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Relationship of induced thyroid gland disorders with fertility in cyclic female rats

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Abstract

The present study examines the association between thyroid disorders and reproductive fecundity in female rats. Three groups of 90 cyclic female rats were created (30 each). For 30 days and two estrus cycles, the control females were drenched with distilled water, the hypothyroidism females were drenched with methimazole solution (0.2 g/L D.W.), and the hyperthyroidism females were dampened with thyroxine solution (0.02 g/L D.W.) as well as gastric gavage of 200 µg/kg BW. Ten females from each group were dissected, and blood samples were taken at late proestrus to measure the serum levels of estradiol, progesterone, inhibin-B, and prolactin. The aromatase, in-α, and fecB gene expression levels were measured in ovarian tissues. The remaining ten females from each group were mated with males to study the fertility index. Body weight gain and ovarian weight were lower in the hypo- and hyper-groups than in the control group. Hypofemale rats had lower levels of serum E2, Inhibin-B, and P4, and ovarian inh-, aromatase, and fecB gene expression, whereas hyperfemale rats had higher levels of E2 and lower levels of inhibin-B, inh- α, and fecB gene expression. The number of delivered litters of hypo- and hyper-group female rats decreased significantly compared to controls. Histological examination of ovaries from hypo- and hyper groups showed a noticeable decline in folliculogenesis compared with control. In conclusion, thyroid disturbances (hypo- and hyperthyroidism) adversely affect the biosynthesis of reproductive hormones, follicular growth and development, and female reproductive fecundity.

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Introduction

Thyroid hormones (THs) have been shown to affect the molecular pathways that regulate ovulation, pregnancy maintenance, estrous cycle regulation, ovulation, sexual development, and maternal capability in several species (1). These effects are brought about by both the direct impact of THs on female reproductive processes and the indirect impact of THs' activity on the bioavailability of additional hormones and growth factors, both necessary for the optimum possible operation of female reproductive processes (2,3). Thyroid disorders may result in low fertility or infertility in different animals. Silva *et al.* (1) reviewed the effect of hypothyroidism and hyperthyroidism on the mechanisms by which thyroid hormones influence female reproduction. Thyroid hormones act on ovarian tissues in both direct and indirect ways, as they interact with numerous other hormones and growth factors, such as E_2, PRL, and IGFs, or through the hypothalamus-pituitary-gonadal axis by regulating the release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus (4-6). Additionally, they act directly through specific nuclear receptors that regulate the development and metabolism of the ovary (4). Infertility, delayed puberty, anovulation, the development of ovarian cysts, irregular estrus cycles, and other reproductive dysfunctions may occur in animals with hypothyroidism

(5,7). However, multiple experts have discovered a connection between primary and secondary female infertility and hyperthyroidism (4). Numerous studies have interconnected hyperthyroidism with the emergence of follicular atresia, ovarian cysts, and aberrant placental morphogenesis (5,8).

The current study aims to determine how thyroid conditions (hypothyroidism and hyperthyroidism) affect the production of reproductive hormones, the growth and development of follicles, and reproductive productivity in cycling female rats.

Materials and methods

Ethical approval

The current study was performed according to the ethics and policies guidelines of the University of Al-Qadisiyah.

Experimental animals

Cyclic female rats were housed in the animal house under controlled temperature (22-23 °C), 12 hours of darkness to 12 hours of light, and feeding ad labium circumstances. They were 75-80 days old and weighed an average of 155±5 g. The females were housed for three to four estrous cycles in groups of five in each cage.

Induction of hypothyroidism

Thirty cyclic female rats were supplemented with methimazole solution 0.2 g/L for 30 days (9). Hypothyroidism was confirmed by assessment of serum T3 and T4 levels.

Induction of hyperthyroidism

Thyroxin 0.02 g/L and T4 200 g/kg BW were administered orally to 30 female cyclic rats for 30 days (9). Serum T3 and T4 levels were checked to confirm hyperthyroidism.

Experimental design

The current study was conducted per Al-Qadisiyah University's ethics and principles. In the investigation, 90 female cyclic rats were used. The females were divided into three equal groups, each with 30 female rats. Control group (C) thirty healthy cyclic females were continuously drenched with distilled water for two estrus cycles. Hypothyroidism group (Hypo) thirty women were continuously drenched with methimazole solution 0.2 g/L for two estrous cycles. Hyperthyroidism group (Hyper) thirty hyperthyroid females were continuously drenched with T4 0.02 g/L and gavage with T4 (200 µg/kg BW) for two estrous cycles. Ten females from each experimental group were anesthetized at the late proestrus phase of each estrous cycle using intraperitoneal injections of ketamine 90 mg/kg BW and xylazine 40 mg/kg BW. They were dissected, and venous blood samples were taken to determine E2, P4, inhibin-B, and PRL serum concentrations. Additionally, ovarian tissue samples were taken to measure the levels of fecB, inh-, and aromatase gene expression. The remaining ten females from each group were mated (1:2) with fertile males to determine the fertility index.

Serum preparation

Blood samples were centrifuged at 5000 rpm for 10 minutes to separate the serum, which was then stored in Eppendorf tubes at -20°C for hormone analysis (10).

Hormonal assay

The ELISA technique was performed to assess serum concentrations of E2, P4, inhibin-B, and PRL, according to the instructions described by the manufacturer (Ltd. Com, China, and Shanghai Biological Co. Ltd., China).

Extraction of total RNA

Total RNA was isolated from the ovarian tissues of female rats using the TRIzol® reagent kit (according to the instructions of Bioneer Co., Korea).

Assessment of the quantity and purity of extracted RNA

The amount of extracted RNA was assessed using a Nanodrop spectrophotometer (THERMO, USA), whereas the RNA concentration (ng/µL) and purity were determined in the extracted RNA (Promega, USA).

DNase I treatment

The DNase I enzyme kit (Promega, USA) was used to remove trace amounts of genomic DNA from the extracted RNA.

cDNA synthesis

DNase-I-treated RNA was used in the cDNA synthesis stage using the AccuPower® RocktScript RT PreMix kit (Bioneer company, Korea).

Quantitative Real-Time PCR (qRT-PCR) master mix preparation

To perform qRT-PCR master mix depending on SYBER Green dye to determine the gene amplification in Real-Time PCR equipment, AccuPowerTM Green Star Real-Time PCR kit was used (Bioneer Company, Korea).

The analysis of the qRT-PCR data

Fold change (the level of gene amplifications) was determined using the ΔCT Livak method to examine the data of qRT-PCR for housekeeping and studied genes (11).

Histological study

Histological sections have been prepared according to Luna (12).

Statistical Analysis

Data was statistically analyzed using GraphPad Prism Version 5. (SAS Institute, Inc., USA). The mean and standard deviation were used to express the results. Newman-Keuls (12) and one-way ANOVA were used to determine the differences in means that were statistically significant. $P<0.05$ is considered necessary (13).

Results

Body weight gain

The results of body weight gain, as clarified in Table 1, showed no significant difference between the hypothyroid and hyperthyroid groups, but they showed a critical ($P<0.05$) decline compared to the control group. When comparing the two estrous cycles, there was no significant difference in body weight gain between the hypo and hyper groups. Still, the control group showed a significant ($P<0.05$) increase at the second estrous cycle compared to the first.

Ovarian weight (mg/100g BW)

In contrast to the control group, female rats in the Hypo and Hyper groups had relative ovarian weights that were lower during both estrous cycles; however, there was no statistically significant difference between the two groups ($P>0.05$). The results did not reveal any statistically significant differences ($P>0.05$) between the two estrous cycles for all groups (Table 1).

Serum estradiol (E_2) concentration

According to table 2, the serum concentration of E2 significantly increased ($P<0.05$) in the Hyper group and significantly decreased ($P<0.05$) in the Hypo group as compared to the control group. The two estrous cycles in each group did not differ, especially ($P>0.05$).

Serum Inhibin-B (Inh-B) concentration

The serum Inhibin-B levels in the hypo- and hyper-groups were significantly lower than in the control (Table 2). On the other hand, there were insignificant changes in the serum Inh-B concentration between the two estrous cycles for any group.

Serum progesterone (P_4) concentration

As illustrated in table 2, female rats in the Hypo group had considerably lower ($P<0.05$) serum progesterone concentrations than the control and Hyper group, which did not differ significantly from one another. On the other hand, there were no differences between the two estrous cycles for each group that were statistically insignificant.

Ovarian in-α gene expression level

In the ovarian tissues of Hypo and Hyper female rats, the in-gene expression level revealed a significant decline in contrast to the control, which showed no significant differences between them ((Figure 1). No differences between the two estrous cycles for each group were discernible.

Table 1: Body weight and relative ovarian weight in euthyroid, hypothyroid, and hyperthyroid cyclic female rats after 30 days and two estrous treatment cycles

Parameter	Period	Groups		
		Control	Hypo	Hyper
Body weight gain (g)	1st estrus cycle	6.45±1.06 ^{aB}	0.62±0.051 ^{bA}	0.49±0.036 ^{bA}
	2nd estrus cycle	8.12±1.47 ^{aA}	0.48±0.055 ^{bA}	0.42±0.038 ^{bA}
Ovarian weight (g/100g bw)	1st estrus cycle	9.14±1.22 ^{aA}	6.35±1.09 ^{bA}	5.88±0.86 ^{bA}
	2nd estrus cycle	8.76±1.15 ^{aA}	5.58±0.97 ^{bA}	6.18±1.06 ^{bA}

Values indicate Mean S.D. Small letters indicate a significant difference ($P<0.05$) across groups. Different capital letters demonstrate considerable difference ($P<0.05$) in the estrous cycles for each group.

Table 2: Serum concentrations in euthyroid, hypothyroid, and hyperthyroid cyclic female rats after 30 days and two estrous treatment cycles

Parameter	Period	Groups		
		Control	Hypo	Hyper
Estradiol (ng/L)	1st estrus cycle	22.14±2.07 ^{bA}	8.53±1.91 ^{cA}	38.31±4.71 ^{aA}
	2nd estrus cycle	23.33±3.38 ^{bA}	9.47±1.76 ^{cA}	34.06±3.87 ^{aA}
Inh-B (ng/L)	1st estrus cycle	27.99±3.84 ^{aA}	8.9±1.24 ^{bA}	9.5±1.06 ^{bA}
	2nd estrus cycle	29.9±4.97 ^{aA}	9.6±1.15 ^{bA}	8.3±1.21 ^{bA}
Progesterone (pmol/L)	1st estrus cycle	121.50±14.89 ^{aA}	113.78±18.41 ^{bA}	120.01±20.29 ^{aA}
	2nd estrus cycle	121.82±20.27 ^{aA}	114.26±17.39 ^{bA}	121.00±18.22 ^{aA}

Values indicate Mean±S.D. Small letters indicate a significant difference ($P<0.05$) across groups. Different capital letters indicate significant differences ($P<0.05$) in the estrous cycles for each group.

Aromatase gene expression level

The ovarian aromatase gene's expression level significantly increased (P<0.05) in the Hyper group and decreased (P<0.05) considerably in the Hypo group when compared to the control (Figure 1). Each group's two estrous cycles did not differ from one another.

Fecβ gene expression level

Figure 1 showed that ovarian fecβ gene expression was decreased (P<0.05) in the Hypo and Hyper groups compared to the female control rats. However, no statistical variations existed between the two estrous cycles for the groups.

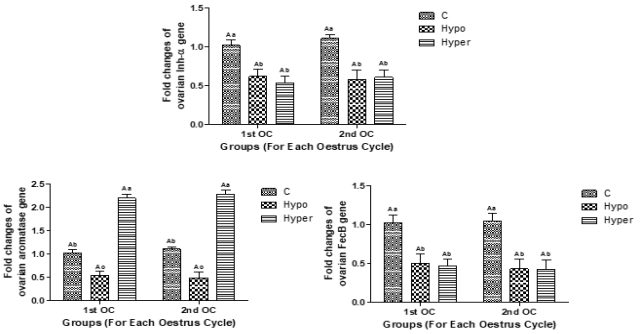

Figure 1: Ovarian in-α, aromatase, and fecB genes in euthyroid, hypothyroid, and hyperthyroid cyclic female rats after 30 days and two estrous treatment cycles. Values indicate Mean S.D. Small letters indicate a significant difference (P<0.05) across groups. Different capital letters indicate significant differences (P<0.05) in the estrous cycles for each group.

Litter number per dam

Female rats in the Hypo and Hyper groups have considerably fewer (P<0.05) delivered litters than control female rats. However, there were no significant differences (P>0.05) between them (Figure 2).

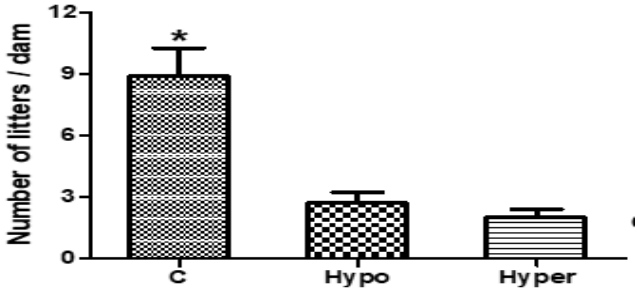

Figure 2: Number of delivered litters in euthyroid, hypothyroid, and hyperthyroid cyclic female rats after 30 days and two estrous treatment cycles. Values indicate Mean S.D. Star denotes significant differences (P<0.05) between the groups.

Histophysiological changes of the ovaries

Female rats in the Hypo and Hyper groups had reduced folliculogenesis in their ovarian tissues compared to the control group, with particular retardation in the granulosa cells, primary and secondary follicles, but primarily intact oocytes and cortical tissue surrounded by stroma. Regular follicular layers, secondary follicle layers, theca interna, zona granulose, antrum, zona pellucid, and oocyte was visible in control female rats. Additionally, the overall number of atretic follicles was higher in the ovarian tissues of the hypo and hyper groups than in the rule (Figure 3).

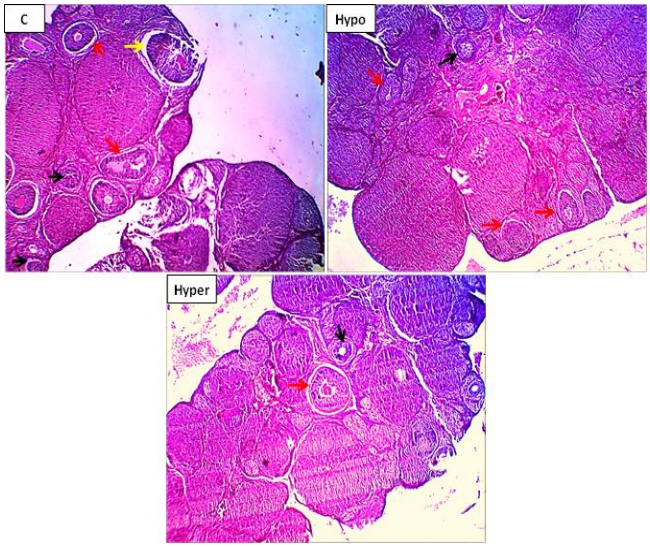

Figure 3: Histological sections were obtained from female rat's ovaries at the late proestrus stage. C: The control female rat's ovary shows normal proliferative ovarian follicles of different stages: primary (black arrow), secondary (red arrow), and mature (yellow arrow). Hypo and Hyper groups: hypothyroid and hyperthyroid female rat's ovaries show an obvious decline in ovarian follicular proliferation and a decreased number of primary (black arrow), secondary (red arrow), and mature (yellow arrow) follicles. H&E. X200.

Discussion

The current study aims to ascertain how thyroid disorders affect female rat reproduction, including hypothyroidism and hyperthyroidism. Thyroid hormone disturbances frequently affect the majority of internal functions, including those of the reproductive system, as it is recognized that these hormones have direct or indirect roles in regulating metabolic processes and energy production inside the body (14). The Hypo and Hyper groups may have experienced modifications to various physiological processes, including growth, differentiation, and the metabolism of lipids, proteins, and carbohydrates. The significant decrease in body weight gain in the Hypo and Hyper groups could be

attributed to various physiological processes, including growth, differentiation, and the metabolism of lipids, proteins, and carbohydrates.

Basal metabolic rate (BMR) and thyroid hormone levels are positively correlated, and as BMR is negatively correlated with energy balance, a high BMR may result in a negative energy balance and weight loss (15). Unlike the control females, the female rats did not gain the anticipated weight due to decreased metabolic rates. The overactive thyroid hormones that cause hyperthyroidism increase BMR. Still, the group's slower rate of weight gain suggests that there may be an imbalance in the metabolic processes that leads to obesity. This may be because there are more fatty tissues than muscles (15).

The retardation of ovarian weights, recorded in this investigation's hypothyroid and hyperthyroid groups, could be attributed to disturbances in the growth and development of ovarian tissue, as this required the influence of thyroid gland function (16). Thyroid dysfunction (hypothyroidism and thyrotoxicosis) may delay ovarian folliculogenesis because thyroid hormones stimulate the metabolic processes and energy production in ovarian tissue cells, which also influence the growth and differentiation of ovarian tissues (14). It might also be explained by the inhibition of pituitary gland production by gonadotropin or indirectly by a rise in PRL (17).

Both female rats with hyperthyroidism and hypothyroidism show significant alterations in the levels of reproductive hormones due to the current investigation, including a reduction in E2 and P4 levels. The production of E2 and P4, as well as ovarian oogenesis, folliculogenesis, and steroidogenesis, were all adversely impacted by this reduction (18). These may have suppressed FSH's ability to stimulate aromatase activity in granulosa cells (19), which would have prevented estrogen production and ovulation. Additionally, Hapon *et al.* (20) identified differences in the levels of reproductive hormones in female short-term hypothyroid cycling rats, which they linked to a reduction in estrogen receptor and cyp19A1 aromatase expression levels during the estrus phase (16).

Some studies have shown that the administration of high doses of thyroid hormones inhibits ovarian functions, which in turn affects granulosa cell proliferation and production of reproductive steroids (18). As a result, increased androstenedione to estrone conversion during steroidogenesis causes elevated plasma estradiol levels in hyperthyroid females. Thus, estradiol and progesterone serum levels were shown to be lower, and ovarian folliculogenesis was reduced in hyperthyroid female rats. However, a confirmed finding showed that excess thyroid hormones were responsible for suppressing ovulation and inhibiting FSH's ability to activate the granulosa cell's aromatase enzyme (19).

It is important to note that in the current study, serum inhibin-B concentrations were significantly lower in female rats with both hyperthyroidism and hypothyroidism. This decline may have coincided with the drop in FSH levels in the serum. Additionally, the study found that both females with hypothyroidism and those with hyperthyroidism had a significantly reduced rate of ovarian follicular development. Since the granulosa cells produce inhibins and any drop in their mitotic activity results in a decrease in the production of ovarian inhibins (21,22), which is reflected in their concentration in the blood, this seems to be accepted. This was supported by molecular analysis, which revealed a decrease in the expression of the inhibin-α subunit gene in hypothyroid and hyperthyroid female ovarian tissues.

The decreased expression of the fecB gene in hypothyroid and hyperthyroid female rats coincided with the deterioration of follicular development shown by histological sections in both groups, in addition to a decrease in fertility index in both groups, indicating a positive relationship between the expression level of the ovarian fecB gene and ovarian follicular development in the current study. Additionally, both groups' levels of FSH decreased along with the results above. This can be a result of a positive outcome. This might result from the gene's ability to make granulosa and theca cells more sensitive to FSH and LH, particularly during the pre-ovulatory stage (23).

Thyroid hormonal disruption is the cause of the decreased number of hypothyroid and hyperthyroid female rat litters (14). In animal models, it has been shown that hypothyroidism and infertility are related. However, no research has been done on the consequences of artificially generated hyperthyroidism on cyclic female rats and its effect on ovarian histological abnormalities, even though the link between hyperthyroidism and infertility is proven (4). Hypothyroidism may influence fertility by altering the peripheral metabolism of estrogen and raising the PRL level, which in turn causes the hypothalamic GnRH production to be suppressed and the release of pituitary gonadotropins to be inhibited (24).

The disturbed fluctuations of estradiol and progesterone due to hyperthyroidism may cause disturbances not only in the estrous cycle but also in the retardation of uterine development because estradiol and progesterone play a vital role in the preparation of the uterus for embryo implantation by inducing the uterine layers' proliferation and differentiation (25). Therefore, granulose cell suppression of ovarian estradiol and progesterone release may cause poor reproductive results in hyperthyroid female rats (26).

Normal ovarian follicular cell proliferation is necessary for normal reproductive processes (27). Since the animals were mature and cyclic, corpora lutea and ovarian follicles of various sizes could be seen in the histological sections of female rats with hypothyroidism and hyperthyroidism before the treatments. Thyroid hormone disruptions may cause the current fall in folliculogenesis, decreased ovarian follicles, and increased atretic follicles in hypothyroid and hyperthyroid female rats. Thyroid hormone indirectly

regulates folliculogenesis through the pituitary-ovarian axis (28).

The increased plasma and ovarian MDA levels may be responsible for the ovarian damage seen in hypothyroid female rats (29). The ovaries of hyperthyroid female rats showed growth retardation and a reduction in the number of follicles. This might be explained by the ovary's inflammatory and apoptotic effects. Wei *et al.* (30) reported an alteration in the antioxidant status in hyperthyroid female rat's ovaries through elevated nitric oxide synthase and accelerating the signaling pathway of ovarian nitric oxide production. The results above suggest that the current result is due to the defect in the oxidant-antioxidant status due to hyperthyroidism via elevating ovarian metabolite contents and the activities of ovarian enzymatic antioxidants.

According to the current histological investigation, certain developing follicles in hyperthyroid female rats' ovaries showed degenerative alterations, lysis of primary oocytes in others, and degeneration of granulosa cells. These findings are consistent with other studies. These alterations could be linked to the inflammatory effects of severe hyperthyroidism and elevated levels of cytokines and IGF-1 (30,31). These excessive hyperthyroidism-related activities may lessen ovarian proliferation and aggravate inflammatory reactions.

Conclusion

In conclusion, the production of reproductive hormones, follicular growth and development, and female reproductive fertility are negatively affected by thyroid disturbances (including hypo- and hyperthyroidism).

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Conflict of interest

There is no conflict of interest.

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العلاقة بين اضطرابات الغدة الدرقية وخصوبة إناث الجرذان

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فرع الفسلجة والأدوية والكيمياء الحياتية، كلية الطب البيطري، جامعة القادسية، الديوانية، العراق

الخلاصة

تهدف الدراسة الحالية إلى معرفة العلاقة بين اضطرابات الغدة الدرقية المستحثة تجريبيا والخصوبة التناسلية لإناث الجرذان. تم إنشاء ثلاث مجموعات من ٩٠ أنثى دورية (٣٠ لكل منها). لمدة ٣٠ يومًا ودورتي شبق، تم تجريع إناث مجموعة السيطرة بالماء المقطر، وإعطاء إناث مجموعة قصور الدرقية محلول ميثيمازول مع ماء الشرب (٠,٢ غم / لتر ماء)، وإعطاء إناث مجموعة فرط الدرقية محلول الثايروكسين مع ماء الشرب (٠,٠٢ جم / لتر ماء) إضافة الى تجريعها الثايروكسين (٢٠٠ ميكروجرام / كجم من وزن الجسم). تم تشريح عشر إناث من كل مجموعة، وأخذت منها عينات دم في نهاية طور قبل الشبق لقياس مستويات الإستراديول والبروجسترون والإنهيبين-ب والبرولاكتين في مصل الدم. تم قياس مستويات التعبير الجيني لكل من *aromatase* و *Inh-α* و *fecB* في أنسجة المبيض. تمت مزاوجة الإناث العشر المتبقية من كل مجموعة مع الذكور لدراسة مؤشر الخصوبة. كان معدل الزيادة الوزنية ووزن المبيض أقل في المجموعتين المعاملتين بالمقارنة مع السيطرة. عانت مجموعة قصور الدرقية من انخفاض مستويات الاستروجين والإنهيبين-ب والبرولاكتين، مع انخفاض مستوى تعبير جينات *Inh-α* و *aromatase* و *fecB* في المبيض، في حين كان لدى إناث مجموعة فرط الدرقية مستويات أعلى من الاستروجين ومستويات تعبير أقل من جينات *Inh-α* و *fecB* بالمقارنة مع السيطرة. عند المقارنة مع السيطرة، انخفض عدد مواليد إناث مجموعتي قصور وفرط الدرقية بشكل معنوي. أظهر الفحص النسيجي للمبايض لإناث مجموعتي قصور وفرط الدرقية انخفاضًا في تكوين الجريبات مقارنةً بمجموعة السيطرة. يستنتج أن اضطرابات الغدة الدرقية (قصور الغدة الدرقية وفرط الغدة الدرقية) تؤثر سلبًا على تصنيع الهرمونات التناسلية، ونمو الجريبات وتطورها، والخصوبة التناسلية للإناث.