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Histological and Ultrastructural Studies on the Effect Amoxicillin on the Stomach of Mouse Fetuses

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ABSTRACT

Introduction: B-Lactam antibiotics are widely used because of their lack of toxicity in humans. However, during pregnancy, exposure of the fetus is likely to occur due to b-lactam antibiotics cross the placenta. The potential adverse effects of amoxicillin were examined in stomach of mice fetuses.

Material and Methods: This study was aimed to evaluate the possible side effects produced by amoxicillin prenatal administration on the stomach of fetuses.

Twenty pregnant mice were used in this study; and were divided into two groups: the first group served as a control group and injected by saline solution (the drug solvent); the second group treated with amoxicillin dose of 205 mg/kg body weight. The treatment was daily administered interperitoneally, from the 7th day of gestation till the 14th day of gestation (GDs 7-14). The developing 19-days old fetuses were examined histologically and ultrastructurally to determine any disorders in the stomach.

Results: This study illustrated marked deleterious consequences in the gastric wall of 19 day old fetus, following the treatment with amoxicillin, ranging from marked vacuolations and erosions in the epithelial and glandular cells of the gastric mucosa to conspicuous necrosis of glandular (parietal and zymogenic) cells. The electron microscopical examination of the gastric mucosal cells of fetuses maternally treated with amoxicillin, revealed conspicuous alterations, in the cytoplasmic organelles of gastric mucosal cells (surface epithelial, peptic and parietal cells). The cisternae of RER were dilated and fragmented. The mitochondria displayed gradual devastations.

Conclusions: Therefore, the destructive impacts of amoxicillin on the stomach of mice fetuses indicated that it should be used under restricted precautions in the medical fields to protect the pregnant women from its hazardous impact.

Keywords: Amoxicillin, Stomach, Histology, Ultrastructure, Mice fetuses.

INTRODUCTION

B-Lactams are the widely spread group of antibiotics used for the treatment of many cases because of their low toxicity which has been reported in the adult (1,2). They also, are prescribed during pregnancy because of their safety and the absence of known fetal toxicity (2,3). B-lactam antibiotics cross the human placenta and so that fetuses exposed to these drugs (4,5). However these drugs are not teratogenic, the absolute lack of toxicity of b-lactam antibiotics to the fetuses remains to be determined. The period of organogenesis, is considered the greatest concern because of any adverse effect of these drugs on developing tissue may impair its formation (6). Thus, the present work was constructed to assess and evaluate the possible toxic effects induced by treatment with one of these B-lactam antibiotics on stomach of fetuses maternally treated during the period of organogenesis. However, none of these drugs has been classified in the class A of Food and Drug Administration fetal risk drug categories, therefore indicating that their absolute lack of developmental toxicity has not been demonstrated [7,8,9]. Hemorrhagic colitis is a rare but well-recognized complication with ampicillin or penicillin derivative treatment [10] . Also, the author reported a patient who developed colitis after amoxycillin therapy in whom 111Indium leucocyte scan demonstrated right-sided colitis. **Blanchi and Pariente** [11] recorded acute hemorrhagic colitis after ingestion of amoxicillin. Even if it is not teratogenic, amoxicillin may induce histological and ultrastructural disturbance during organ formation. **Yun *et al.*** [12] in their study on the effects of amoxicillin treatment of piglets on the prevalence of hernias and abscesses, growth and ampicillin resistance of intestinal coliform bacteria in wanted pigs reported that the amoxicillin treatment of new-born piglets produced statistically significant effect in some studied parameters. The authors added that these effects were only minor and they did not find grounds to recommended preventive

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antibiotic treatment. Further, continuous antimicrobial treatment of new-born piglets could negatively influence the development of normal microbiota of the piglets and promote selection of antimicrobial resistance genes in herds. Therefore they suggest rejection of the use of routine administration of anti-microbial agents at birth.

MATERIALS AND METHODS

Experimental animals

The present investigation was carried out on mature albino mice of pure CD-1 strain with an average body weight of 20-23g obtained from the breeding unit of Theodor Bilharz Research Institute (TBRI), Imbaba, Giza, A.R. Egypt. Females and males were housed separately in plastic cages, each cage contained two mice in order to avoid over crowding. Mice were fed on cubes consisting of crude proteins, minerals and fibres. Vitamins were added as fresh vegetables and the animals were provided with milk and tap water *ad libitum*. Pregnancy was achieved by housing one adult virgin female with one well marked fertile male overnight, from 5 pm until 9 am of the next day. Successful mating was indicated either by the presence of a vaginal plug or by the presence of spermatozoa in the vaginal smears according to the method suggested by **Snell, ([13])**. Females which give positive vaginal smears are considered pregnant and the day of detection was defined as the first day of pregnancy.

The drug used

The beta-lactam antibiotic drug used in the present investigation is amox . E mox is available in the form of vials, each containing 1000mg of the active ingredient. The dose of this drug for mice was calculated according to **Paget and Barnes** [(14)]. The chosen dose was nearly comparable to the human effective therapeutic dose (ETD). The dose of E mox used in the present study was 205 mg / kg. body weight and was estimated according to the weight of mouse and injected intraperitoneally (i.p.)

Experimental design

Twenty pregnant female mice were divided into two groups comprising 10 animals in each group. The first group is considered as the control group (A) and the second group (B) is the treated group and treatment of these groups was achieved in the following manner:-

Group (A): Each pregnant female was injected intraperitoneally with 0.1ml saline solution (the solvent of the drug) daily for 8 days during pregnancy from day 7 till day 14 of gestation (GDs 7-14).

Group (B): Each pregnant mouse was intraperitoneally injected with 205 mg/kg body weight of E mox daily for 8 days during pregnancy (GDs 7-14).

Pregnant mice of both control and experimental group were sacrificed on day 19 of pregnancy. They were dissected and their uteri were removed, placed in normal saline solution and the fetuses were taken out. For light microscopic examination small pieces of the stomach of fetuses of control and maternally treated animals were fixed for 24 hours in aqueous Bouin's fixative. The specimens were then dehydrated, cleared in terpineol and embedded in paraffin wax. Serial transverse sections of about 5 µm thickness were stained with haematoxylin and eosin, microscopically examined and photomicrographs were made as required.

For the electron microscopic studies, small pieces of the stomach were fixed in 2.5% glutaraldehyde for 4 hours and 2% paraformaldehyde in 0.1M cacodylate buffer (pH7.4).The samples were post-fixed in 2% buffered osmium tetroxide at 4C° for one hour. This was followed by dehydration in ascending series of ethyl alcohol for two changes, clearing in two changes of propylene oxide, 5 min each. Then, specimens were embedded in Epon-epoxy-resin. Semi-thin sections of 1µm thickness were stained with toluidine blue and examined, for general orientation under a bright field light microscope. Ultrathin sections were prepared, stained with uranyl acetate and lead citrat [(15)]. Sections were examined and photographed on a Joel 1200 EX 2 transmission electron microscope, at the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University.

RESULTS

Histological studies

I-The control group

The wall of the stomach of control mice fetus consist of four consecutive layers; serosa, muscularis, sub-mucosa and mucosa. The serosal

layer is formed of simple squamous epithelium. The muscularis is constructed of an outer thin layer of longitudinal muscle fibres and an inner layer of circular muscle fibres as seen in figure 1. The sub-mucosal layer consists of loose connective tissue fibres supported by fewer aggregations of small blood vessels and lymphoid cells and the connective tissue layer belonged to the mucosa called the lamina propria. The latter serves mainly to connect the sub-mucosa with the mascularis as well as with the tubular glands of the mucosal layer (Figs. 1&2).

The mucosal layer is formed of compound tubular glands with surface epithelial layer formed of columnar epithelial cells. This gastric mucosa consists of surface epithelial cells and glandular (zymogenic and parietal) cells. The surface epithelium containing separated simple gastric epithelial infolds which invaginate to varying extents into the lamina propria forming gastric pits (Figs. 1&2). The peptic cells are mainly located at the bases of the gastric glands, they are principally responsible for secretion of pepsinogen, and they have basophilic cytoplasm and basally situated spherical nuclei (not well distinguished by light microscope). The parietal cells (also, not well distinguished) are commonly known as the acid-forming cells, since they are the principal secretories of HCL in the stomach. They are moderately large in size and their cytoplasm is acidophilic. Each cell possesses a centrally placed spherical nucleus. It is worth to mention that, in the present investigation and at the light microscopic level, non of the epithelial cells showed complete glandular differentiation in the gastric epithelium of mice fetuses on day 19 of gestation.

II- Maternally treated group

More remarkable cellular injury was observed in the stomach of 19-day old fetuses maternally treated with 205 mg/kg body weight of amoxicillin. The surface epithelial cells showed noticeable vacuolar degeneration of their cytoplasm with conspicuous nuclear karyolysis. However, the cellular constituents (zymogenic and parietal cells) of the gastric mucosal layer manifested marked signs of swelling in some areas of the gastric glands and necrosis in other regions; they appeared with disrupted cellular membranes, damaged cytoplasm and their nuclei illustrated clear features of karyolysis as seen in figures 3-5.

The connective tissue of the supporting lamina propria near the mucosa was greatly damaged with conspicuous aggregations of inflammatory cells. The blood micro-vessels localized in these regions were damaged and thus signs of haemorrhage apparance were observed (Fig. 6).

Electron microscopical studies

I- The control group

The electron microscopical examination of the gastric mucosa of a control mouse fetus showed three distinct cell types, i.e., the surface epithelial cells, the zymogenic (peptic) cells and the parietal (oxyntic) cells.

The surface epithelial cells

The apices of surface epithelial (mucous) cells were often covered with many short microvilli (Fig. 7). The cytoplasm showed scant mitochondria that were ordinary present among the secretory granules at the cell apex but appeared randomly distributed elsewhere in the cytoplasm (Fig. 8). The nucleus was located towards the basal part of the cell and may be oval or elongated in shape, having double-layered nuclear envelope and the heterochromatin was mainly concentrated on the inner aspect of the nuclear envelope (Fig. 7). Secretory granules, which vary in size, shape and apparent density were generally clustered in the apical portion of the cell (Fig. 8).

The zymogenic cells:

The zymogenic cells of 19-day old control mouse fetus illustrated that the cytoplasmic part of these cells contained numerous rounded zymogenic granules, being either scattered all over the cytoplasm or aggregated towards the luminal part of the cell near their secretory surfaces (Fig. 9). Cisternae of the rough endoplasmic reticulum were loosely packed parallel stacks curved or concentric arrays of evenly spaced lamellae. They were localized near the nuclear envelope or scattered into the cytoplasm. Their bounding membranes were studded with numerous ribosomes. Golgi apparatus appeared as well developed cisternal spaces (Fig. 10). Mitochondria were also apparent in these cells being spherical or elongated in shape. The nuclei displayed distinct irregular nuclear envelope, with prominent centrally located nucleolus. Their nucleoplasm exhibited aggregations of euchromatin and

heterochromatin materials as illustrated in figure 10.

The parietal cells

The electron micrographs of the cytoplasm of parietal cells of 19-day old control mouse fetus contained numerous mitochondria, being ovoid or spherical in shape, with distinguished mitochondrial cristea or ridges which perpendicularly oriented along their membranes. They were hollow tubular in configuration as shown in figures 11 and 12. These mitochondria are dispersed all over the cytoplasm. Numerous intracellular canaliculi consisting of many elongated microvilli as well as some tubulovesicles being randomly scattered in the cytoplasm; they are considered as the sites of hydrochloric acid secretions. Very smaller cisternae of rough endoplasmic reticulum are seen occupying narrow areas of the cytoplasm. The nuclei of these cells showed distinct nuclear envelope, and their nucleoplasm contained aggregations of euchromatin as well as numerous heterochromatin (Figs.11& 12).

II- Maternally treated group

The surface epithelial cells

The surface epithelial (mucous) cells of maternally treated mice fetuses with 205 mg/kg. body weight of amoxicillin, appeared erosion of their microvilli. The secretory granules were inconspicuously lost and were not demarcated in the apical secretory parts of the surface epithelial cells (Fig.13). The bodies of rough endoplasmic reticulum were distinctly degranulated and fragmented into smaller stacks which lost their membrane configuration and the detached ribosomes were randomly scattered all over the cytoplasm which exhibited highly granulated appearance (Fig. 14). The mitochondria showed obvious lost of their internal ridges and matrices, with rupturing of their membranes; they contained tiny flocculent materials.

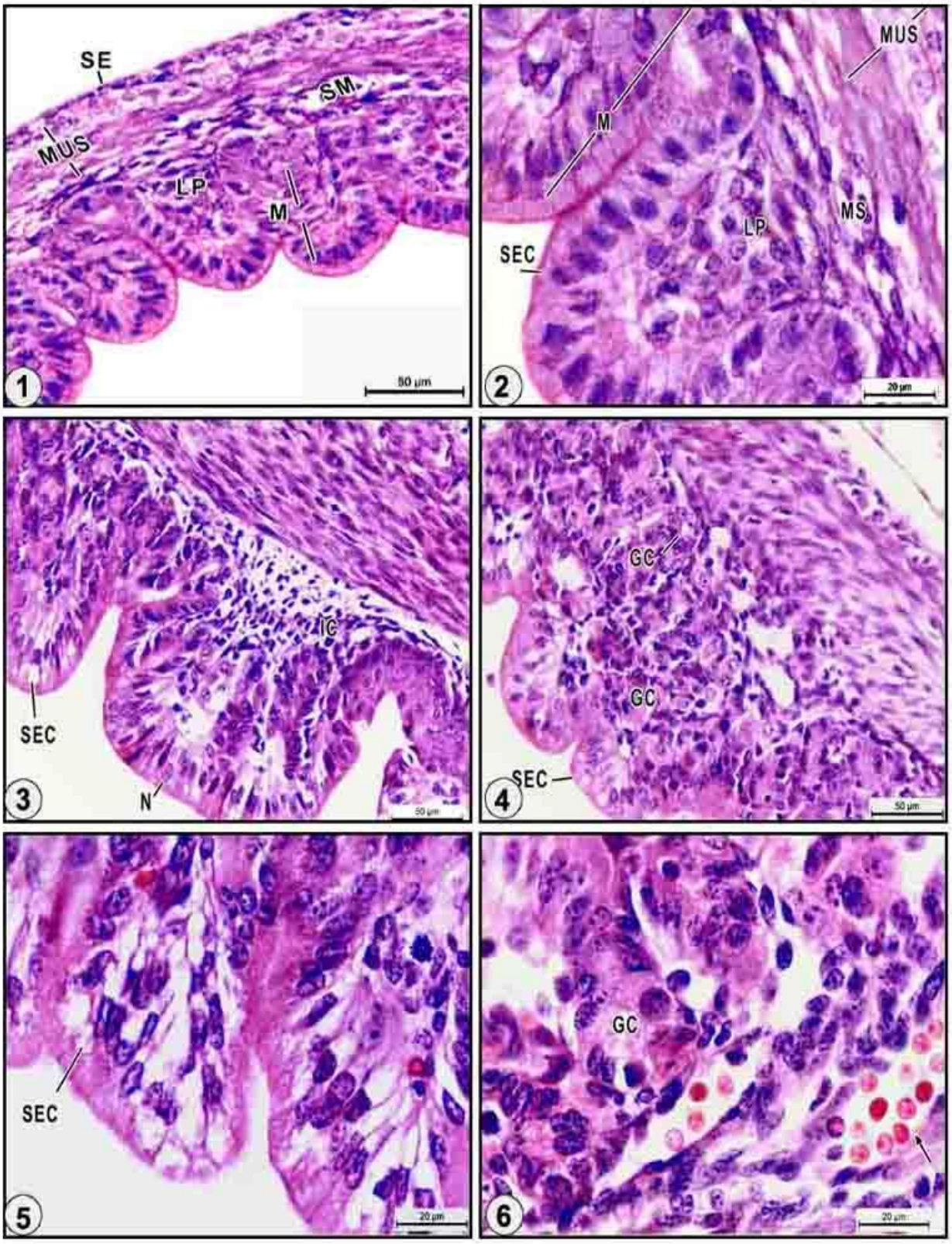
The nuclei of such devastated cells displayed obvious diminution of their chromatinic materials and also, appeared with irregular form (Fig.14).

The zymogenic cells

The zymogenic cells of the same treated group manifested symptoms of devastation as symptomized by diminution of their secretory zymogenic granules (Fig. 15). The cisternae of the rough endoplasmic reticulum were dilated and fragmented into smaller stacks, dissoluted and lost their parallel membrane configuration, besides their marked degranulation (Fig. 15). The mitochondria showed distinct feature of condensed matrices; they underwent swelling and some of them lost parts of their internal matrices (Fig. 15).

The parietal cells

Severe cellular devastations were observed in the parietal cells of 19- day old fetuses subjected to treatment with amoxicillin ; the parietal cells in such condition formed principally damage of their mitochondria which lost their regular configuration. Their internal ridges and matrices were obviously detached from the inner core of the mitochondria, (Fig. 16). The rough endoplasmic reticulum showed dilation and fragmentation of their cisternae as well as distinct loss of their attached ribosomes (Fig. 16). The intracellular canaliculi as well as the tubulovesicles were not demarcated or poorly developed due to the treatment in that period. However, figure 16 showed more or less aggregation of cytoplasmic tubulovesicles which referred to the beginning of the development or formation of the intracellular canaliculi.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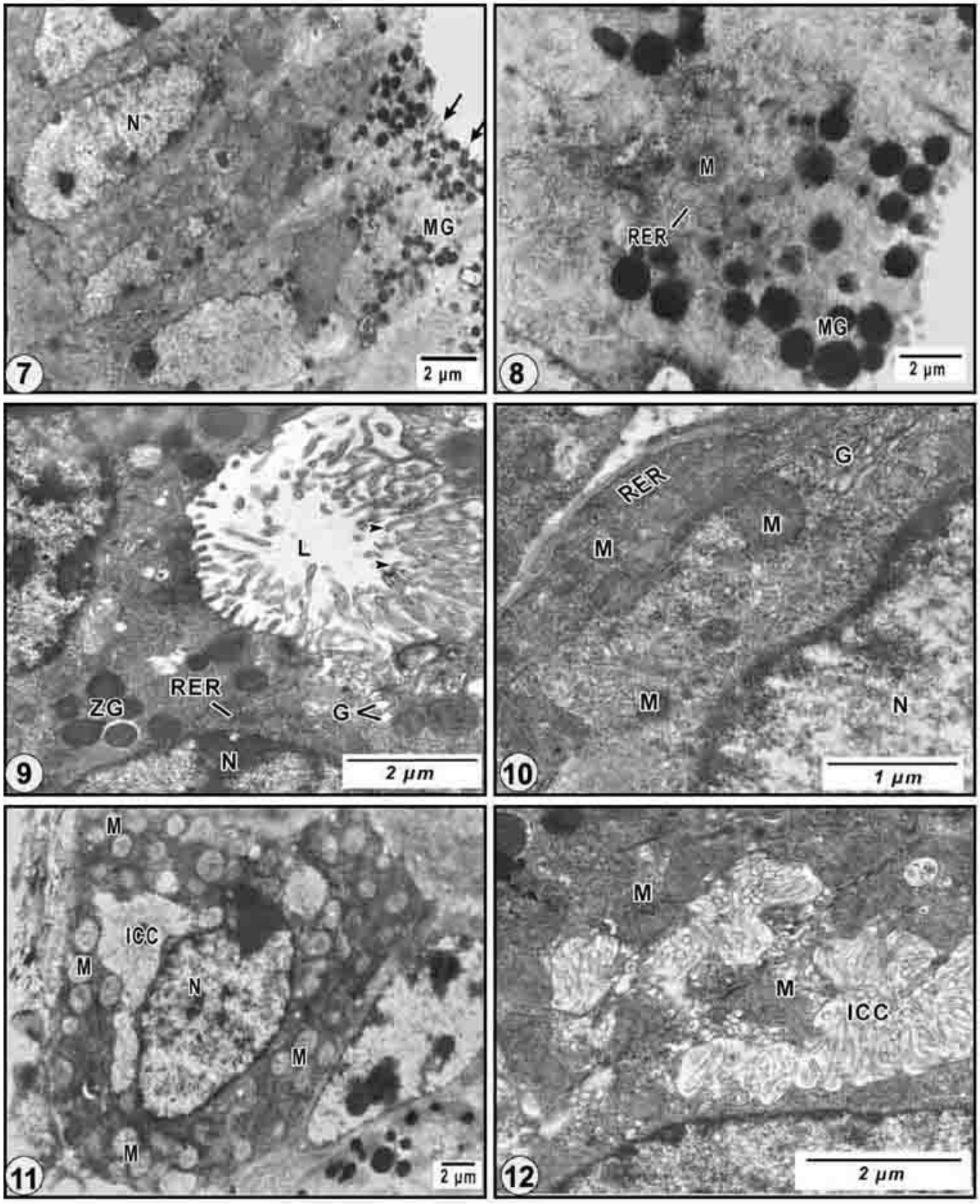
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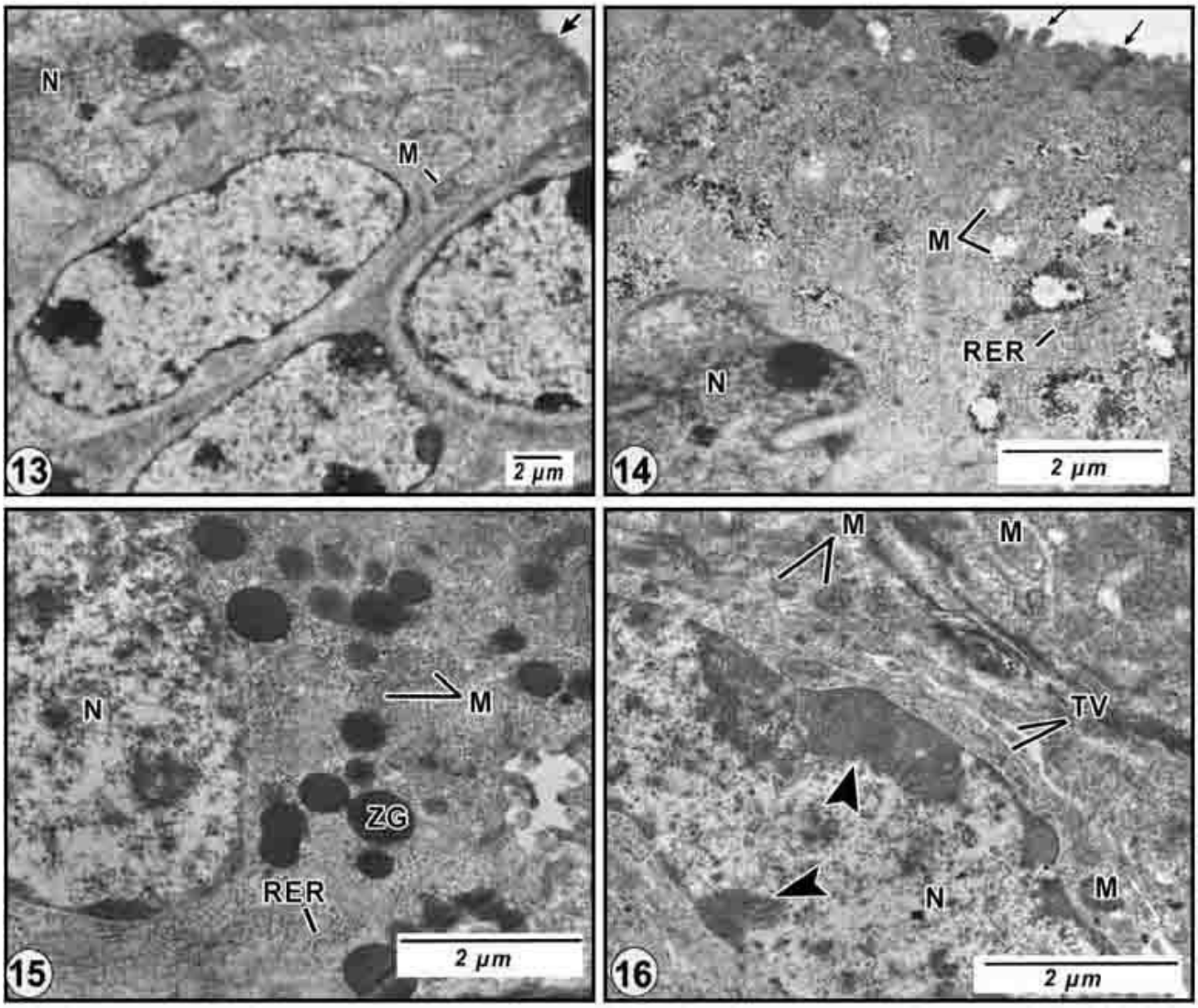

EXPLANATION OF FIGURES

Figures (1-2): Photomicrographs of a section of the stomach of 19-day old control mouse fetus.
Fig. 1: Illustrating that the wall of the stomach consists of serosa (SE), muscularis (MUS), the supporting lamina propria (LP), sub-mucosa (SM) and the mucosa (M) layers.
Fig. 2: Revealing the mucosal layer being formed of early developed tubular glands consisting of surface epithelial cells (SEC) of simple columnar type. The figure also illustrates the supporting lamina propria (LP), the sub-mucosa (SM) and the muscularis (MUS) layers.
Figs. 3-6: Photomicrographs of a section of the stomach of 19-day old fetus maternally treated with 205mg/kg body weight of amoxicillin,
Fig.3. Revealing vacuolar degeneration of the cytoplasm of the surface epithelial cells (SEC).The nuclei (N) of these cells exhibit signs of karyolysis. Focal collection of inflammatory cells (IC) are also observed.
Fig. 4. Illustrating coagulative necrosis of the surface epithelial cells (SEC) and glandular cells (GC).
Fig. 5. Showing vacuolar degeneration of the surface epithelial cells (SEC) and their nuclei exhibit karyolysis
Fig. 6. Manifests coagulative necrosis of glandular cells (GC). Extravasations of blood from the damaged capillaries of the sub-mucosal layer forming haemorrhagic appearance (arrow).
Fig. 7-12: Electron micrographs of the gastric mucosa of 19 day old control mouse fetus,

Fig.7. Showing surface epithelial cells with microvilli (arrows) projecting from their apical surfaces. The cytoplasm shows many electron dense mucous granules (MG) that aggregate at the apical secretory part of the cytoplasm. The nuclei (N) are located towards the basal part of these cells.

Fig. 8. Enlarged portion obtained from the previous figure showing, many spherical or oval mitochondria (M), cisternae of rough endoplasmic reticulum (RER) as well as many electron dense mucous granules (MG).

Fig. 9. Revealing several zymogenic cells arranged around their lumen (L); their apical secretory surfaces show extension of minute microvilli (arrow heads). Their cytoplasm displays cisternae of rough endoplasmic reticulum (RER),Golgi apparatus (G), aggregations of many electron dense secretory zymogen granules (ZG) in addition to centrally located oval nuclei (N)**.**

Fig. 10: Magnified part of azymogenic cell showing abundant rough endoplasmic reticulum (RER), mitochondria (M) and Golgi apparatus (G). The figure also displays well organized nucleus (N).

Fig. 11. An electron micrograph of a parietal cell obtained from the gastric mucosa of 19 day old control mouse fetus, showing large number of spherical mitochondria (M), bodies of intracellular canaliculi (ICC) and centrally located oval nucleus (N).

Fig. 12. High magnification of a parietal cell, illustrating mitochondria (M), bodies of intracellular canaliculi (ICC).

Figs 13-16. Electron micrographs of the gastric mucosal cells of fetuses maternally treated with 205mg/kg body weight of amoxicillin

Fig. 13: An electron micrograph of the surface epithelial cell, showing deteriorated mitochondria (M). The apical microvilli (arrow) show conspicuous erosion. The nucleus (N) shows deterioration of chromatin materials**.**

Fig.14: Enlarged portion obtained from the previous figure showing highly deteriorated mitochondria (M), fragmented rough endoplasmic reticulum (RER) The apical microvilli (arrow) show conspicuous erosion. The figure also explain irregular shaped nucleus (N).

Fig. 15. Revealing peptic cell with dilated cisternae of rough endoplasmic reticulum (RER). The mitochondria (M) are deteriorated with rather condensed matrices and demolished ridges. Also the zymogenic granules are appeared in this figure.

Fig. 16: Showing a parietal cell with devastated mitochondria (M) which lost their ridges and internal matrices and contain tiny flocculent materials besides few contents of tubulovesicles (TV)**.** The nucleus exhibits aggregation of heterochromation on the inner surface of nuclear envelope (arrow heads).

DISCUSSION

Histology and histopathology of the stomach

Kyzekova and Mour [16] in the eradication therapy with amoxicillin 1000 mg b.i.d., clarithromycine 500 mg b.i.d. recorded chronic inflammation, mucosal atrophy , intestinal metaplasia persisted and signs of chemical gastropathy with hemorrhages in the esophageal papillae. **Also, Beraldo *et al.*** [17] recorded that amoxicillin/clavulanate can cause adverse effects, mainly cutaneous, gastrointestinal, hepatic and hematologic, in some cases.

A sequence of changes in epithelial cell proliferation and migration in developing gastric mucosa has been described in several laboratory species . In most of these studies a similar pattern of development was proposed involving the presence of several cell types and the complexity of their anatomical arrangement especially during early postnatal life [18]. Rapid differentiation processes occur in the gastric mucosa during the last five days of gestation in rodents [19].

The mucosa of the fetal rat stomach matures strikingly during the perinatal period (the last days of gestation and the early days after birth). By day 20 of gestation the gastric epithelia are simple columnar and become invaginated to form early pits and glands . Immediately before birth, the pit / gland development has progressed further [20]. The authors added that, zymogen and parietal cells were not confidently identified before birth by light microscopy; they were easily identified at day 14 postnatally [20]. At birth, the gastric mucosa of newborn rat had developed and differentiated considerably with an increase in number and size of gastric glands [21]. A similar

study carried out on fetal and neonatal mouse stomach [21] showed that the parietal cells were distinguished in the stomach of newly born mice. On the other hand, the same authors added that, immune-fluorescence reactivity with parietal cell antibody (PCA) revealed that the earliest reaction of parietal cells with PCA was seen in the stomach of 19-day old fetuses. On the other hand , the results of **Pettitt *et al.*** [22] have shown that parietal cells were first recognizable ultrastructurally within the gastric glands of 19-day old mouse fetus.

The general findings in the present study in relation to development do not conflict with the main conclusions of the previously mentioned studies and the present observations regarding the stomach of fetuses of control mice did not differ radically from that of other studies. It is worth to mention that, in the present investigation and at the light microscopic level none of the epithelial cells showed complete glandular differentiation in the gastric epithelium of mice fetuses on day 19 of gestation. On the other hand and at the ultrastructural level, the electron microscopical examination of the gastric mucosa of control mouse fetus showed three distinct cell types, i.e., the surface epithelial cells, the zymogenic (peptic) cells and the parietal (oxyntic) cells.

Although amoxicillin is recommended for anthrax prevention in pregnancy **Andrew *et al.*** [23] suggested that amoxicillin concentrations adequate to prevent anthrax may be difficult to achieve during pregnancy and postpartum because amoxicillin effect reflect on kidneys by increasing infiltration and secretory transport or diminished reabsorption in the kidneys. Amoxicillin may not be an appropriate antibiotic for post-anthrax exposure prophylaxis.

Amoxicillin proved to have good penetration into the fetal tissues and placenta after intravenous administration since its concentration was highest in umbilical cord blood compared with amniotic fluid, maternal blood and placenta.

The present study illustrated marked deleterious consequences in the gastric wall of 19 day old fetus, following the treatment with 205 mg/kg body weight of amoxicillin, ranging from marked vacuolations and erosions in the epithelial and glandular cells of the gastric mucosa to conspicuous vacuolar degeneration of the cytoplasm of the surface epithelial cells and glandular (parietal and zymogenic) cells. Their nuclei exhibited features of pyknosis and karyolysis.

The present findings are in agreement with those reported by **Reyes-Garcial *et al.*** [24] and **Sabry** [25] who demonstrated gastric damage in the form of sloughing and erosion of the gastric wall of rats treated with diclofenac. In the same direction, **Choi *et al.*** [26] observed histopathological changes in the stomach of male rats treated with 400 mg/kg body weight of aspirin represented by predominant mucosal hyperemia and hemorrhagic lesions with oedema covering the total glandular area of the stomach. In addition to gastric mucosal damage with conspicuous dilation and exfoliation of the gastric epithelial cells and disruption of the mucosal layer are also observed. Also **Langner *et al.*** [27] in a study on three cases of acute segmental hemorrhagic antibiotic-associated colitis after treatment with oral ampicillin or amoxicillin, showed right-sided segmental hemorrhagic colitis and histopathological examination demonstrated edema, patchy superficial hemorrhage and a scattered predominantly mononuclear infiltrate of the lamina propria and the surface epithelium was partly desquamated and displayed foci of grouped intraepithelial red blood cells.

The sloughing and erosions observed (in the present study) in the superficial layer of the gastric mucosal cells (surface epithelial cells) and necrotic lesions displayed in the gastric glandular cells as well as the supporting lamina propria may be attributed to the damage of both superficial and deeper micro-vessels, since the present investigation showed marked damage in the blood vessels or micro-vessels of the supporting lamina propria and in the sub-mucosal connective tissue.

Ultrastructure of the gastric mucosal cells

The use of amoxicillin antibiotic in the present investigation had produced marked consequences in the ultrastructure of the gastric mucosal cells of the fetuses of mice during the period of organogenesis. Among those consequences were the distinct loss of their apical microvilli and conspicuous diminution of their secretory granules.

The observed decrease and loss of the secretory granules of the surface epithelial (mucous) cells as well as decreasing the secretory granules of the zymogenic cells were previously reported by **Fung *et al.*** [28] as a consequence of

treatment with several NSAIDs including acetylsalicylic acid, indomethacin, paracetamol and ibuprofen.

The present investigation also, illustrated fragmentation of the RER cisternae as well as their marked degranulation features so that free ribosomes are aggregated in the form of clusters in the cytoplasm. Such results are in confirmation with the studies carried out by **Fung *et al.*** [28] and **Sabry** [25] who illustrated that there were certain ultrastructural alterations of RER cisternae with marked cytoplasmic vacuolations as consequences of treatment with several NSAIDS including acetylsalicylic acid, indomethacin, phenylbutazone, paracetamol, ibuprofen, naproxen and sodium diclofenac.

The current study showed conspicuous deterioration of the mitochondria of such injured surface epithelial (mucosal) cells and parietal cells, among these changes were the obvious swelling, condensation of the mitochondrial matrices**.** Similarly, **Rainsford and Willis** [29] have obtained distinct mitochondrial changes in the gastric mucosal cells of animals treated with several NSAIDs. Rather recently, **Khattab** [30] showed that treatment of rats with ethylene glycol, revealed conspicuous damage of Golgi apparatus, mitochondria and endoplasmic reticulum in the epithelial , peptic and parietal cells as represented by the noticeable dilation, fragmentation and degranulation of the cisternae of RER, rather condensed matrices of the deteriorated mitochondria as well as demolishing of their internal ridges.

The present investigation illustrated certain pathogenic consequences of the fine structure of the gastric parietal cells of mice fetuses treated with amoxicillin during GDs 7-14. These changes included poorly developed intracellular canaliculi and damaged tubulovesicles. The nuclei of such damaged cells displayed obvious signs of chromatinolysis.

Such pathogenic consequences of the gastric parietal cells are in confirmation with the studies carried out by **Furuhashi *et al.*** [31] who showed that the volume density of the microvilli of the membranes of the secretory canaliculi in the parietal cells was decreased during treatment of rats with omeprazole for 35 days whereas that of their lysosomes were clearly decreased. Nonetheless, **Ramadan and Rahmy** [32] stated that treatment of adult male albino mice with the therapeutic doses of indomethacin (0.7 mg/kg. body weight) for 3 weeks showed marked swelling of the mitochondria, prominent proliferation of the secretory canaliculi and the RER cisternae showed noticeable deterioration. However, in the condition of treatment with 1.4 mg/kg body weight for two weeks, the mitochondria were severely damaged with conspicuous loss of their matrices and ridges and changed to empty spaces. The intracellular canaliculi were disrupted, reduced in size and their microvilli and tubulovesicles had lost their regular attachment with the canalicular system and changed into inner core of the vacuolar spaces. Moreover, the RER cisternae were demolished after their degranulation. Along the same direction, **Yousif** [33] observed significant ultrastructural changes in parietal cells of mice exposed to tenoxican, including fragmentation of RER cisternae, increase of the ribosomes and decrease of tubulovesicles.

In conclusion, the present study showed that amoxicillin administration into pregnant female mice during organogenesis period exerts a clear effect on the stomach structure and ultrastructure. These changes reflect on their function in secretion. So, it should be utilized under restricted precaution in the medical fields to protect the pregnant females from its hazardous impact.

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