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CORRELATION BETWEEN ABNORMAL OVARIAN STRUCTURES AND UTERINE HISTOPATHOLOGICAL ALTERATIONS IN SHE-DONKEYS

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ABSTRACT

In this study, which extended from May 2014 to December 2015, histopathologic techniques made on both ovaries and uteri of 83 slaughtered she-donkeys. Histopathologically, variable ovarian abnormalities were recorded including follicular cyst, paraovarian cyst, granulosa cell tumor, cavernous hemangioma, oophoritis and ovarian hematoma. In correlation to these abnormalities, the uterine examination revealed variable degrees and types of pathological alterations; some of which were relied on these ovarian abnormalities and others were not.

Keywords: *Ovarian pathology, uterine changes, equine, she-donkeys.*

INTRODUCTION

Equine ovaries are unique in their structure and functions. Ovarian pathological structures may interfere with the normal cyclic activity in mares leading to reduced fertility or even infertility **(Evans et al., 1997)**.

Pathological conditions of the ovaries may be found in the equine species may be classified into: pathophysiological disturbances, circulatory disturbances, ovarian neoplasia and chromosomal abnormalities. Pathophysiological disturbances may include some conditions as, cystic ovaries, persistent corpus luteum, anovulatory follicles, age related dysfunction, equine Cushing's syndrome, ovarian enlargement during pregnancy and exogenous hormone treatment. However, ovarian neoplasia in mare included one of the most common neoplasms that occurred in equine females, granulosa cell tumor (GCT). Granulosa-theca cell tumor, cystadenoma; teratoma and dysgerminoma may be included with lower incidence than GCT. The relationship between the presence of abnormal ovarian structures and the uterine histopathological changes was studied **(McCue et al., 1998)**. The aim of this study was to investigate the pathological ovarian abnormalities and their correlation with uterine changes in she-donkeys.

MATERIALS AND METHODS

This study was carried out on 83 she-donkeys from May 2014 to December 2015 (including slaughtered she-donkeys at Giza

Zoo and necropsied she-donkeys at Hospital of Veterinary medicine, Mansoura University). Ages of she- donkeys were also recorded. After gross examination of ovarian and uterine tissues, tissue specimens were taken from both ovaries and uterine horns then fixed in buffered neutral formalin (10%). Formalin fixed specimens were processed for H&E staining according to **Bancroft and Gamble (2007).**

RESULTS

The histopathological examination of 83 she-donkeys' ovaries revealed that 34 animals showed pathological structures (40.96%) collectively including follicular cysts, paraovarian cysts, cavernous hemangioma, granulosa cell tumors, ovarian endometriosis, ovarian hematoma, haemosidrosis and oophoritis. Pathological alterations were recorded only in 28 of their corresponding uteri (33.73%). Number, percentage and ages of different cases and relationship between ovarian abnormalities and uterine histopathological changes were summarized in (**Table 1**).

Follicular cysts

It was observed in 14 cases out of 34 (16.87%). Macroscopically their sizes vary from one case to another, as in some cases they may reach 6 cm. Most of them have thin semitransparent well vascularized walls but also others may have white fibrous walls, most of them are spherical and bulging from the ovarian surface. The thin walled cysts contained watery straw yellow colored follicular fluid while other thick walled cysts contained more viscous yellow to brown fluid. Microscopically, the cysts were classified into active and inactive. Cumulus oophorus and ova were not found in all of these cysts. Active cyst was lined with several layers of granulosa cell layers. Inactive cysts were seen in most cases in which the granulosa cells are compressed and flattened. It became difficult to differentiate between theca interna and externa beside most cysts surrounded with thick theca layers with variable degrees of fibrosis and edema. The cyst lumen may contain homogenous, structureless and eosinophilic material. These cysts appeared in some cases as multiple cystic spaces some of which had no granulosa cells **(Fig. 1 a-d)**. In one ovary, follicular cyst was associated with chronic non-suppurative oophoritis which characterized by the presence of lymphocytes, macrophages and few plasma cells, and another one was associated with haemosidrosis in some areas.

The corresponding 14 uteri microscopically showed normal histology in two uteri (14.28%), acute pathological changes in two uteri (14.28%) and chronic pathological changes in ten uteri (71.42%). Two cases with acute pathological changes revealed endometritis in one case characterized by infiltration of polymorphnuclears (PMNs) and prominent edema in lamina propria. In the other case, metritis appeared in the form of inflammatory cells aggregation in whole uterine wall including numerous PMNs, lymphocytes and eosinophils **(Fig. 2a)**. Cases with chronic pathological changes demonstrated mild to severe infiltration of the endometrial stroma with leukocytes (lymphocytes, plasma cells, macrophages and eosinophils), fibrotic nests with variable degrees of fibrosis, cystic dilated endometrial glands **(Fig. 2b)** and lymphangiectasis.

2- Paraovarian cysts

It was observed in one case (1.2%) Macroscopically, the cyst was oval, fluctuating having thin transparent wall, contained clear brownish brown serous fluid and found

attached to the ovarian surface. Microscopically, the cyst was lined by layer of cuboidal epithelial cells and surrounded with layer of fibrous connective tissue. The histopathological examination of corresponding uterus revealed a case of severe endometrial gland degeneration **(Fig. 3 a-c)**.

3- Cavernous hemangioma.

It was observed in 4 cases (4.82%). It was bilateral in one case and unilateral in the other 3 cases. Macroscopically, cavernous hemangioma was small, dark red and bulging from the ovarian surface. Microscopically, the tumor foci consisted of different sized-blood spaces and channels that lined by mature endothelial cells and these spaces are separated by a variable amounts of connective tissue, and one case was associated with inflammatory reaction in which lymphocytes and macrophages were seen. The histopathological examination of corresponding uteri revealed normal histology in one uterus (25%), acute pathological changes in the other 3 uteri (75%) characterized by severe congestion, edema and PMN infiltration in the lamina propria **(Fig. 4 a-d)**.

4-Granulosa cell tumors (GCT)

This type of sex cord tumor was only demonstrated microscopically in five cases (4 of them were unilateral and one case was bilateral). Two patterns of granulosa cell tumors were detected in all cases; diffuse and micro-follicular. The diffuse pattern appeared as aggregates of granulosa cells within the theca externa, some of which appeared larger in size with prominent nuclei **(Fig. 5a)**. The micro-follicular pattern had small eosinophilic Call-Exner bodies surrounded by granulosa cells in the form of rosette **(Fig. 5 b&c)**. In the unilateral types, contralateral ovary appeared functioning. The uteri of these cases had cystic dilated endometrial glands, congestion of blood vessels and sub-epithelial edema.

5-Ovarian Endometriosis.

It was observed in 4 cases (4.82%). It was detected only microscopically that revealed parts of glandular tissue embedded in the ovarian stroma **(Fig. 6 a&b)**.

The histopathological examination of corresponding uteri revealed endometrial glands degeneration in one case (25%), chronic pathological changes in three cases (75%) accompanied with metritis in one case of them. The chronic changes included chronic polypoid endometritis at which the surface epithelium thrown into the lumen forming finger like projections **(Fig. 6c)**.

6- Haemosidrosis.

It was observed in 8 cases (9.64%). This pathological condition was associated with many other major abnormalities as in case of cavernous hemangioma. It was detected only by microscopical examination that revealed hemosidrin golden yellow pigment either free or trapped inside macrophages “sidrophages” **(Fig. 7a)**.

The histopathological examination of corresponding uteri revealed normal histology in three uteri (37.5%), acute changes in one uterus (12.5%), endometrial gland degeneration in one uterus (12.5%), and the chronic changes in the other three cases (37.5%).

7-Ovarian hematoma

It was observed in one case (1.2%). Macroscopically, it was unilateral and appeared as blood tinged area on the ovarian surface**.** Microscopically it appeared as extravastaion of

RBCs from blood vessels **(Fig. 7 b&c)** with destructed blood vessels. The histopathological examination of corresponding uterus revealed normal uterus.

8-Oophoritis

It was observed in 5 cases (6.02%). It was recorded microscopic only and all cases were unilateral. Three of five cases were associated with other pathological conditions; one case was associated with cavernous hemangioma and the other two cases were associated with follicular cysts. Microscopically, "chronic non-suppurative oophoritis" was seen in two cases manifested by infiltration of lymphocytes, macrophages and few plasma cells. In the other two cases, PMNs were detected with edema in the ovarian stroma. Meanwhile in the last case many eosinophils were seen **(Fig. 8 a-c)**. The histopathological examination of corresponding uteri revealed two normal uteri (40%), and three cases revealed chronic pathological changes (60%).

Table 1: Number, percentage, age range of the cases and relationship between ovarian abnormalities and uterine histopathological changes

Ovarian structures	No. of cases	%	Age range	No. of cases with uterine lesions	%	Nature of uterine lesions
Ovaries with Pathological structures	34	40.96%		28	33.73%	
1. Follicular cysts	14	16.87%	3- 33	12	14.46%	- acute changes (2 cases) -chronic changes (9 cases) -degeneration of endometrial glands (1 case)
2. Paraovarian cysts	1	1.20%	16	1	1.20%	-degeneration of endometrial glands (1 case)
3. Cavernous hemangioma	4	4.82%	4- 32	3	3.61%	-acute changes (3 cases)
4. Granulosa cell tumor	5	6.02%	5-27	5	6.02%	- chronic changes (5 cases)
5. Ovarian Endometriosis	4	4.82%	16- 26	4	4.82%	-chronic changes, one with metritis and another with chronic polypoid endometritis (3 cases) -degeneration of endometrial glands (1 case)
6. Haemosidrosis	8	9.64%	3- 27	5	6.02%	- acute changes (1 case) -chronic changes (3 cases) -degeneration of endometrial glands (1 case)
7. Ovarian hematoma	1	1.20%	12	-	0%	-
8. Oophoritis	5	6.02%	3- 20	3	3.61%	- chronic changes (3 cases)

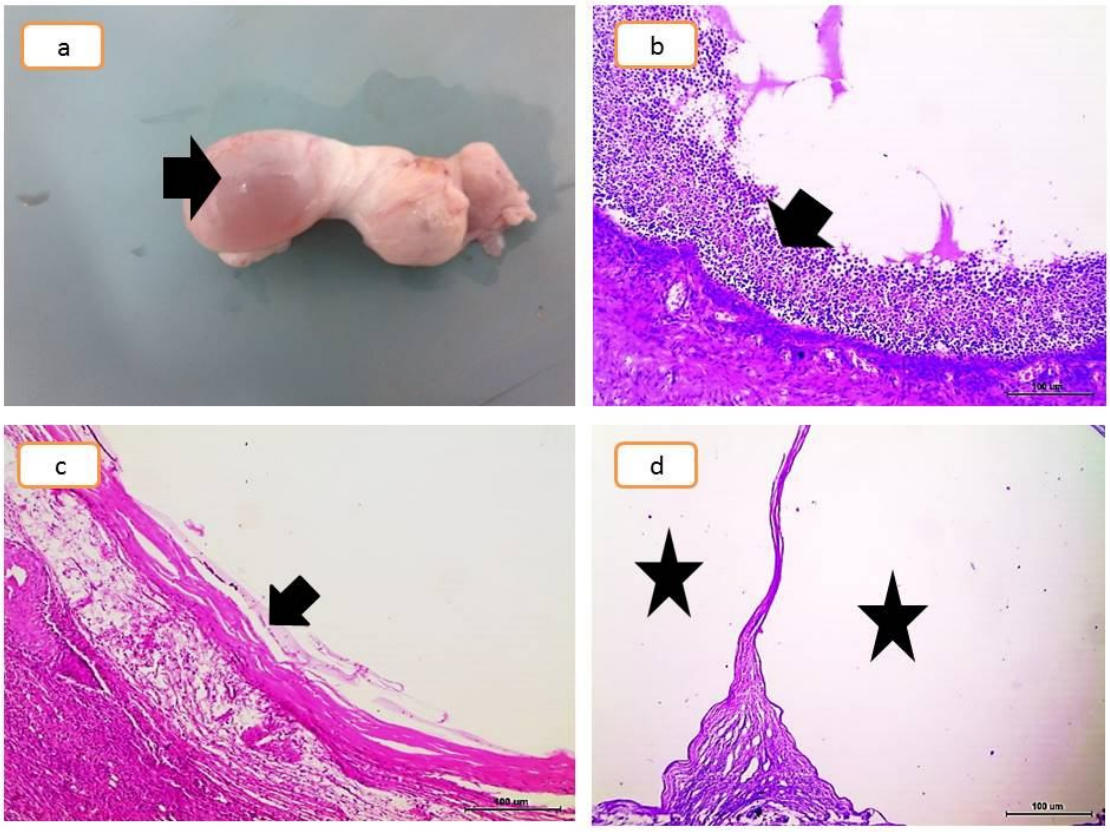

Fig. 1(a-d): Gross picture of ovary (9 years old) shows bulging cyst (arrow) **(a)**. Microscopic picture of ovary shows wall of active follicular cyst, note that granulosa cells arranged in many layers (arrow) **(b),** fibrous wall of follicular cyst (arrow) surrounded by edematous stroma, **(c)** and fibrous wall of two inactive follicular cysts (asterisks) **(d)**, H&E.

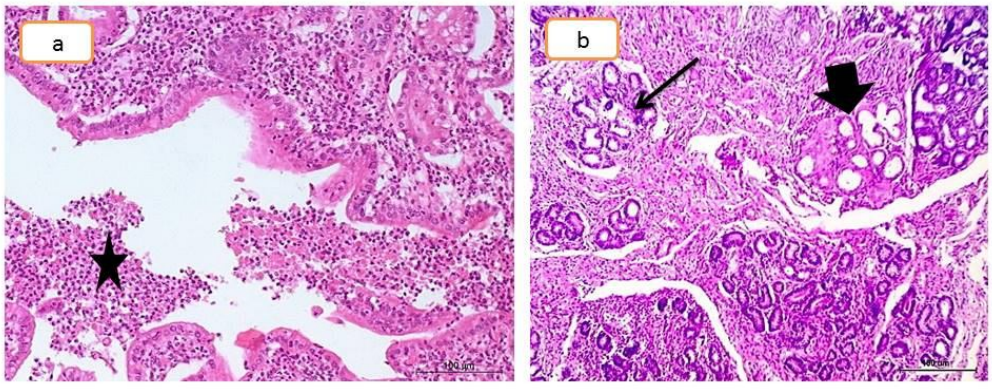

Fig. 2(a&b): Microscopic picture of left uterine horn (4 years old) shows presence of inflammatory cells in uterine lumen including numerous PMNs, few lymphocytes and eosinophils (asterisk) **(a).** Microscopic picture of right uterine horn (19 years old) shows fibrotic nests due to peri-glandular fibrosis (thin arrow) and cystic dilation of some glands (thick arrow) **(b)**, H&E.

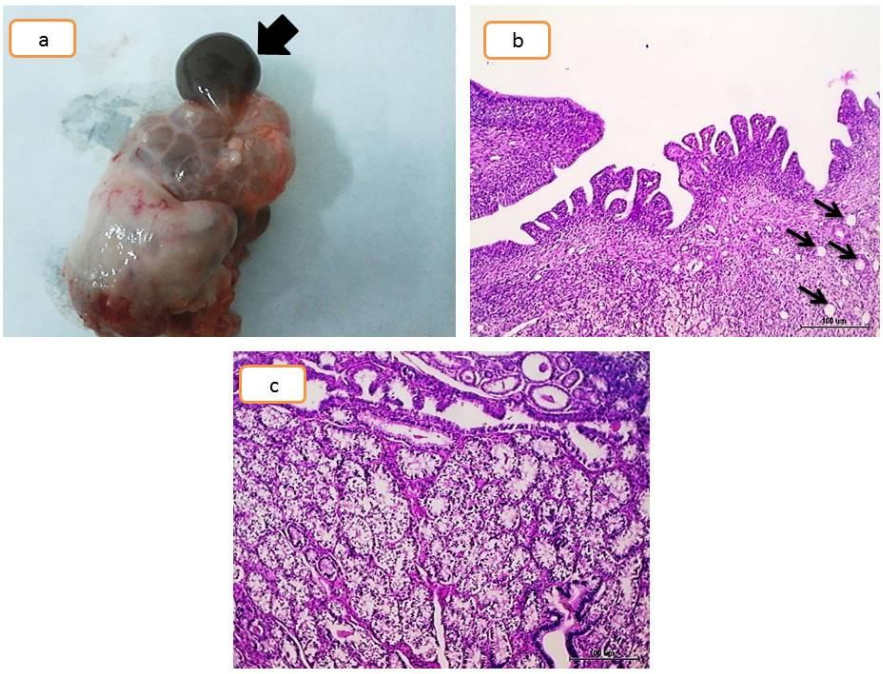

Fig. 3(a-c): Gross picture of left ovary (16 years old) showing cyst protruding from ovary surface contains brownish fluid (arrow) **(a)**. Microscopic picture shows wall of paraovarian cyst surrounded by numerous primordial follicles (thin arrows) **(b)**. Microscopic picture of left uterine horn shows degenerated endometrial glands **(c)**, H&E.

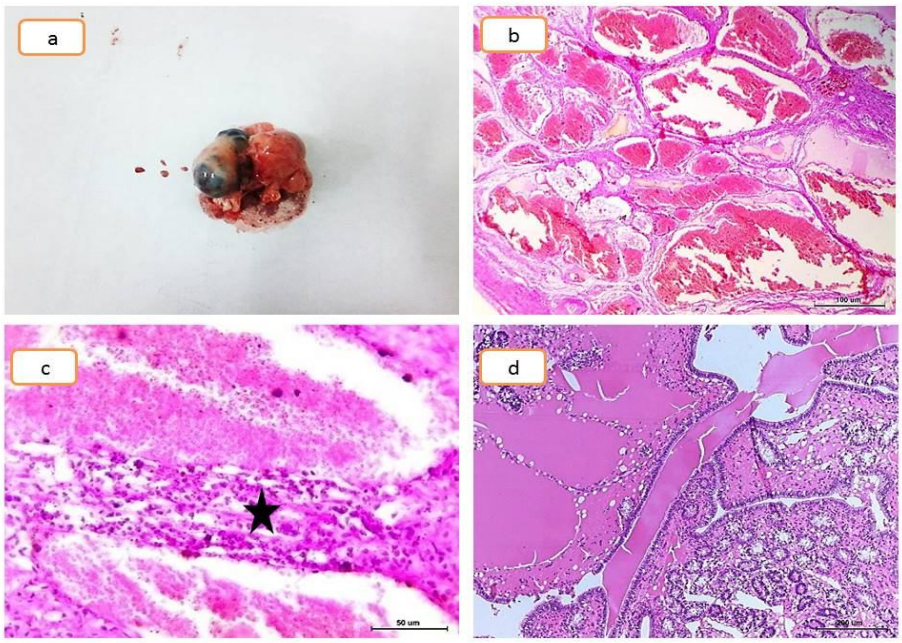

Fig. 4 (a-d): Gross picture of left ovary (11 years old) showing bulging on ovarian surface **(a)**. Microscopic picture shows cavernous hemangioma characterized by cavernous blood spaces lined by endothelium and filled with blood **(b)**. Leukocytic infiltration is seen between blood spaces (mainly lymphocytes and macrophages) **(c).** Microscopic picture of left uterine horn shows marked edema **(d)**, H&E.

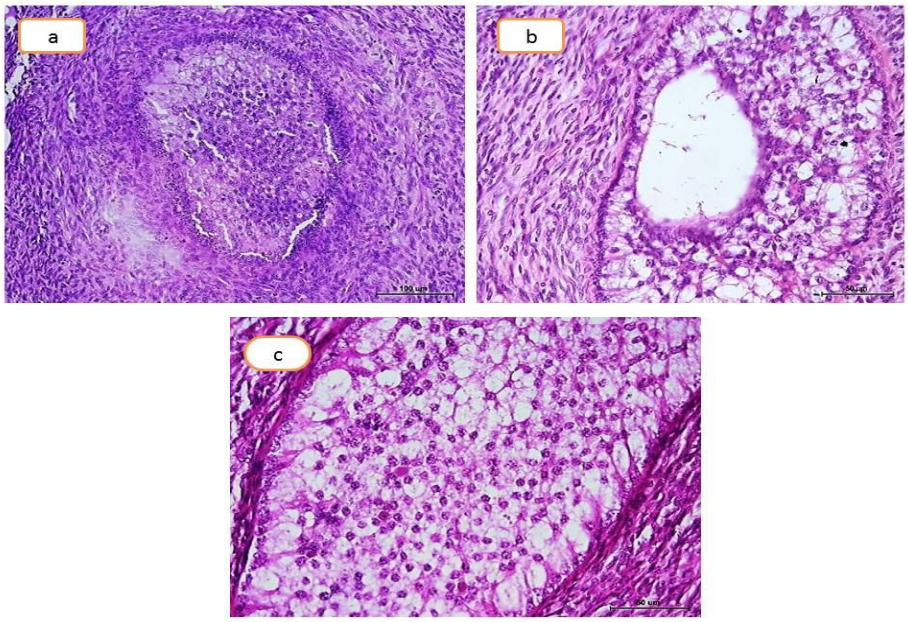

Fig. 5 (a-c): Microscopic picture of right ovary (14 years old) shows aggregates of granulosa cells within the theca externa, some of which appeared larger in size with prominent nuclei, H&E **(a)**. Microscopic picture of right ovary (22 years old) shows small eosinophilic Call-Exner bodies surrounded by granulosa cells in the form of rosette, H&E **(b)**. Microscopic picture of left ovary (17 years old) shows small eosinophilic Call-Exner bodies surrounded by granulosa cells in the form of rosette, H&E **(c)**.

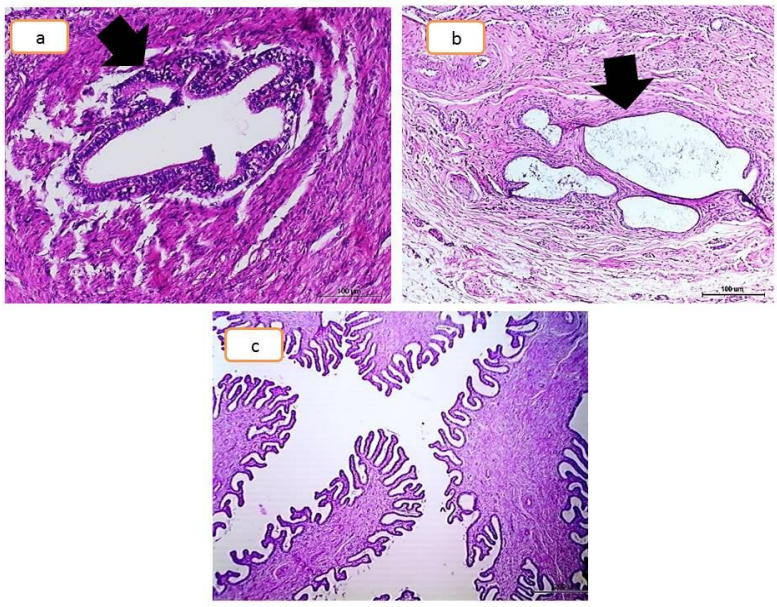

Fig. 6 (a-c): (a) Microscopic picture of left ovary (26 years old) shows glandular tissue in ovarian stroma (ovarian endometriosis) (arrow). **(b)** Microscopic picture of left ovary (23 years old) shows ovarian endometriosis characterized by presence of glandular tissue in the ovarian stroma (arrow). **(c)** Microscopic picture of uterine horn (23 years old) reveals chronic polypoid endometritis characterized by finger like projections of surface epithelium, H&E.

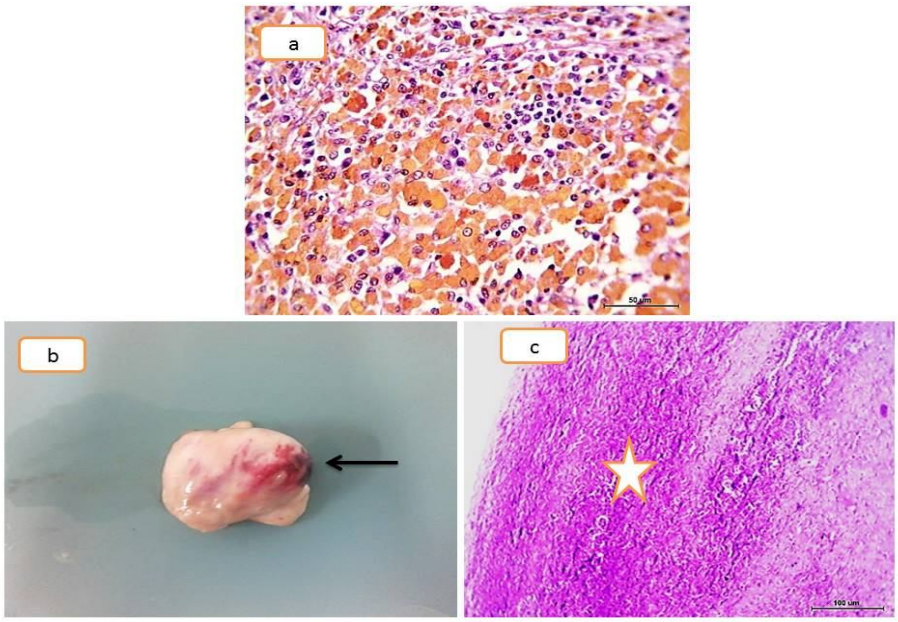

Fig. 7 (a-c): Microscopic picture of left ovary (21 years old) shows golden yellow hemosiderin pigment either free or trapped inside macrophages **(a)**. Gross picture of the left ovary (12 years old) shows bloody tinged ovarian surface (arrow) **(b)**. Microscopic picture shows collection of extravasted RBCs (asterisk) **(c)**, H&E.

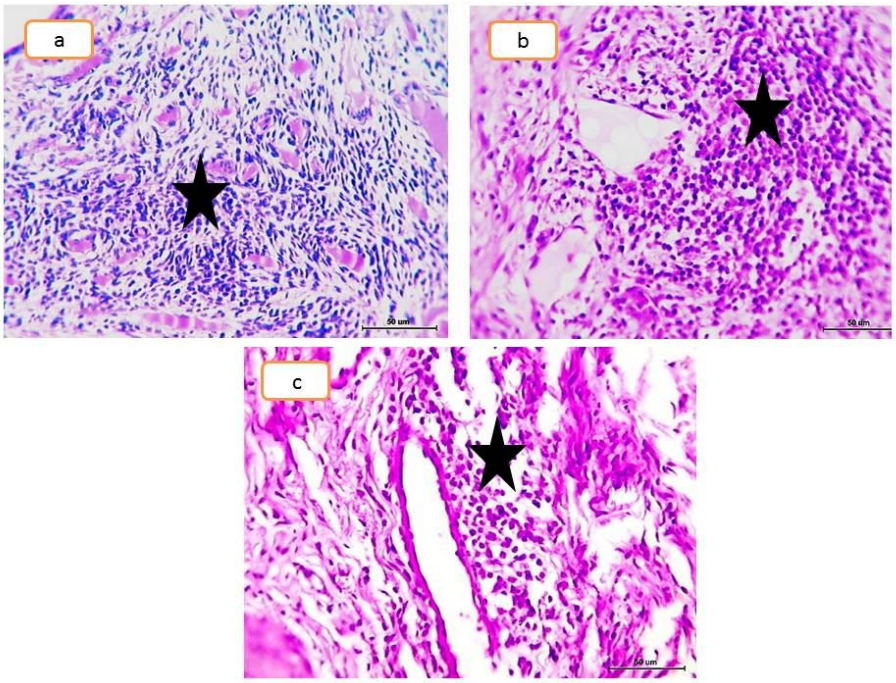

Fig. 8 (a-c): Microscopic picture of left ovary (20 years old) shows lymphocytes and macrophages aggregation in ovarian stroma **(a)**. Microscopic picture of left ovary (13 years old) shows focal PMN aggregation **(b).** Microscopic picture of right ovary (4 years old) shows perivascular edema and eosinophils infiltration **(c)**, H&E.

DISCUSSION

Histopathological examination of follicular cysts revealed loss of the cumulus oophorus and ova. The granulosa cell layer varies among these cysts, either compressed or completely absent. The basement membrane was usually absent. The continuous distention of the cyst may be the cause of absence of basement membrane and the gradual destruction and disappearance of the granulosa cells; this comes in harmony with that stated by **Mckenzie and Kenney (1973)**.

According to **McEntee (1985)**, paraovarian cyst may arise from persistent embryonal structures which are vestiges of wollfian ducts as in other animals. It doesn`t cause blockage of the lumen of the oviduct or interfere with reproductive performance of the animal **(Alam, 1984)**.

Cavernous hemangioma composed of vascular channels lined by mature endothelial cells. Similar lesions were recorded by **Carlton and MacGavin (1995)** who considered ovarian hemangioma as vascular hamartomas.

GCT arises from specialized stroma of the ovary and considered as sex cord stroma tumors **(Hinrichs et al., 1990; Jones at al., 1997)**. **McCue et al., (1998)** suggested that GCTs account for more than 85% of tumors of reproductive tract in equine, and it`s about 2.5% of all neoplasms in these species.

Ovarian endometriosis may be the result of either inversion and progressive invagination of the ovarian cortex after adhesion to the pelvic peritoneum caused by local implantation of endometrium regurgitated through the tubes **(Brosens et al., 1994)** or metaplasia of the coelomic epithelium covering the ovary **(Nisolle et al., 1997).**

Haemosidrosis usually associated with other major condition. **Abdel-Rahman (2000)** mentioned that haemosidrosis detected by presence of hemosidrin golden yellow pigment either free or trapped inside macrophage (sidrophages).

Ovarian hematoma or hematocysts are believed to arise from excessive hemorrhage into the follicular cavity following ovulation. They may reach sizes of 10 cm in diameter and persist for several days to weeks; they usually regress by the next ovulation without any effect on the length of the cycle **(Hughes et al., 1980).**

Oophoritis defined as inflammation of the ovarian tissue. According to **Jones et al. (1997)** oophoritis may be due to direct extension or hematogenous spread of infection.

According to **Rickets and Alonso (1991),** the endometria of mare are classified into 4 grades (I, IIa, IIb and III), where grade I concerned with normal endometria or with mild inflammatory reaction, grade IIa concerned with acute inflammatory reaction, while both grade IIb and III are concerned with chronic inflammatory reactions but with variable degrees as grade III endometria showed more severe chronic infiltrative reaction and chronic degenerative reactions.

CONCLUSION

The uterine changes are greatly affected by ovarian structures especially those secreting hormones (estrogen and/or progesterone). Uterine reaction to pathological structures on the ovary differ according to the secreting nature of these structures, e.g., some structures

as GCT and active follicular cysts were found related to severe degenerative changes in the corresponding uteri.

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الملخص العربي

التراكيب المرضية الموجودة علي المبيض وعلاقتها بالتغيرات الباثولوجية في أرحام إناث الحمير

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لقد أصبح مجال التناسليات في الخيول ذات أهمية اقتصادية كبيرة، حيث تمت في الاونة الاخيرة أبحاث عدة للمساهمة في تحسين هذا المجال، وستكون هذه الدراسة واحدة من هذه المساهمات في هذا المجال، والهدف من هذه الدراسة هو تحديد العلاقة بين تركيب المبيض والتغييرات الباثولوجية في ارحام الفصيلة الخيلية .

هذه الدراسة قد اجريت علي ٨٣ من انثي الحميرالمذبوحة لاغراض مختلفة، بدأت تلك الدراسة من مايو ٢٠١٤ إلى ديسمبر ٢٠١٥، وقد تم جمع العينات من حديقة حيوان الجيزة ومستشفى الطب البيطري، جامعة المنصورة، تم تجميع كلا المبيضين الايمن والايسر وارحام هذه الذبائح وتمت دراستها عن طريق الفحص الهستوباثولوجي.

وكشف الفحص الهستوباثولوجي أن ٣٣ حالة من هذه الحالات تحتوي علي تراكيب طبيعية من الجريبات علي المبايض (٣٩,٧٦ ٪) مع ٢١ رحم من هذه الحالات تحتوي علي تغييرات باثولوجية (٢٥,٣٠٪)، وايضا ١٦ حالة سجل فيها وجود الجسم الأصفر (١٩,٢٨ ٪) مع ١٢ رحم مقابل به جتغييرات باثولوجية (١٤,٤٦٪)، و ٣٤ حالات وجود حالات باثولوجية علي المبايض (٤٠,٩٦٪) مع وجود ٢٨ رحم مقابل به ايضا تغييرات باثولوجية (٣٣,٧٣٪).

ووفقا لنتائج هذه الدراسة، تم اثبات ان حالة المبايض والتغيرات المرضية داخل الارحام المقابلة ترتبط أساسا بالهرمونات التي تفرزها التركيبات الموجودة علي المبيض سواء كانت طبيعية او مرضية وتغييرات الرحم لا ترتبط بالاساس إلى طبيعة النسيج لهذه التركيبات.