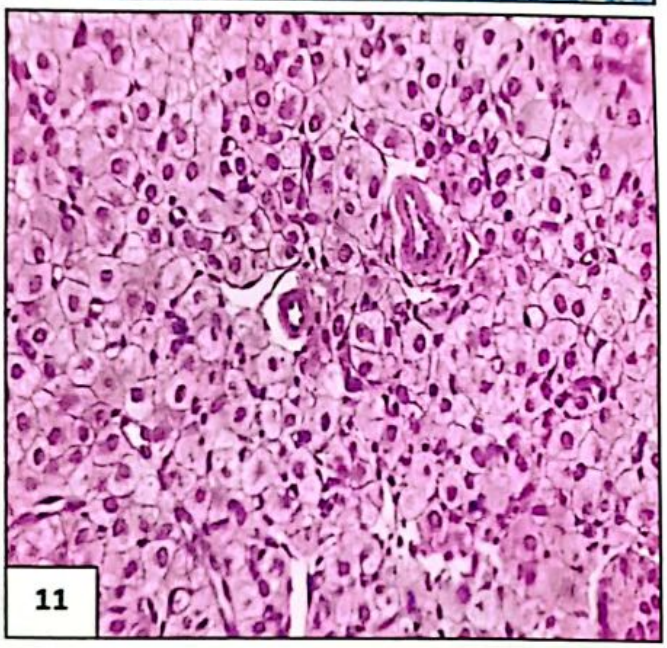
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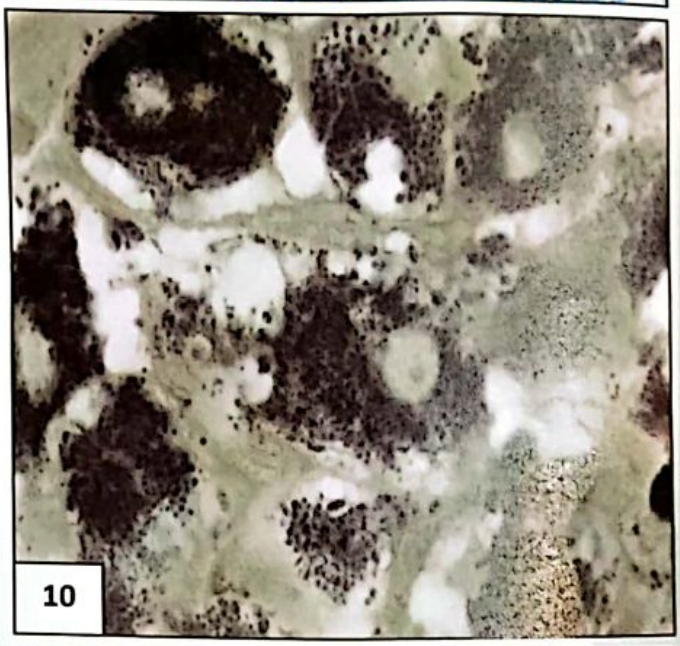
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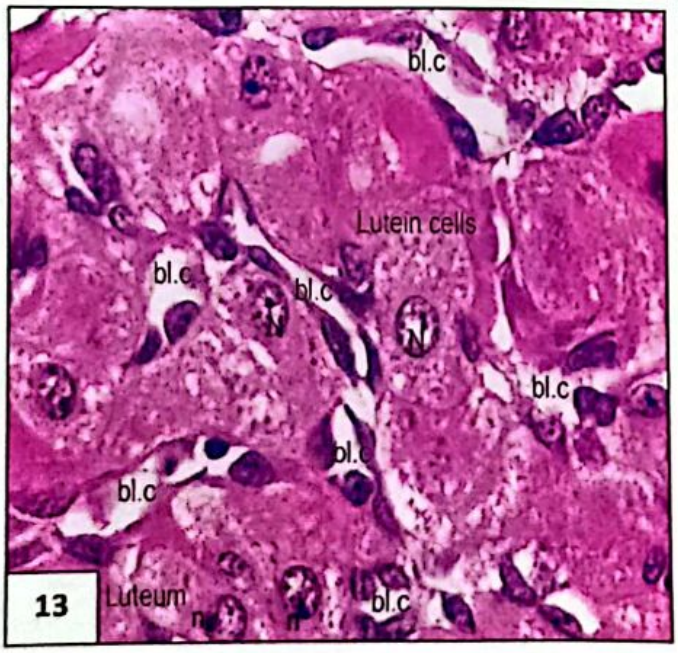

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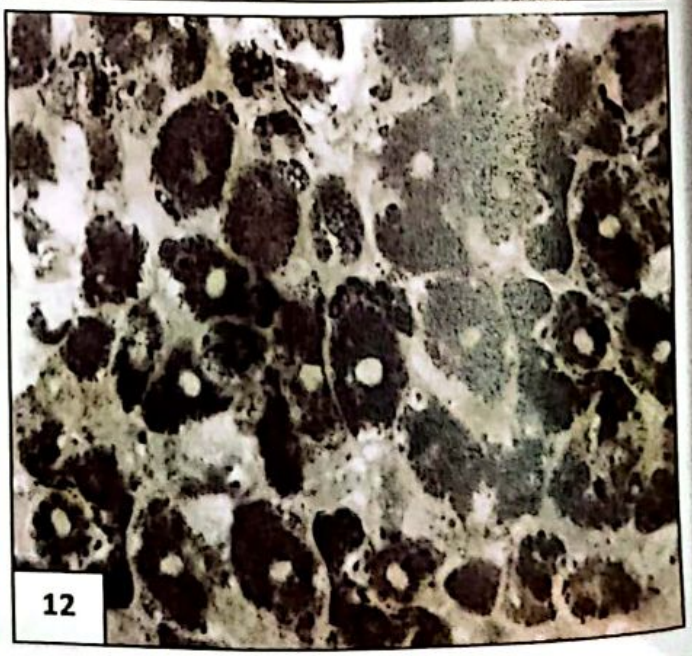
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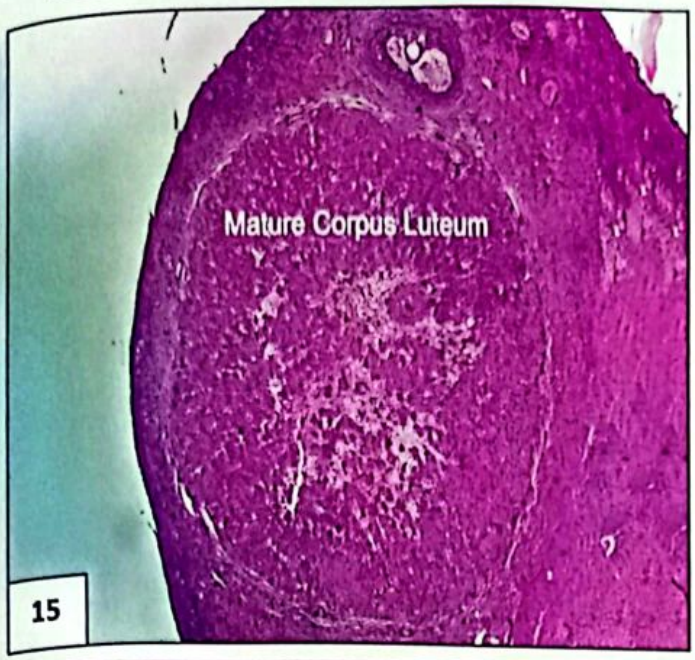

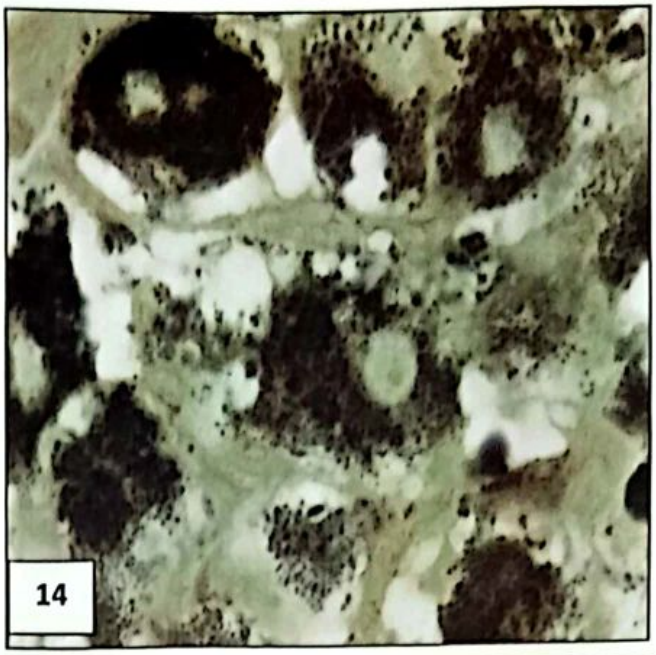

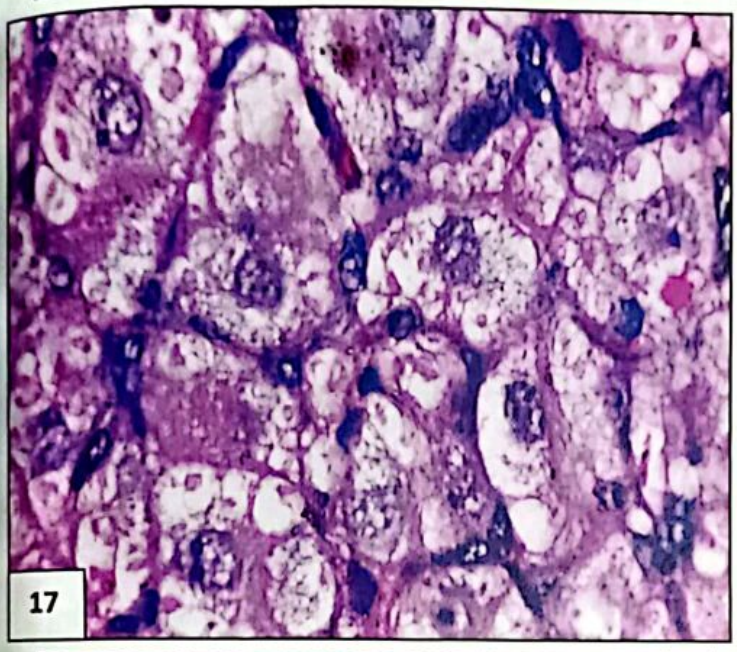

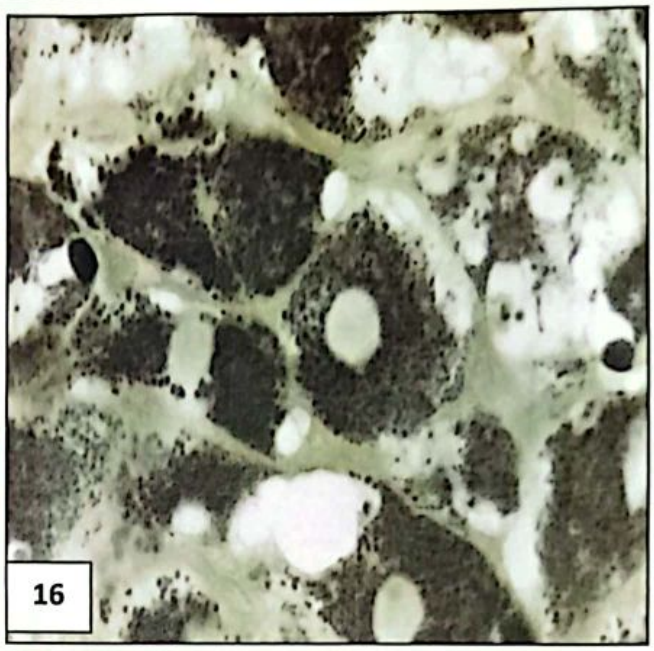

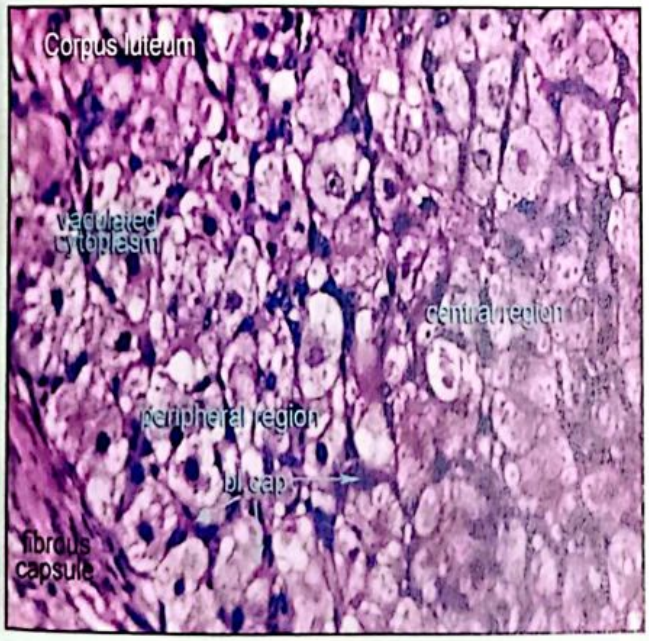

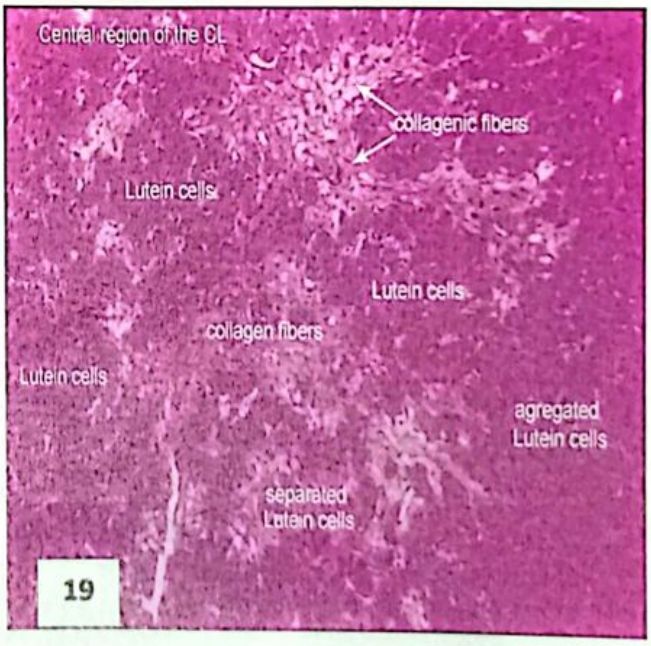

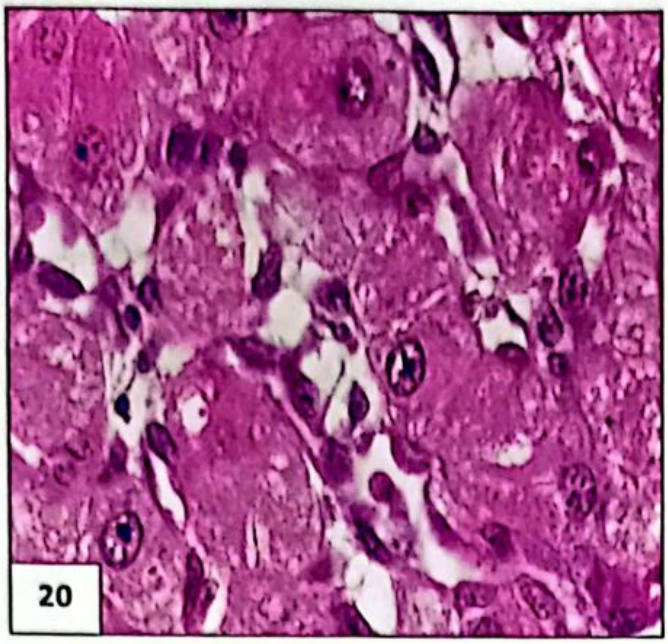
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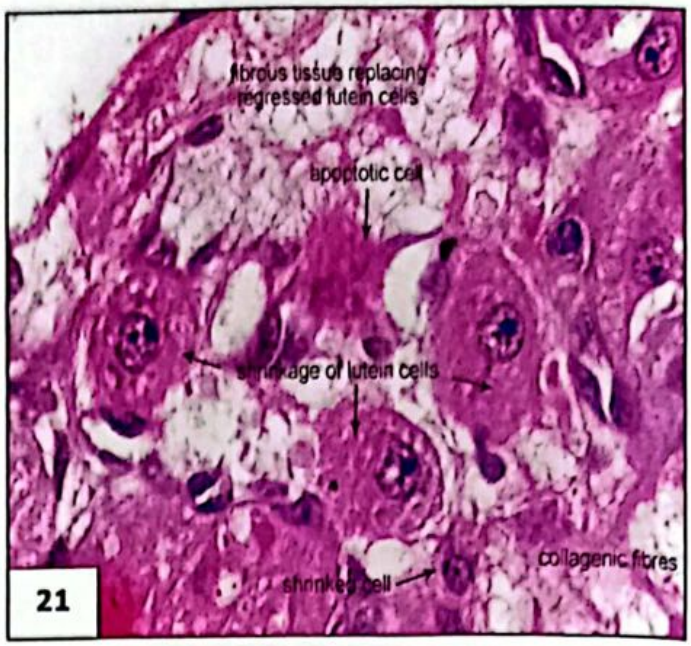

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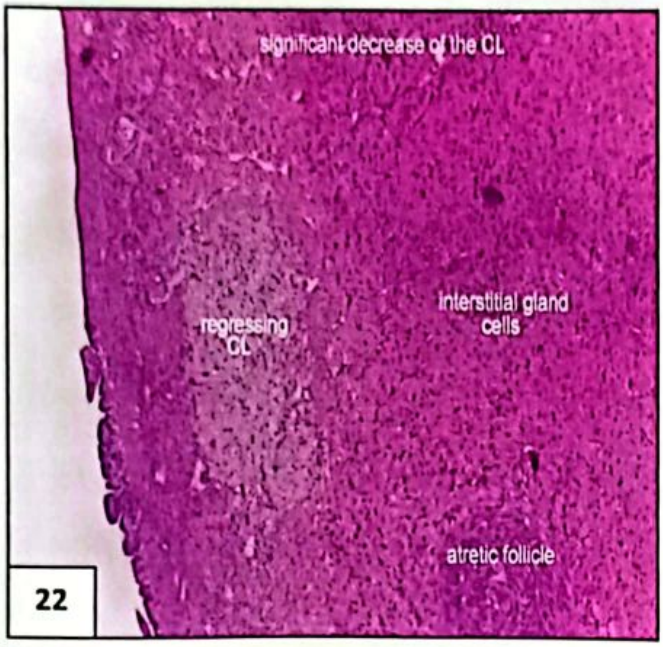

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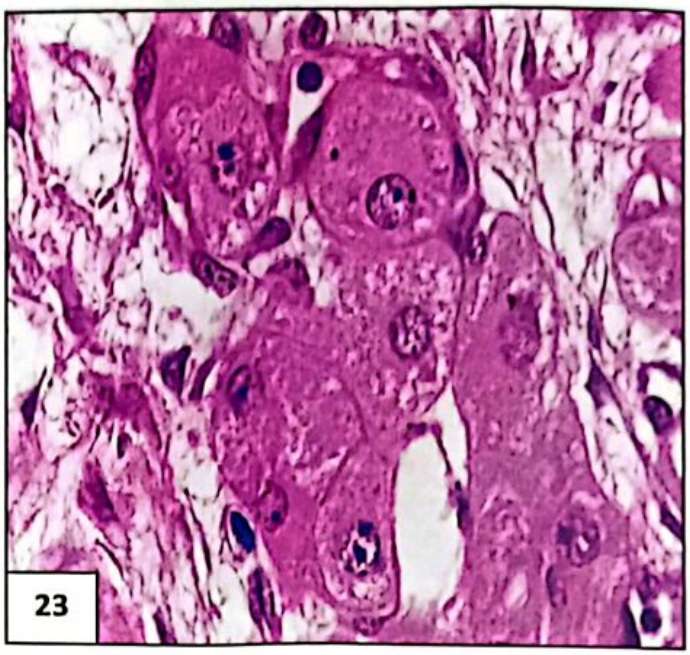
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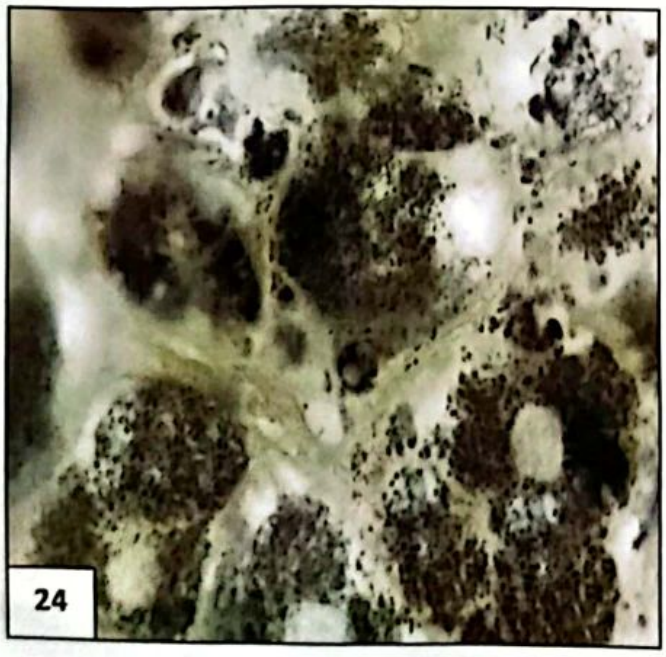
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List of Figures

Early pregnancy

Fig.1: Photograph of a rabbit ovary during early pregnancy showing antral follicles on the surface of the ovary (arrow). Some corpora lutea are also seen bulging on the surface.

Fig.2a&b: At the 3rd day post-mating, capsulated functioning highly vascular corpus luteum was seen bulging onto the ovarian surface. SEM photomicrograph X35, X70.

Fig.3a&b: Light photomicrograph of a paraffin and semithin sections of the peripheral cortex of a doe at the 3rd day post-mating. The ovarian surface is covered by simple cuboidal epithelium (arrow). H&E and Toluidine blue stains, X 25

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Figs. 9: Light photomicrograph of semi thin sections of the CL of a doe at the 7th day showing large lutein cells loaded with abundant lipid droplets of different sizes. Three types of lipid droplets could be distinguished in their cytoplasm of the large lutein cells:

Fig.9a: Large clusters of very fine droplets in the whole cell.

Fig.9b: The lipid appears as moderate circular droplets of uniform size forming large aggregations in the cytoplasm.

Fig. 9c: Large patches of lipids occupying most of the cytoplasm. Toluidine blue stain, X 40 & X 100.

Fig.10: Light photomicrograph of a section of the CL of a doe at the 7th day. The lipid droplets in the peripheral cytoplasm of the CL were more intensely stained with osmium tetroxide than those in the interior region. Osmium tetroxide stain, X100

Mid-pregnancy:

Fig.11: Light photomicrograph of a section of the CL of a doe at the 14th day. The CL is well- developed and is formed of a large highly vascularized cellular mass H&E stain, X10

Fig.12: Light photomicrograph of a section of the CL of a doe at the 14th day. The lutein cells are increased in size and become loaded with abundant lipid droplets Osmium tetroxide stain, X40

Fig.13: Light photomicrograph of a section of the CL of a doe at the 14th day showing more marked capillary spaces between the lutein cells than before. The nuclei of the vascular endothelium appear flattened and vesicular. H&E stain, X100

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Late-pregnancy

Fig.16: Light photomicrograph of a section of the CL of a doe at day 21st. Many lutein cells are characterized by a decrease in size with uniform lipid droplets. Osmium tetroxide stain, X100.

Fig.17: Light photomicrograph of a section of the CL of a doe at day 21st manifesting regressing lutein cells with irregular nuclear membrane. The cytoplasm is condensed and shows vacuoles. H&E stain, X100

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Fig.24: Light photomicrograph of a section of the CL of a doe at day 28th showing relatively abundant fine osmiophilic lipid droplet in the cytoplasm of the regressed lutein cells. Some droplets are coalesced to form large droplets or vacuoles. Osmium tetroxide stain, X100

الملخص العربي

دراسة ميكرومورفولوجية للجسم الأصفر فى الأرانب أثناء فترة الحمل

مختار موسي ، محمد السخاوي، عبد العليم السبع ، عبدالسلام التونى

تمت دراسة الخصائص الميكرومورفولوجية لنمو وتراجع الجسم الأصفر في الأرانب بواسطة المجهر الضوئي والمجهر الإلكتروني الماسح خلال فترة الحمل. ولقد وجد أن الجسم الأصفر يزداد تدريجيا في القطر، ويبلغ الحجم الأقصى في منتصف فترة الحمل (اليوم 14 من التزاوج) . ثم يبدأ حجمه فى النقصان بشكل طفيف في اتجاه نهاية الحمل. ويرافق هذه الزيادة والنقصان في حجم الجسم الأصفر زيادة ونقصان في حجم الخلايا اللوتينة المكونة له. ولقد لوحظ أنه في مراحل الحمل الأخيرة تختفي المحفظة الليفية التى تفصل الجسم الأصفر عن الخلايا الغدية الخلالية مما يؤدى إلى اختلاط خلايا الجسم الأصفر بهذه الخلايا الغدية في المراحل الاحقة من تراجع الجسم الأصفر. أيضا خلال التراجع الهيكلي انخفض متوسط عدد الخلايا اللوتينة بشكل ملحوظ بينما ارتفع متوسط عدد الخلايا الغدية الخلالية بشكل كبير . لم تظهر الخلايا البلعمية الكبيرة وغيرها من خلايا النسيج الضام خلال فترة تراجع الجسم مشيرا إلى أن هذه الخلايا في الأرانب، على عكس الأنواع الأخرى، قد لا تلعب دورا هاما في إنحلال الجسم الأصفر.