



Research Article:

## Histological and Morphometric Effect of Amiodarone on the Ovary in Adult Female Albino Rats

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### Abstract

**Background and objectives:** Amiodarone is an antiarrhythmic medication used to treat abnormal heart rhythms. This study aimed to analyze the histological variations in ovarian follicles of rats after treatment with different doses of amiodarone and evaluate its effects on follicular growth parameters. **Methods:** Thirty female albino rats were divided into control, therapeutic dose (20 mg/kg), and toxic dose (200 mg/kg) groups. Hormonal analysis showed insignificant changes in the therapeutic group but significant declines in follicle-stimulating hormone, estrogen, and increases in luteinizing hormone and prolactin in the toxic group. **Results:** Morphometric analysis revealed non-significant changes in primordial and primary follicles across groups but significant declines in secondary and mature follicles in the toxic group compared to the control. Histological examination showed mild variations in the therapeutic group but serious disturbances in ovarian follicular architecture, increased collagen fibers, congestion, inflammation, and corpora lutea hypertrophy in the toxic group. The degenerative effects were dose-related, confirming the safety of a low therapeutic dose. **Conclusion:** Amiodarone inflicts dose-dependent damage to the ovaries. Doctors can safely prescribe therapeutic doses tailored to patients' medical status.

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## 1. Introduction

Amiodarone is an antiarrhythmic medication that controls abnormal heartbeats by regulating the contractions of the heart muscle, helping the heart function normally (1,2). As a sodium and potassium channel blocker, it also weakly affects calcium channels, which enables its use for treating potentially fatal ventricular arrhythmias when other drugs have failed (3,4). In ventricular tachycardia or fibrillation, amiodarone blocks adrenergic receptors, slows sinoatrial and atrial nodal conduction without affecting intraventricular conduction, reduces myocardial excitability, and prolongs the refractory period (5,6). It also has an antianginal effect by lowering oxygen consumption due to decreased heart rate and total peripheral resistance from direct vasodilatory effects on arterial muscles and increased coronary blood flow (7). Furthermore, the drug supports cardiac output and reduces myocardial contractility (2).

While highly effective for heart conditions, amiodarone can adversely affect many tissues, including endocrine, hepatic, pulmonary, ophthalmic, neural, integumentary, and gastrointestinal (8). Despite its potentially dangerous side effects, it remains a first-line treatment for life-threatening arrhythmias (5,9). However, amiodarone also exhibits antioxidant and anti-inflammatory properties at low doses (1,6). However, amiodarone was not sufficient to reduce oxidative stress and inflammation. TLR4 and NF- $\kappa$ B, which were up-regulated by triggering oxidative stress and inflammation, were not regressed by the effects of amiodarone (6). The ovary produces eggs and sex steroids, with about 300,000 follicles present in each ovary at birth (10-13). Only around a million mature over a woman's reproductive years (14). The hypothalamic-pituitary-gonadal axis involving the hypothalamus, pituitary gland, and gonads controls reproduction (15,16). Disrupting this pathway by unnecessary drugs can impact oocyte differentiation and follicular development, warranting caution (11,17).

As a benzofuran derivative, amiodarone's high iodine content of 37.3% of its molecular weight resembles thyroid hormones (7). Consequently, thyroid dysfunction often occurs, especially in women (7,18). The dosage and duration of amiodarone therapy significantly influence its harmful effects, prompting investigations into using low doses (9,19).

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Several observational studies have demonstrated the safety of very low doses in protecting various organs (6,20).

The effect of amiodarone on gonadal structure in female rats is underreported (21). This study analysed histological variations in ovarian follicles after different amiodarone doses in rats and evaluated its effects on all stages of follicular growth.

## 2. Materials and Methods

**2.1. Materials:** Commercially available 200mg amiodarone tablets (Amiodarone HCl Cordarone® Sanofi Aventis, Cairo, Egypt) were dissolved in purified water and a suspension prepared in methylcellulose 1% and syrup to yield a concentration of 5 mg/ml. ELISA kits were supplied by ELK Biotechnology (USA). All other chemicals and stains were supplied by Atom Scientific manufacturer (UK).

**2.2. Experimental Animals:** Thirty healthy female albino rats aged 10-12 weeks and weighing 150-220 grams were obtained from the Animal House of the College of Veterinary Medicine, University of Mosul. The rats were housed under proper housing conditions with free access to food and water and a 12-hour light/dark cycle. The study was approved and registered in the College of Medicine/Ninevah University (03 on 29.05.2023). Weights were recorded initially and at the end of the study end. Rats were divided into three groups (n=10 each) as follows:

- CG: Given distilled water orally for 6 weeks
- ATD: Given amiodarone 20 mg/kg orally twice daily for 6 weeks (21).
- AHD: Given amiodarone 200 mg/kg orally twice daily for 6 weeks (22,23).

**2.3. Biochemical Analysis:** Blood samples were collected through rats' eyes without anaesthesia, serum separated, and frozen. Serum follicle-stimulating hormone (FSH), estrogen (E2), luteinizing hormone (LH), and prolactin (PRL) levels were measured by ELISA.

**2.4. Histological Analysis:** After six weeks, rats were sacrificed by cervical dislocation and ovaries washed, fixed in 10% formalin at room temperature for 48-72 hours, dehydrated through ascending alcohol concentrations, cleared in xylene, and embedded in paraffin. 5 µm sections were cut, deparaffinized, rehydrated, and stained with Hematoxylin and Eosin (H&E) and Masson's Trichome (MT) (24,25).

**2.5. Morphometric Analysis:** Sections were examined to quantify primordial, primary, secondary, and mature ovarian follicles. The morphometric parameters were measured using a colour USB digital camera presented with computer Graphics software. The software of the microscopic camera was standardized with the help of an ESM-11 0.01mm stages micrometres (Japan) at, X100, X200, and X400 magnification. To translate pixels into micrometres, the software was calibrated for each microscopic magnification. This was accomplished with the assistance of stage micrometres a type of measuring

device. By adjusting the colour threshold, the primary mask masks the area to be measured. The area percentage is calculated by dividing the number of pixels in the mask by the number of pixels in the microscopic field.

**2.6. Statistical Analysis:** Data are expressed as mean ± SD. One-way ANOVA and post hoc Duncan test were used to compare the groups using SPSS v27. P<0.05 was considered significant.

## 3. Results

### 3.1. Body weight changes

The control group showed a significant weight gain while the therapeutic dose caused a non-significant decline. The toxic dose resulted in a highly significant weight loss (Table 1).

**Table 1.** Changes in mean body weight of control and amiodarone-treated rats after six weeks

Groups	Body Weight (g)		p-value
	Before	After	
CG	185±4.28	245.8±9.24	0.013*
ATD	200±4.52	188.4±4.08	0.097
AHD	210±4.27	172.6±6.92	<0.001**

\*p<0.05, \*\*p<0.001, Paired t-test

### 3.2. Hormonal Analysis

The therapeutic dose group showed insignificant differences in FSH, LH, and PRL versus control with significantly reduced E2. The toxic dose group exhibited highly significant decreases in FSH and E2 but increases in LH and PRL compared to control and therapeutic dose groups (Table 2).

**Table 2.** Hormonal levels across groups

Hormone	Control	ATD	AHD
FSH (mIU/ml)	6.85±4.95*	4.32±2.27*	1.39±1.6
LH (mIU/ml)	7.01±2.1	9.03±2.75	12.35±5.81#
E2 (pg/ml)	84.1±5.66*^	30.1±1.45*	12.6±0.76
PRL (ng/ml)	13.52±5.13	11.59±4.37	20.56±9.53#

Data expressed as mean±SD  
 One-way ANOVA with Post hoc analysis  
 \* Significantly higher as compared to AHD  
 ^ Significantly higher as compared to ATD  
 # Significantly higher as compared to control and ATD  
 \*^# P<0.001

**3.3. Morphometric Analysis**

There were no significant intergroup differences in primordial and primary follicles. Secondary follicles declined significantly in AHD versus control and ATD. Mature follicles decreased significantly in ATD and AHD versus control (Tables 3 and 4).

**Table 3.** Ovarian follicle counts

Follicle	CG	ATD	AHD	P-value
Primordial	2.175±0.31	2.113±0.23	1.461±0.20	0.433
Primary	5.34±0.42	7.71±1.10	3.71±0.60	0.422
Secondary	4.47±0.49	2.65±0.26	1.27±0.17	0.041
Mature	4.23±0.57	2.48±0.38	1.37±0.31	0.029

One-way ANOVA with Post hoc analysis  
Data expressed as mean±SE

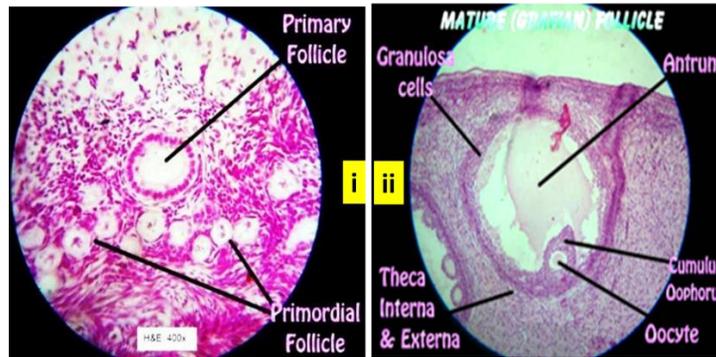
**Table 4.** Post hoc analysis of ovarian follicles

Post hoc analysis	G1 vs G2	G1 vs G3	G2 vs G3
Primordial follicles	0.145	0.250	0.270
Primary follicles	0.284	0.284	0.083
Secondary follicles	0.667	<0.001	0.037
Mature follicles	0.005	0.026	0.041

G1: Control; G2: ATD; G3: AHD

**3.4. Histological Analysis by Eosin and Haematoxylin Stain**

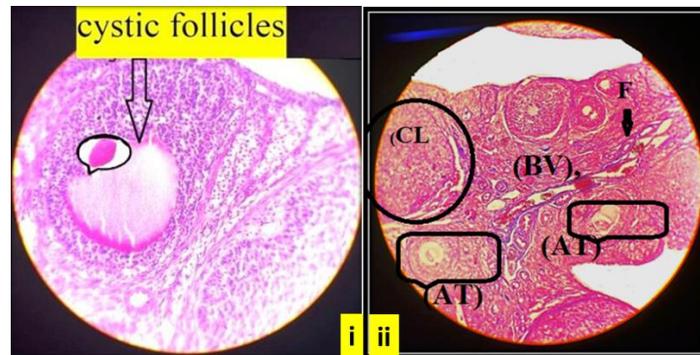
Control Group: Ovarian sections showed an outer cortex with an inner medulla and no distinct border. The cortex was enclosed by the tunica albuginea and contained ovarian follicles at different developmental stages - primordial, primary, secondary, mature follicles and corpora lutea (Figure 1).



**Figure 1.** Ovarian histology of the control group: (i) Primordial (PF) and primary multilayer (PMF) follicles. (ii) Mature Graafian follicle showing oocyte (O), zona pellucida (ZP), corona radiata (CR), antrum (A), granulosa cells (GC), and lutein cells. (H&E 100X)

ATD Group: The cortex contained many large developing follicles, corpora lutea, and microcystic follicles pressing the medullary tissue. Noticeable interstitial cell crowding,

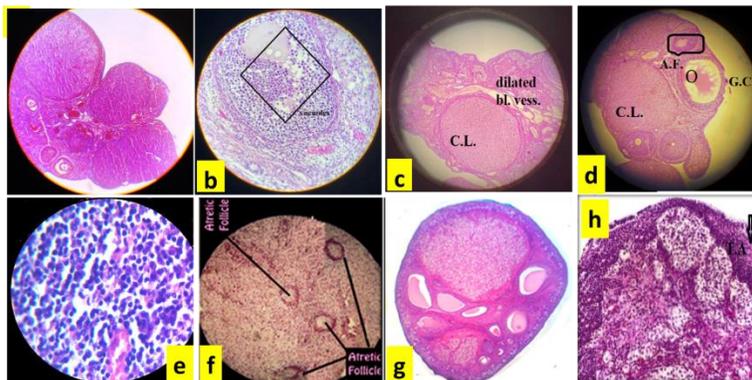
congested blood vessels and fibrosis were seen in the cortex and medulla (Figure 2).



**Figure 2.** Ovarian histology of the therapeutic amidarone group: Cystic follicle (CF), corpus luteum (CL), congested blood vessels (BV), fibrosis (F), and atretic follicles (AT). (H&E 100X)

AHD Group: Serious disturbances in ovarian follicular architecture were observed, including vacuolated follicles, follicular corpus luteum hypertrophy, preserved atypical frameworks of some intact follicles, widened interstitial spaces with vascular engorgement and inflammatory cell infiltration, increased atretic follicles versus ATD group

(**Figures 3**). Most follicles were atypical with large cystic masses. Some showed degenerative changes like missing oocyte nucleoli, thinned zona pellucida and disordered granulosa cell layers. The tunica albuginea was thicker than normal.

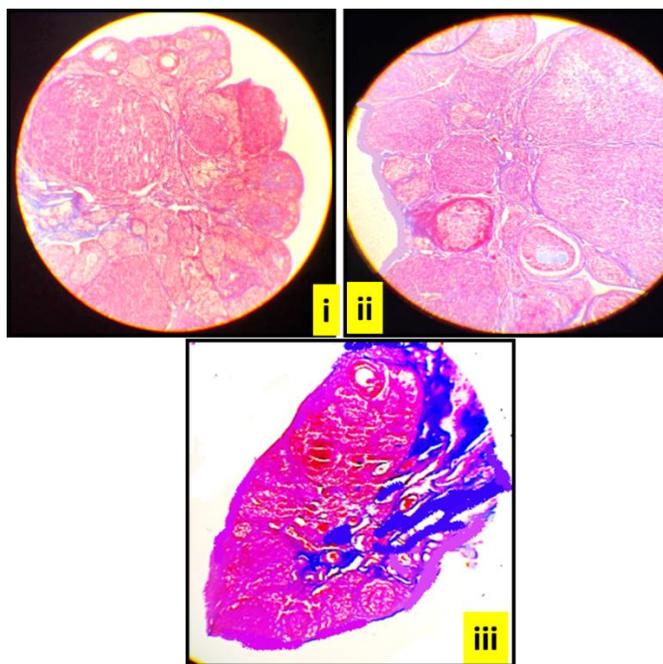


**Figure 3.** Ovarian histology of the toxic amiodarone group. (a) Dilated medullary blood vessels (BV). (b) Vacuolated follicles (VF). (c) Large corpus luteum (CL). (d) Atretic follicle (AF) with disrupted zona pellucida (ZP) and granulosa cells (GC). (e) Inflammatory cells (IC) in the interstitium. (f) Atretic follicles (AF). (g) Cystic follicles (CF). (h) Thickened tunica albuginea (TA). (H&E 100X)

### 3.5. Histological Analysis by Masson's Trichome Stain

Control Group: Blue collagen fibres were seen in the medulla and around blood vessels (**Figure 4i**).

Treated Groups: Mildly increased collagen fibre thickness in the therapeutic dose group and marked increases in the medulla and around blood vessels were observed in the toxic dose group versus control (**Figures 4ii and 4iii**).



**Figure 4.** Collagen staining in ovarian sections. (i) Control group showing collagen fibres (blue) in the medulla. (ii) Mildly increased collagen in the therapeutic group. (iii) Marked collagen deposition in the toxic group. (Masson's Trichrome, 40X)

#### 4. Discussion

Amiodarone affects molecular processes, with several studies evaluating its effects on different organs (14,26). However, this is the first study analysing its influence on rat ovarian histology. Rats provide a good model for human ovarian lesions based on morphological and histopathological similarities (27,28). Oral amiodarone administration resembled its clinical use in humans (28).

The therapeutic dose did not significantly alter rat weight unlike the toxic dose, consistent with Oyedjei et al. (28) using 5.71 mg/kg amiodarone in rats. Weight loss from the toxic dose concurred with Jiang et al., (29) attributed to amiodarone-induced blood lipid imbalance or dyslipidaemia involving lipoproteins. Amiodarone alters lipid metabolism and lipoprotein lipase, unlike low doses that do not affect fat breakdown in adipose tissue, preserving weight (29,30).

Hormonal analysis revealed insignificant gonadotropin, estrogen, and prolactin variations with the therapeutic dose versus marked changes with the toxic dose, including declines in FSH and estrogen and increases in LH and prolactin. The reduced FSH and estrogen with hyperprolactinemia and elevated LH explained the numerous corpora lutea, while fewer developing follicles resulted from diminished estrogen needed for granulosa cell survival and apoptosis resistance (31,32). The present findings agree with Aguilar et al., (33) confirming the safety of low-dose amiodarone on gonadal hormone secretion. The dosage and duration of amiodarone generally influence endocrine hormone secretion, especially anterior pituitary hormones, which accounts for the differences between groups (19,34). Amiodarone disrupts the hypothalamic-pituitary-gonadal axis, impacting granulosa cell development and lowering gonadal steroid-binding protein secretion by hepatocytes, increasing serum-free estradiol, suppressing gonadotropins by negative feedback and reducing normal follicles and estrogen further (9,35).

Morphometric analysis revealed non-significant primordial and primary follicle changes across groups but dose-dependent declines in secondary and mature follicles, concurring with Sakr et al. (21) which reported impaired spermatogenesis in male rats after 18 mg/kg/day oral amiodarone for five weeks. As an iodine-

containing compound comprising 37.3% iodine, amiodarone can cause hypothyroidism and negatively impact ovarian follicular growth, explaining the histological changes (7,36).

Multiple large cystic follicles compressing interstitial stroma and varying degrees of atypical follicular progression were observed, especially with the toxic dose. Interstitial luteinizing stromal cell hypertrophy from the enlarged corpora lutea increased pressure, due to thickening, on the surrounding tissues. Hypothyroidism or hyperthyroidism affecting the hypothalamic-pituitary axis causes gonadal hormonal abnormalities, consistent with these findings (9, 26). According to Meng et al., (26), the large corpora lutea resulted from altered anterior pituitary hormone secretion by amiodarone treatment influencing follicular cell swelling and raised serum progesterone or luteinization. Thyroid-stimulating hormone (TSH) with FSH stimulates synergistically follicular cell growth. In contrast, triiodothyronine (T3) and thyroxine (T4) regulate FSH-mediated follicle excitation and inhibit apoptosis (11,37).

Decreased ovarian follicle growth paralleled their increased degeneration and resorption, which displays signs of programmed cell death, and agrees with altered ovarian hormones (38,39). Marked luteinized stromal cell concentration with foamy or vacuolated cytoplasm adversely impacted folliculogenesis and reduced follicle numbers, accompanied by zona pellucida and granulosa cell layer disturbances (39). Amiodarone-induced oxidative stress encourages fibroblast deposition via the TGF-beta pathway to produce collagen, explaining the mild to severe collagen changes in therapeutic and toxic doses, respectively (6,34).

Recent studies promote using satisfactory low doses to effectively treat arrhythmias with fewer side effects (1,20). Furthermore, low doses exhibit antioxidant and anti-inflammatory properties (1,6).

The limitations of the present study include a small sample size and the rat's normal oestrous cycle cannot exactly reflect the women's menstrual cycle. Additionally, the duration of the study in the present study cannot replicate the chronic use of amiodarone as is the case in amiodarone use for human chronic cardiac arrhythmia disease.

## 5. Conclusion

Amiodarone can cause dose-dependent damage to rat ovaries, with mild changes from low therapeutic doses but serious gonadal injury from high toxic doses, which confirms the safety of low effective doses. Amiodarone toxic dose has increased LH and PRL together with reduced FSH and E2. Histological and morphological changes have been notified with toxic doses compared to therapeutic ones.

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### التأثيرات النسيجية والمورفومترية للأمبودارون على المبيض في إناث الجرذان البيضاء البالغة

#### الخلاصة

**المقدمة:** الأمبودارون هو دواء مضاد لاضطراب النظم يستخدم لعلاج نظم القلب غير الطبيعي. هدفت هذه الدراسة إلى تحليل الاختلافات النسيجية في بصليات المبيض للجرذان بعد العلاج بجرعات مختلفة من الأمبودارون وتقييم آثاره على معايير النمو الجريبي. **طريقة العمل:** تم تقسيم ثلاثين من إناث الجرذان البيضاء إلى مجموعتين مراقبتية وجرعة علاجية (20 مغ / كغ) وجرعة سامة (200 مغ / كغ). **النتائج:** أظهر التحليل الهرموني تغيرات طفيفة في المجموعة العلاجية ولكن انخفاضات كبيرة في الهرمون المنبه للجريب والإستروجين وزيادة في هرمون اللوتين والبرولاكتين في المجموعة السامة. كشف التحليل المورفومتري عن تغيرات غير معنوية في الجريبات الأبتدائية والأولية عبر المجموعتين ولكن انخفاضات كبيرة في البصليات الثانوية والناضجة في المجموعة السامة مقارنة بالسيطرة. أظهر الفحص النسيجي اختلافات طفيفة في المجموعة العلاجية ولكن اضطرابات خطيرة في بنية مسامي المبيض، وزيادة ألياف الكولاجين، والاحتقان، والالتهاب، وتضخم الجسم الأصفر في المجموعة السامة. كانت الآثار التنكسية مرتبطة بالجرعة، مما يؤكد سلامة الجرعة العلاجية المنخفضة. **الاستنتاج:** يلحق الأمبودارون أضراراً تعتمد على الجرعة في المبايض. يمكن للأطباء وصف جرعات علاجية بأمان وحسب حالة المريض عند استخدامها سريريًا.

**الكلمات المفتاحية:** أمبودارون، المبايض، التغيرات النسيجية، التغيرات الشكلية، هرمون الكونادوتروبين، إستروجين، هرمون الحليب.