

## **BIOCHEMICAL AND ULTRA STRUCTURAL ASPECTS ON EFFECT OF INDUCED HYPOTHYROIDISM IN PREGNANT RATS AND FETUS**

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### **ABSTRACT**

The study was evaluated the effect of propylthiouracil(PTU) drug on both maternal and fetus rats (*Rattus norvegicus*). Experimental animals were housed, breeding and adapting, then only (50) virgin females were chosen for mating, the mean weight of the animals was (200±50) gm and (8-10) week of age, all females subdivided into two groups, first group regarded as control while the second group were treated with (PTU) dose as (0.05%) to induced hypothyroidism, then the females mating and the gestation day (G0) was determined. All the biochemical and ultra-structural changes on thyroid gland of maternal rats was clarified at each period of gestation (14.5, 16.5, 18.5, 20.5 and 21.5) days post gestation. Biochemical results in this study referred to non significant increase in (TSH) concentration while there was decrease in (T3 and T4) level on blood serum of pregnant rats related to hypothyroidism group compared to their values in control group at (P≤0.05). Also levels of some oxidative enzymes (GSH and MDA) was determined, the data showed significant increase in the concentration of these enzymes in serum of pregnant rats related to an induced hypothyroidism group compared to their



concentration in rats of control group at each period of gestation.

In this study the ultra structural changes in thyroid gland from maternal and fetus related to the induced hypothyroidism females at each period of gestation were identified by electron microscopy and included changes in apical surface of follicular cells by alteration the shape of surface like microvillus, blebs and protrusions, also dilated with rough endoplasmic reticulum cisternae, increased number of lysosomes and more empty vacuoles within follicular cells cytoplasm than the dense vesicles in all sections from hypothyroidism thyroid gland.

In addition to that there was increased in mitochondria and Golgi apparatus number in sections from maternal and fetus thyroid gland of hypothyroidism group, also the follicular cells appeared with congested, irregular nucleus and dense chromatin as well as some of cellular debris was noticed, the surrounded connective tissue thick and septa extend to separated thyroid follicles, also pictures from hypothyroidism thyroid gland showed deposition of iodine salts crystals in most follicular cells.

## INTRODUCTION

Thyroid gland play a vital role in the overall body function during all stages of life, although it was relatively small but it produce hormones that regulate the body metabolism, in addition to their important effect on the other hormones action(1).

Thyroid gland produces the hormones(T<sub>4</sub>), (T<sub>3</sub>) and calcitonin, more than(80%) of (T<sub>4</sub>) was converted to (T<sub>3</sub>) by peripheral organs such as liver, kidney and spleen, so (T<sub>3</sub>) is about ten times more active than (T<sub>4</sub>) (2). Thyroid stimulating hormone (TSH) stimulate thyroid gland to secrete both hormones (T<sub>4</sub> and T<sub>3</sub>).



Thyroid diseases have been known to affect the females reproductive system, who thus have trouble in conceiving or have more miscarriage, also thyroid dysfunction has high prevalence during pregnancy, affecting up to 5% of all pregnant women(3,4).

Hypothyroidism is almost caused by disease within thyroid gland lead to decrease in the production of thyroid hormones, and the most disorder may be the(TSH) dependent hypothyroidism which causes abnormalities during fetal development or early infancy growth, and infants not treated within the first three months suffer irreversible mental retardation(5).

The was interaction between thyroid hormones and antioxidants enzymes, these enzymes include superoxide dismutase(SOD) and (GSH),the balance between activities of these enzymes and the intercellular levels of these antioxidants essential for the survival of organisms and their health(6).

Hypothyroidism was found to be associated with marked oxidative stress, one of the earliest manifestations of which was decline in the level of glutathione(7).

Previous studies showed that the increased activity of(SOD)and (GSH) and increased(TSH)concentration in thyroid tissue induced to the reactive response to increased free radical generation moreover higher concentration of(GSH)in plasma and tissue indicate compensator(8,9).

Since the fetus completely depend on maternal thyroid hormones supplied during early period of gestation which it was crucial in organogenesis, so the present study planned to evaluated the ultra-structural changes on maternal thyroid and their fetuses, also estimated the effect of induced hypothyroidism on hormones(T3,T4andTSH) and some oxidative enzymes(GSH and MAD).



## MATERIALS AND METHODS

### 2.1 Experimental animals

In this study Wister albino (*Rattus norvegicus*) were used aged (8-10) weeks and weighting about (200-250) gm. All animals were kept in animal house under controlled conditions, for mating only the virgin females were chosen and placed as (2:1) ratio females to males for mating, when vaginal plug was observed then this day consider as day zero of gestation (G0).

### 2.2 Induction of hypothyroidism

Fifty pregnant rats isolated and divided into two groups the experimental and each group of (5) rats with (10) rats for each period (14.5, 16.5, 18.5, 20.5 and 21.5) days of gestation. Hypothyroidism was induced by adding 0.05% of propyl thiouracil (*ptu*) to drinking water gives to pregnant rats start from (8.5) day of gestation and continue stillbirth (10). While euthyroid rats regarded as control were received only tap water during the same period of gestation.

### 2.3 Samples collection

Pregnant rats from each group (control and hypothyroidism) were sacrificed after anaesthetized on each period of gestation with overdose of chloroform, then directly the blood (5ml) was collected from it by heart puncture into sterilized tube without anticoagulant to separate the sera and then keeping in freezer to determine some biochemical parameters like thyroid hormones (TSH, T3 and T4) and oxidative enzymes (GSH and MDA). Also thyroid tissue related to maternal rats and their fetus were obtained and very thin pieces prepared for electron microscopy examination.

### 2.4 Biochemical study

#### 2.4.1 Measurement of (TSH, T3 and T4)

Thyroid hormones concentration were measured in the serum of control and hypothyroidism rats by Cusabio Eliza Kit from CusaBiotech Co. This assay employs the quantitative sandwich



enzyme immunoassay technique. The concentration of (TSH, T3 and T4) expressed according to the standard curve which prepared from standard solution dilution and then the optical density (OD) were read, the concentration expressed as ( $\mu$ l/ml, ng/ml,  $\mu$ g/dl) respectively.

#### **2.4.2 Estimation of rat (GSH and MDA) enzymes.**

Briefly as above the blood from each pregnant rats at each period of gestation were used and within serum separate tube (SST) allow samples to clot for (30) min. before centrifugation for (15) min. at (3000) rpm then we removed serum, to determine of each kits was followed, this assay employs the competitive inhibition enzymes immunoassay technique.

Absorbance at (450) nm was reader with Eliza reader within (5) min and the concentration of (GSH and MDA) enzymes level was estimated for all samples compared to control, the normal values was (16-400)  $\mu$ g/ml for (GSH) enzyme and (31.2\_2000) pmol/ml for (MDA) enzyme.

#### **2.5 Ultrastructural study by transmission electron microscopy (TEM) exam.**

Specimens from each maternal thyroid gland and very small pieces of fetus thyroid gland were excised on each period of gestation (14.5, 16.5, 18.5, 20.5 and 21.5) days, then prepared for electron microscopy study, so the samples processed as follow, the fixation with two steps, the primary fixation with De-Castro fixative (1) which composed from two solutions mixed just before used, the samples fixed for (2hrs) at (4C<sup>o</sup>).

The post fixation established with osmium tetra oxide (OSM4) for (2hrs), and then the samples were passed through series of alcohol concentration 50%, 70%, 90% and absolute alcohol for (20 min) on each concentration. Then the samples embedding pure araldite with appropriate steps, then the blocks were providing for cutting, this sections (50-80) nm were cut and attach on EM gridded for used to examination by (TEM). Staining with uranyl acetate and lead citrate, then examining and photographed (11).

**NOTE:** The steps starts from dehydration completed in Bendahaari, University Malaya, Electron microscopy unit, Faculty of Medicine.



## **2.6 Statistical analysis**

The results were analyzed with Anova test by analysis of variance, the data were expressed as (mean±SD),also(LSD) was used to test different between groups<0.05 was considered significant.

## **RESULTS**

### **3.1 Biochemical study**

#### **3.1.1 Effect of hypothyroidism on thyroid hormones on pregnant rats compared to control.**

The results referred to an increased in(TSH)while decreased with(T3 andT4) hormones concentration in blood serum of hypothyroidism pregnant rats at  $p \leq 0.05$  compared to control group (table 1,2 and 3), on each period of gestation (14.5,16.5,18.5,20.5 and 21.5) days, the results expressed as(means).

#### **3.1.2 Estimation of (GSH and MDA) oxidative enzymes concentration of pregnant rats (treated and control).**

The data were determined concentration of GSH in all pregnant rats with hypothyroidism and results of statistical analysis referred to significant increased at( $p \leq 0.05$ ) in all hypothyroidism rats compared to control on each periods of gestation compared to control group except at(20.5)day the data was referred to mild decrease in(GSH) level on hypothyroidism rat compared to control(table 4).

Also concentration of(MDA) was determined and showed increased significantly in all pregnant rats with hypothyroidism at ( $p \leq 0.05$ )compared to control group,the results clarified gradual increased with(MDA) start from (14.5) days post gestation till(21.5)days in all rats with hypothyroidism except on day(18.5and20.5) showed mild decrease with(MDA) level in hypothyroidism rat compared to control(table 5).



**Table 1: Effect of hypothyroidism on thyroid hormones TSH on pregnant rat compared to control group. Values expressed as (mean±SD) .(μIU) , (p≤0.05).**

Period of pregnancy day	14.5	16.5	18.5	20.5	21.5	Total	LSD
Control	1.4±0.75	0.84±0.40	0.71±0.31	13.14±8.20	4.02±4.72	3.97±6.20	*
Treatment	55.34±2.35	6.88±5.42	6.027±4.66	14.22±6.52	6.22±7.59	7.73+- 6.11	*

\*: Referred to significant difference, the number of animal in each group: 5 rats.

**Table 2: Effect of hypothyroidism on thyroid hormones T3 on pregnant rat compared to control group. Values expressed as (mean±SD) .(ng/dl), (p≤0.05).**

Period of pregnancy day	14.5	16.5	18.5	20.5	21.5	Total	LSD
Control	0.19±0.15	0.42±0.11	0.48±0.15	0.37±0.13	0.54±0.19	0.40±0.18	NS
Treatment	0.28±0.10	0.42±0.45	0.24±0.15	0.28±0.13	0.29±0.14	0.30±0.22	NS

NS: Mean no significant, the number of animals in each group: 5 rats.

**Table 3: Effect of hypothyroidism on thyroid hormones T4 on pregnant rat compared to control group. Values expressed as (mean±SD) .(μg/dl), (p≤0.05).**

Period of pregnancy day	14.5	16.5	18.5	20.5	21.5	Total	LSD
Control	4.01±0.51	2.45±0.48	1.89±0.66	1.24±0.66	2.29±1.07	2.37±1.16	*
Treatment	1.42±0.33	1.71±0.39	1.42±0.61	1.05±0.36	2.46±1.31	0.61±0.80	*

\*: Referred to significant difference, the number of animal in each group: 5 rats.



**Table 4: Effect of hypothyroidism on thyroid hormones GSH compared to control group. Values expressed as (mean±SD) (p≤0.05).**

Period of pregnancy day	14.5	16.5	18.5	20.5	21.5	Total	LSD
Control	28.42±3.7 9	21.26±5.0 3	0.36±0.11	27.92±9.7 9	9.32±1431	17.45±13.5 0	*
Treatment	30.4±1.90	27.18±3.1 8	25.78±8.8 9	26.72±5.6 4	20.94±23.4 4	26.20±11.0 5	*

\*: Referred to significant difference, the number of animal in each group: 5 rats.

**Table 5: Effect of hypothyroidism on thyroid hormones MDA compared to control group. Values expressed as (mean±SD) (p≤0.05).**

Period of pregnancy day	14.5	16.5	18.5	20.5	21.5	Total	LSD
Control	827.4±424.04	1109±805.75	1288.80±742.41	12656.60±602.4 6	12672.20±516. 10	1151.60±6 05.48	NS
Treatment	12698±587.63	13066±442.06	977.8±268.09	1135.4±414.23	1373.8±589.85	1212.68±4 57.55	NS

NS: Mean non-significant, the number of animal in each group: 5 rats

### 3.2 Transmission electron microscopy study.

#### 3.2.1 Thyroid gland of hypothyroidism maternal rats.

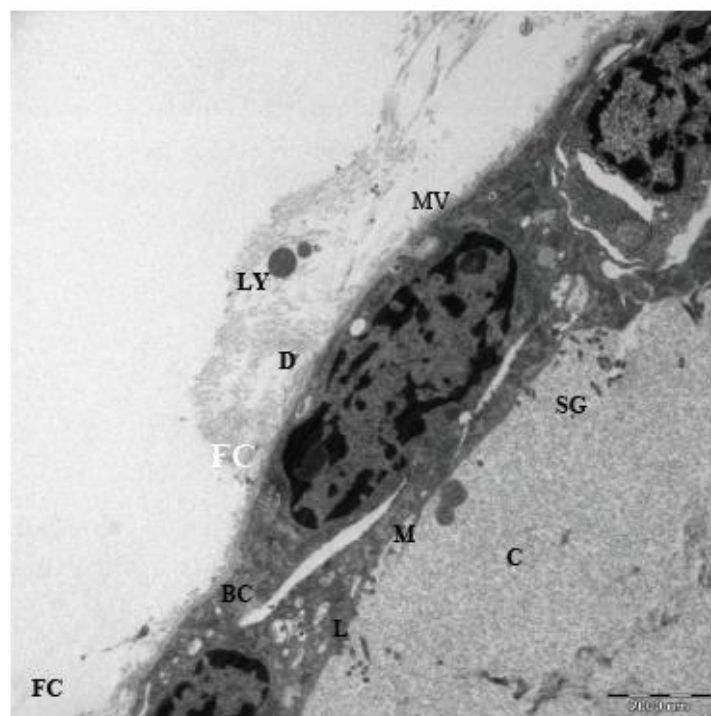
Results of (TEM) on specimens of thyroid gland from hypothyroidism pregnant rats showed variable follicles lining with cubical follicular epithelium cells with its organelles, pyknotic nucleus in the centre of follicular cells, there was developed rough endoplasmic reticulum with rich cisternae at the base of follicle cell while at the apical surface of follicle cell there was large number





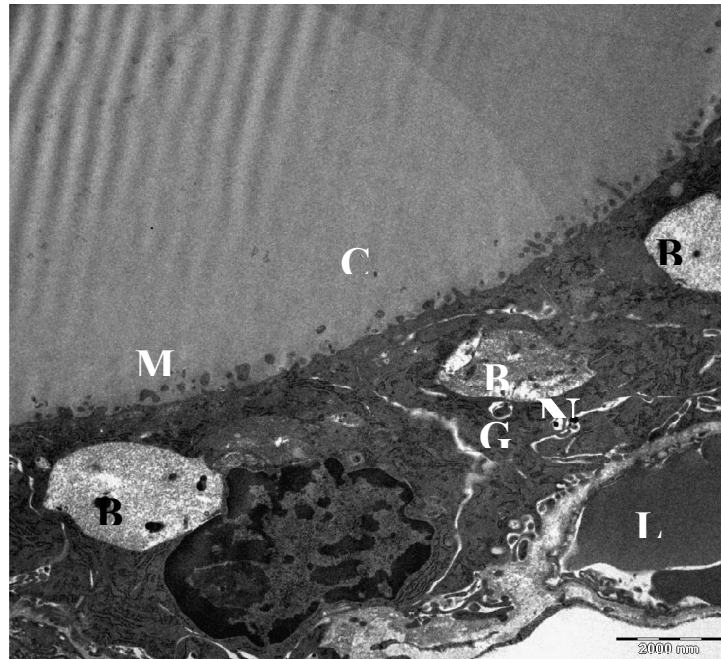
of small ,short projection microvillus these faced to the lumen filled with colloid material. Also the parafollicular cells(C-cell) may be appeared surrounded with basal lamina or as clusters between follicles, the figures also clarified few number of mitochondria, dilated capillaries with erythrocytes, the basement membrane thick and delineated the follicles, dense secretary granules and well developed Golgi apparatus(fig 1,2).

Moreover the same changes shown at(20.5)day post gestation on thyroid gland section from hypothyroidism rats, the follicular cells with sparse and irregular microvillus at apical surface, the(RER)with developed cisternae and irregular,euchromatic nuclei and dilated lymphatic vessels(fig3and4)



**Fig1:** photograph of T.E.M show follicular cells (FC) with noticed colloid material (C), almost dilated blood capillary (BC), packed microvillus like sheath(MV)few number of mitochondria(M)large number of lysosomes (L), and few number of secretion granules (SG) in hypothyroidism pregnant rat at (20.5) day of gestation, 2000nm.

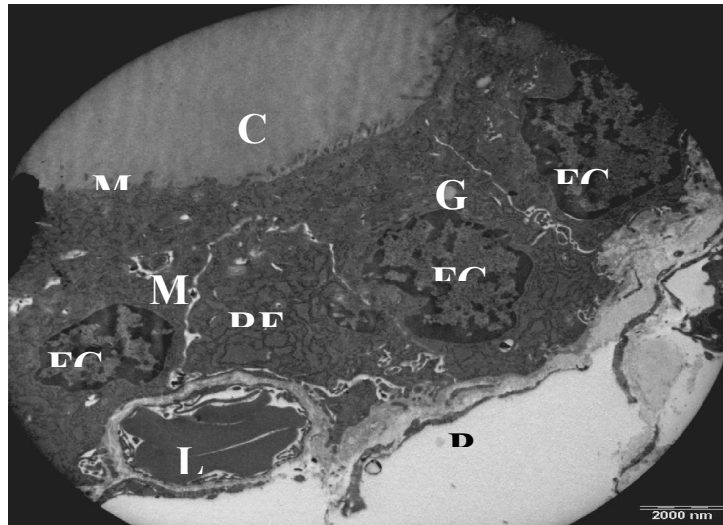




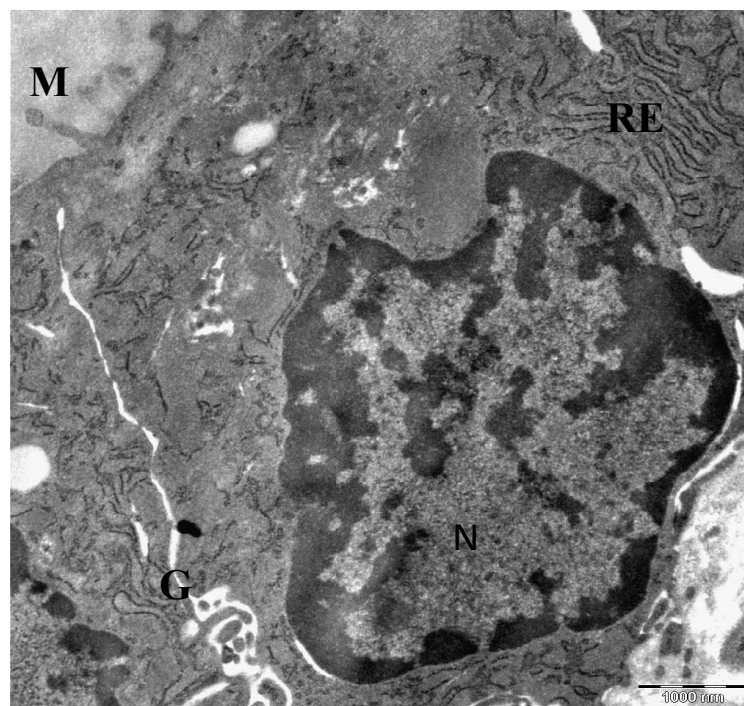
**Fig2:** Photograph of T.E.M on thyroid gland from pregnant rat treated with (PTU) showed large follicular cell (FC) with euchromatic nucleus, irregularly spaced apical microvilli (MV) facing lumen, dilated lymphatic vessel (LM) and well dilated developed rough endoplasmic reticulum (RER), few Golgi apparatus (GR), dilated congested blood capillaries (BC) and lumen with colloid(C) material. 2000nm.

Also sections on thyroid gland from pregnant rats at(20.5)day post gestation showed ultra-structural changes on follicular cells that appeared with irregular microvilli at apical surface, dilated rough endoplasmic reticulum with developed long ,slender cisternae,euchromatic nuclei, and thickening with basement membrane but less number of Golgi apparatus with few secretory granules(fig 3and4).





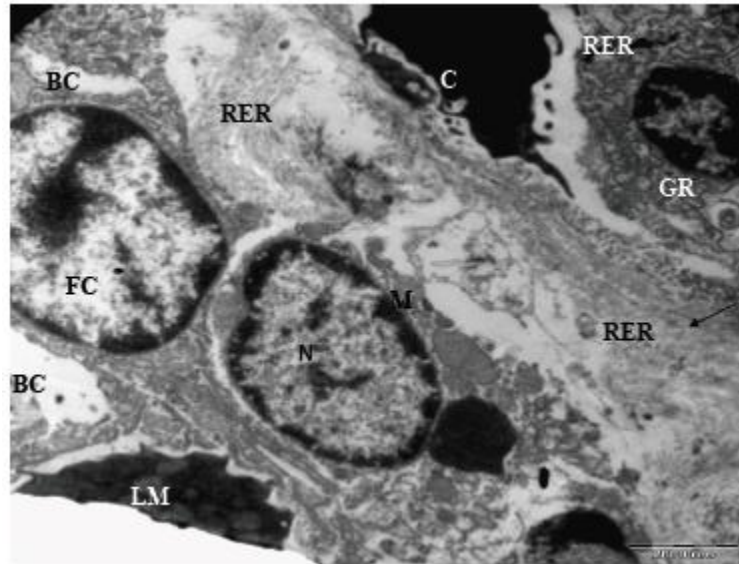
**Fig3:** section of T.E.M from hypothyroidism rats at(20.5)days of gestation show follicular cells (FC) with pyknotic nuclei, each cells separated by very narrow spaces(S) colloid material (C), irregular microvillus (MV), less number of mitochondria (M), irregular dilated of rough endoplasmicreticulum (RER) cisternae, undeveloped Golgiapparatus (GR),thickening basement membrane (Bm),dilated lymphatic vessels (LM) 2000nm.



**Fig4:** Section in rat thyroid gland treated with (ptu) showed follicular cell (FC) with clear nucleus(N), dilated arranged rough endoplasmic reticulum (RER), few number of Golgi apparatus (GR)with secretory granules , bleb microvillus (MV) and nucleus (N) was euchromatic with irregular outline, number of blood capillary (BC), 1000nm.



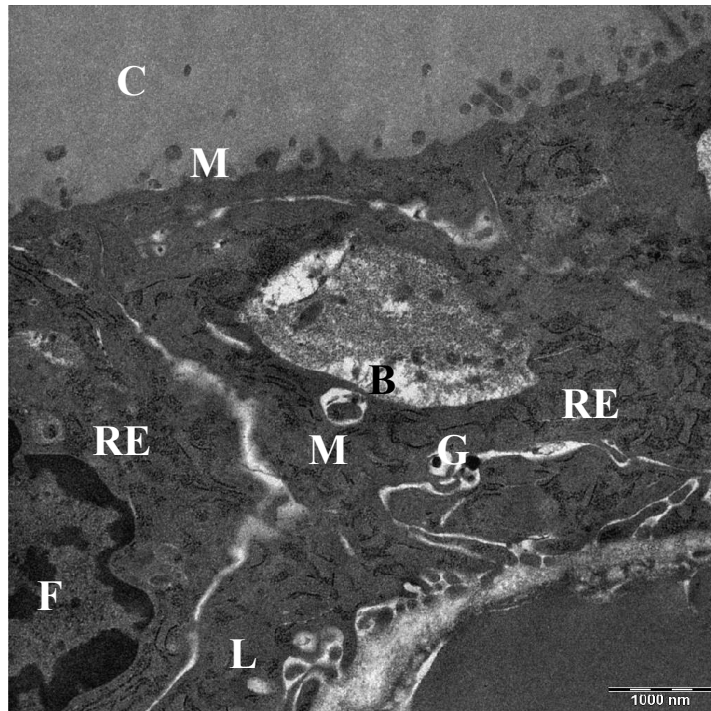
Electron micrograph on thyroid gland of fetus from the hypothyroidism rats showed degenerated cytoplasm of follicular cells with nuclei(rounded) and dispersed chromatin, large number of mitochondria and lymphatic vessels were noticed(fig5)



**Fig 5:** Electron micrograph on fetus thyroid gland from hypothyroidism group showed follicular cell (FC) with rounded nuclei and dispersed chromatin (CH), degenerative product (C), dilated (RER), well developed Golgi apparatus (GR), with secretory granules (→), with dilated blood capillary (BC) , lymphatic vessels (LM) and elongated mitochondria (M),also degenerative secretory vesicles was shown, 2000 nm.

The results clarified changes on thyroid gland from fetus on(18.5) day post gestation like irregular, sparse microvillus on follicular cells apical surface and their basal surface resting on basal lamina, congested blood capillary, well developed rough endoplasmic reticulum occupy the sub nuclear region and developed Golgi apparatus closed to packed secretory granules at the same region (fig 6)

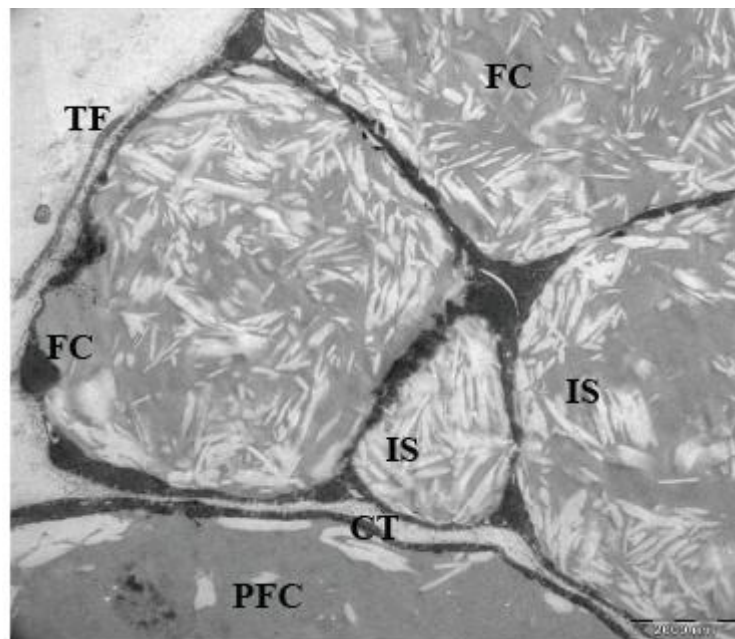




**Fig 6:** Electron micrograph on fetus thyroid gland(18.5)days post gestation showed follicular cell with irregular, sparse microvillus (MV),dilated cisternae of(RER),congested blood capillary(BC),well developed Golgi apparatus(GR)and number of lysosomes (LY),1000nm

Also photograph referred to sections from fetus thyroid gland treated with propyl thiouracyl(PTU) at(18.5) day of gestation appeared that the follicular cells full with deposit of iodine salt crystals each follicle is lined by single layer of epithelial cells enclosing cavity. Delicate connective tissue surrounding the follicles and thick connective tissue septa separated between these follicular cells, and the para follicular cells at the base was noticed (fig7).





**Fig 7:** Electron micrograph on thyroid gland from hypothyroidism fetus at (18.5)days showed variable thyroid follicles(TF)lining with follicular cells(FC)filled with iodine salt(IS)crystals, thick septa of connective tissue(CT)separated the follicles and at the base para-follicular cell(PFC)was noticed follicles.2000n

## DISCUSSION

The biochemical results referred to an increased with(TSH)and decreased in (T3 and T4) hormones with significant differences at( $P \leq 0.05$ ) in all hypothyroidism pregnant rats treated with(PTU) compared to the control group, this may be related to the important roles of these hormones as markers to thyroid gland function, this agreed with (12) who commonly used these hormones as reliable indicators of thyroid function in humans and experimental model.

Thyroid gland affected by(PTU)which may be caused inhibition in peroxidase and de-iodinase key enzymes involved in thyroid hormones biosynthesis, this lead to decreased levels of circulating hormones that caused increased secretion of(TSH) by provide growth stimulus to the thyroid(13).



The recent results showed the significant decrease with(T3 and T4) in all pregnant

rats with hypothyroidism from (10)day post gestation and continue up to the delivery period, this may be suggested to the effect of(PTU) which caused changes with thyroid hormones appeared clearly at all gestation period, this result agreed

with (14). Who discussed these results previously.

(15).investigated relatively large number of samples and found a linear relationship between(PTU) and (TSH)in women with different type of thyroid disorders such as thyroid autoantibody levels in healthy subjects, patients with autoimmune thyroid disease(AITD) and women with nodular goiter evaluated.

Also an increased with oxidative enzymes(GSH and MDA)was recorded in this study in serum of hypothyroidism all pregnant rats compared to control rats at different period of gestation, this may be related to the effect of(PTU)which caused changes with thyroid gland structure, damaged of most follicular cells and disturbances in enzymes secretion this also discussed by other studies referred to decline in the level of (GSH) and this found to be associated with oxidative stress(7).Inhibition of these enzyme(GSH) and (MDA)result in decreased level of thyroid hormones in blood and lead to increase secretion of(TSH)by provide growth stimulus to the thyroid, resulting in goiter(13)

The present study focus on the ultra structure changes on thyroid gland related to hypothyroid rats and results showed most follicles small,irregular,vacuolated cytoplasm of follicular cells, the nucleus with irregular outlines, dilated cisternae of



rough endoplasmic reticulum, less developed Golgi apparatus and increased with basement membrane thickness, these results may be caused by the (PTU) which disturb the normal structure, cytoskeleton of cells, damaged on plasma membrane, and this agreed with (12;16) who suggested that many changes take place like dense colloid material deposited within cells resulted from colloid endocytosis and inhibition of phagocytosis/pinocytosis of the colloid (thyroglobulin) caused it to accumulate in the follicular lumen and this lead to diminishing the height of the follicular epithelium.

Dilation of (RER) in follicular cells of hypothyroidism thyroid gland illustrate the role of (RER) in damaged cells caused by (PTU) or may be reflect the metabolic activity needed in these cells, this confirmed by (17) who showed that the dilation caused since the injured cells need for oxidative enzymes which are required for detoxification.

Results of present study revealed that (PTU) was significant harmful effect of structure and function of thyroid gland, and these effects clarified the pathogenesis of (PTU) was multifactorial, interrupting protein synthesis (15).

Electron microscopy also showed that thyroid cells separated by two layers of basement membrane from capillaries which showed as dilated congested blood capillaries, this may be attributed to the high level of (TSH) hormone which induced follicular cells hypertrophy and increased vascularity.

The dilated of (RER) and nucleus irregularity which also recorded in this study discussed by (18) who clarified that dilation of (RER) compressed the follicular cells nuclei causing its indentation and irregularity.





Photograph on section from fetus thyroid gland treated with(PTU)showed most follicular cells lining with flatted cells and this caused by present of colloid material inside it which caused convert of cuboidal cells to squamous, also an increase with lysosomes number, increased blood supply and this may be regarded to the functional state and reflect changes occurs because of(PTU) during pregnant period and the effect of mothers with hypothyroid on its fetus.

An increased with lysosomal number reflect the increased in the synthesis of hydrolytic and detoxifying enzymes secondary to the degenerative and apoptotic seen in many cells (17)

The figure referred to an accumulation of salts and iodine crystals within follicular cells cytoplasm this may be considered as result of (PTU) which disturb the enzymes that inhibit transformation rate from T4.



## التأثيرات البايوكيميائية والمجهريه الفوقيه لقصور الغدة الدرقية المستحدث في الجرذان البالغة وأجنثها

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### الخلاصة

تم في هذه الدراسة تقييم تأثير عقار ال PTU على امهات الجرذان الحوامل واجنثها نوع *Rattus norvegicus*. استعملت الحيوانات المختبرية بعد تربيتها وتكاثرها وتركها لتتكيف ثم عزل منها الاناث العذاري البالغ عددها (50) انثى واختيرت لغرض التزاوج وباوزان (200±50) غم وبعمر (8-10) اسبوع قسمت الى مجموعتين المجموعة الاولى اعتبرت كمجموعة سيطرة بينما المجموعة الثانية عوملت بما يعادل (0.05%) من ال PTU لحدث نقص الدراق، تركت للتزاوج وتم تحديد اليوم (صفر) من الحمل.

سجلت كافة التغيرات البايوكيميائية وتغيرات التركيب النسيجي الدقيق للغدة الدرقية في الجرذان الحوامل والاجنة وللفترات (14.5 و16.5 و18.5 و20.5 و21.5) يوم من الحمل.

اوضحت نتائج الدراسة زيادة معنوية في هرمون البايوكيميائية الغدة الدرقية TSH ونقصان في مستوى T3, T4 في مصل دم للجرذان ضمن مجموعة نقص الدراق المستحث وخلال فترات الحمل المختلفة بفارق معنوي  $P \leq 0.05$  مقارنة مع القيم

لمستوى هذه الهرمونات في مجموعة السيطرة، كما تم تحديد بعض الانزيمات التاكسدية GSH, MDA

اظهرت القيم زيادة في تركيزهما واطهرت القيم زيادة في تركيز هذين الانزيمين في مجموعة الجرذان ذات الدراق المستحث مقارنة مع تركيزهما في مصل الجرذان الحوامل لمجموعة السيطرة وخلال الفترات المختلفة.

تم في هذه الدراسة التعرف على التغيرات في التركيب النسيجي الدقيق للغدة الدرقية من الامهات الحوامل والاجنة بواسطة المجهر الالكتروني وبينت التغيرات وجود زغابات دقيقة عند السطح القمي للخلايا الحوصلية تباين اشكالها من زوائد خيطية، مقطعة، امتدادات مع اتساع الاعراف للشبكة الاندوبلازمية الخشنة، زيادة في اعداد الاجسام الحالة، وجود فجوات فارغة أكثر في سايتوبلازم الخلايا الحوصلية من تلك الفاتحة.

كما اوضحت المقاطع النسيجية من الغدة الدرقية للامهات والاجنة وجود زيادة في العضيات التنفسية، اجسام كولجي كمان الخلايا الحوصلية ذات انوية غير منتظمة، احتقان وتغلط الكروماتين مع وجود فضلات خلوية. واطهر الغشاء القاعدي زيادة في السمك مع امتداد حواجز لتفصل بين حوصلات الغدة الدرقية و اشارت الاشكال الى ترسب لاملاح اليود بشكل بلورات في معظم الخلايا الحوصلية.



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