Pathomorphological Features of The Ovaries in Infertile Women of Reproductive Age With Hypothyroidism

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Abstract: The present study revealed that morphological alterations in the ovaries of women with hypothyroidism were characterized by developmental retardation of all morphofunctional components. Changes included an altered ratio between the cortical and medullary layers, as well as a hypercellular pattern within ovarian follicles. These findings predominantly reflected enhanced proliferation of mesenchymal cells, accompanied by a reduction in both the size and number of epithelial cells. In addition, ovarian blood vessels demonstrated increased volume and branching, while the medullary layer exhibited a marked expansion of mesenchymal tissue. Collectively, these observations indicate the predominance of metabolic disturbances within the ovaries under hypothyroid conditions.

Keywords: hypothyroidism, ovarian hypoplasia, primordial follicle, atrophy.

Introduction

In recent years, female infertility has become one of the most significant medical and social challenges in global healthcare. Numerous clinical studies have demonstrated that endocrine disorders, particularly thyroid dysfunction, negatively affect reproductive function in women of reproductive age (Poppe & Velkeniers, 2016; Unuane et al., 2011) [1].

Hypothyroidism and subclinical hypothyroidism are common among infertile women and have been associated with ovulatory dysfunction, luteal phase deficiency, and reduced chances of achieving pregnancy (Poppe & Velkeniers, 2016). Thyroid hormones play a crucial role in regulating the hypothalamic– pituitary–ovarian axis, and their deficiency leads to alterations in gonadotropin secretion and disruption of the estrogen–progesterone balance (Krassas, 2000). Under hypothyroid conditions, impairment of these neuroendocrine regulatory

mechanisms results in diminished ovulatory activity, disrupted folliculogenesis, and various forms of menstrual dysfunction (Silva et al., 2018) [2].

Recent studies have demonstrated that thyroid hormones exert not only central but also local effects on ovarian function. The expression of thyroid hormone receptors in ovarian tissues and the presence of a local deiodinase system indicate that hypothyroidism directly influences the morphofunctional state of the ovaries (Silva et al., 2018). These alterations may manifest as impaired follicular growth, increased apoptosis, and a decline in ovarian reserve (Silva et al., 2018) [3].

Particular attention has been directed toward thyroid autoimmunity, as autoimmune thyroiditis may adversely affect reproductive function even when thyroid hormone levels remain within the normal range (Unuane, Velkeniers, & Poppe, 2006). The detection of thyroid autoantibodies within the ovarian follicular environment suggests their potential direct detrimental effects on granulosa cell function (Monteleone et al., 2011). The “ovarian follicle hypothesis” provides an immunological and morphological explanation for the pathogenic relationship between thyroid autoimmunity and infertility (Monteleone et al., 2011).

It is well established that follicular growth and atresia are regulated by a balance between cellular proliferation and apoptosis, processes that are significantly influenced by hormonal and immunological factors (Zhang et al., 2006). Under hypothyroid conditions, disruption of these cellular mechanisms may accelerate follicular atresia. However, the pathomorphological and immunohistochemical characteristics of these processes in human ovaries remain insufficiently investigated (Zhang et al., 2006) [4].

The ovary is considered an immunologically active organ, where local immune cells and cytokines play critical roles in folliculogenesis and ovulation (Bukovsky & Caudle, 2008). Nevertheless, the specific pathomorphological and immunohistochemical manifestations of ovarian immune responses in the context of hypothyroidism and thyroid autoimmunity have not yet been fully elucidated (Bukovsky & Caudle, 2008; Mintziori et al., 2012).

Therefore, a comprehensive investigation of the pathomorphological and immunohistochemical changes in the ovaries of infertile women of reproductive age with hypothyroidism—including the assessment of cellular proliferation, apoptosis, hormone receptor expression, and immunological markers—is of considerable scientific and practical importance. The findings of such research may contribute to the optimization of therapeutic strategies for infertility associated with thyroid dysfunction [5].

Aim of the Study

To comprehensively investigate the pathomorphological alterations of the ovaries in infertile women of reproductive age with hypothyroidism.

Materials and Methods

The present study was conducted using clinical-morphological, immunohistochemical, and analytical research methods. The study included the analysis of materials obtained from infertile women of reproductive age diagnosed with hypothyroidism [6-8].

The research consisted of two stages and involved a total of 120 patients. During the first stage, retrospective data from 60 patients were analyzed. The retrospective assessment included clinical and endocrinological records, laboratory findings (including thyroid hormone profiles), histological specimens of ovarian tissues obtained during surgical procedures, and available pathomorphological reports. At this stage, the relationship between clinical parameters and morphological alterations was evaluated [9-11].

Results and Discussion

Morphological alterations of the female reproductive organs under hypothyroid conditions indicate a generalized slowing of metabolic processes and delayed normal development, resulting in systemic hypoplasia of the reproductive system. In ovarian tissue, which is predominantly composed of highly labile cellular elements, hypothyroidism was associated with a marked reduction in follicular stimulation. Furthermore, germ cells arrested at the oogonial stage during intrauterine development demonstrated a decrease in number, size, and quality, frequently persisting in the form of residual reduction bodies [12].

These changes were accompanied by increased proliferative activity of mesenchymal cells within the ovarian stroma, reduction in the mass of both the corpus luteum and corpus albicans, a substantial decrease in primordial follicles, and the development of atrophic alterations [13].

Morphological examination revealed that the functional regions of both the cortical and medullary layers of the ovary are composed of highly labile cell populations, including surface mesothelial cells, epithelial cells, theca cells, luteinized granulosa cells, epithelial cords, and related cellular structures. Under normal physiological conditions, these cellular elements possess a continuous regenerative capacity. However, hypothyroidism adversely affects these regenerative processes.

Under hypothyroid conditions, ovarian hypoplasia was characterized by disruption of the normal arrangement of epithelial cells forming primordial follicles, accumulation of myxoid substances rich in neutral mucopolysaccharides, and a marked reduction in cellular density despite the absence of

significant changes in overall ovarian size. These findings indicate developmental delay and structural immaturity of ovarian tissue [14-16].

Small-caliber blood vessels located around the corpus luteum within both the cortical and medullary layers demonstrated signs of vascular congestion.

Accumulation of mucopolysaccharides within the interstitial tissue, increased oncotic pressure in the extracellular matrix, and enhanced tissue hydrophilicity promoted the extravasation of intravascular fluid into surrounding tissues (see Figure 1).

Although no pronounced structural abnormalities were observed in the ovarian venous vessels, persistent venous congestion, thickening of vascular walls, and developing interstitial edema around the vessels were frequently identified. The relatively small size of theca cells, enlargement of the corpus luteum, and disruption of the normal sequence of oocyte differentiation were indicative of developmental hypoplasia [17].

The cortical layer of the ovary was generally characterized by uniform thickness along its perimeter, suggesting that the developmental delay associated with hypothyroidism occurred in a diffuse manner. The outer ovarian surface was lined by a single layer of epithelial cells exhibiting cellular swelling and pale-staining cytoplasm. Follicular cells demonstrated irregular hydropic degeneration, while numerous atretic bodies were observed surrounding the corpus albicans.

These morphological findings indicate impaired transformation of primordial follicles into oocytes and secondary or tertiary follicles. In addition, the surrounding follicular cells exhibited signs of hydropic degeneration, reflecting disturbances in folliculogenesis and ovarian maturation associated with hypothyroidism.

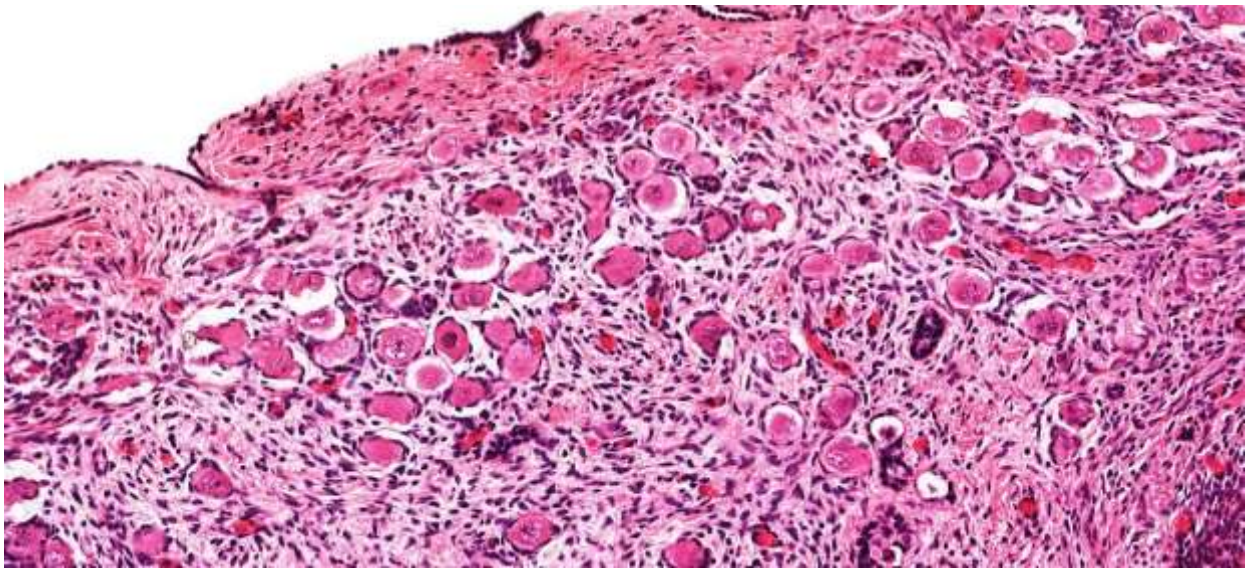

Figure 1. Microscopic view of the ovary against the background of hypothyroidism.

The boundaries between the cortical and medullary layers of the ovary were poorly differentiated and predominantly composed of immature primordial follicles. The central regions of the primordial follicles located within the ovarian cortex exhibited

a pale pink staining pattern, while interstitial edema was observed in the surrounding areas. Hematoxylin and eosin (H&E) staining; magnification ×40 (4×10).

The ovarian mesenchyma demonstrated marked interstitial edema accompanied by hydropic degeneration of epithelial cells. Accumulation of intensely eosinophilic mucopolysaccharides was observed between the theca cells, together with stromal swelling and vascular congestion. These

morphological alterations indicate significant disturbances in metabolic processes within the ovarian tissue [18].

The developing germ cells were characterized by incomplete maturation, accompanied by interstitial edema and the presence of loosely organized connective tissue surrounding the immature cellular structures. In addition, pseudofollicular formations were frequently identified. These structures were predominantly filled with serous fluid, resulting in the formation of cystic cavities.

Within the medullary region of the ovary, no significant alterations in the size of the corpus luteum were observed. However, primary and secondary follicles surrounding the corpus luteum remained underdeveloped, while the majority of follicles were represented by atretic bodies. Vascular congestion persisted in both the cortical and medullary layers of the ovary [19].

Perivascular edema was also evident and, as previously noted, may be attributed to the accumulation of neutral mucopolysaccharides and the resulting increase in tissue hydrophilicity. These changes promote the movement of plasma fluid from the vascular lumen into the extracellular matrix due to differences in oncotic pressure, leading to pronounced interstitial fluid accumulation (see Figure 2).

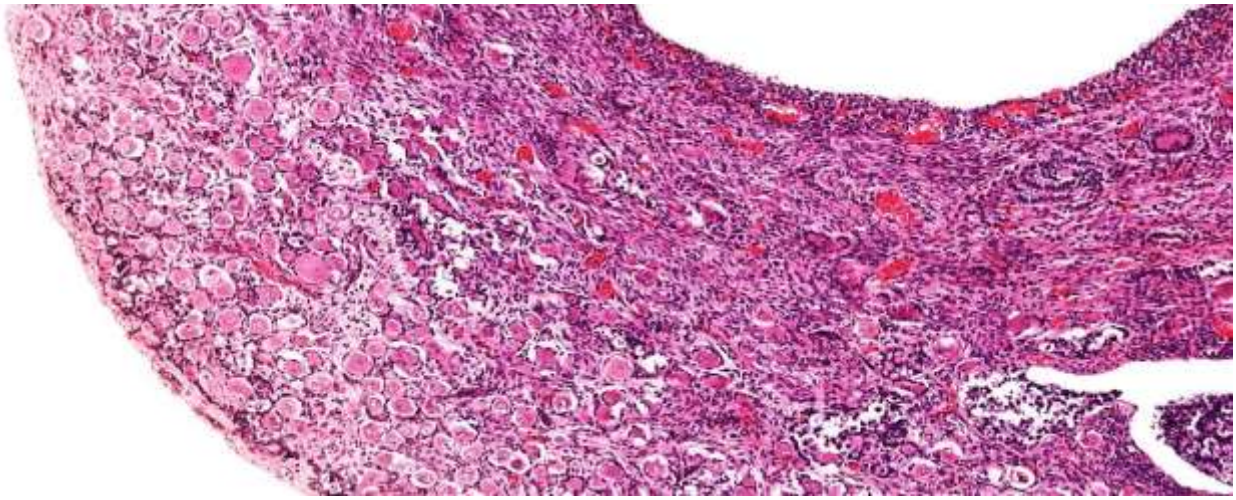

Figure 2.

Morphological structure of the ovary against the background of hypothyroidism.

The boundaries of the medullary layer of the ovary are unclear. Signs of congestion are detected in the blood vessels of the medullary layer (1), and edema has formed in the perivascular areas (2). The center of the premordial follicles in the cortical

region is light pink, and intermediate tumors are formed around them. Paint G.E. Size 4x10.

The majority of oocytes in the premordial zone are small and irregular in shape and size, and the epithelial cell nuclei that make up their structure are enlarged and relatively hyperchromic, while other oocytes in the surrounding area also change in the same way. The cytoplasm of most epithelial cells is opaque, with the appearance of reticular fibrous structures in the interstitium. Most follicles are deformed, oval in shape, and foci of metaplasia are identified in the squamous epithelium surrounding the oocyte [20].

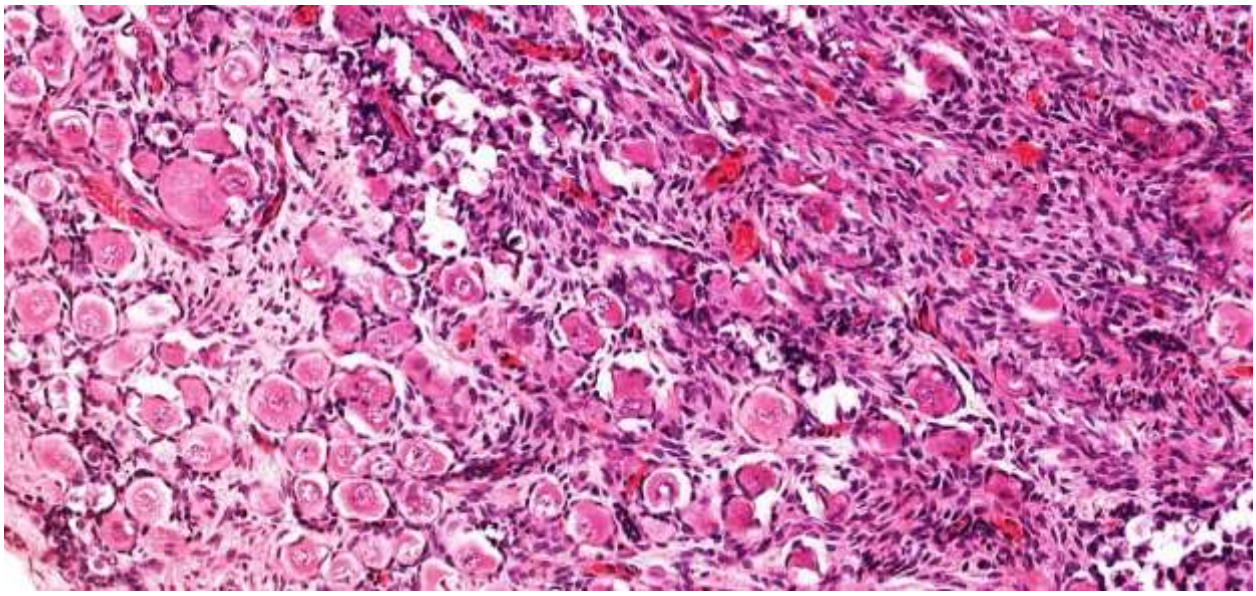

Figure 3.

Ovary against the background of hypothyroidism. The cortical area is light pink, and the center of the premordial follicles is light pink (1), with the formation of intermediate tumors around them. Paint G.E. Size 4x10.

It was found that the Teka cells surrounding the egg cells are small to medium in size. Various degrees of protein dystrophy are identified in the luteocytes of the yolk body areas of the ovary, and the formation of collagen fibrous structures in the stroma is established. It is characterized by immaturity of the white matter, signs of congestion in the interstitial vessels, and the presence of interstitial edema.

The majority of fibrous structures around the cells of the cortex and medullary layer of the ovary have a rough appearance, postnatal ontogenesis is manifested in the appearance of stroma covering due to the delay in the development of morphofunctional cells, to fill the naked and undeveloped parenchyma, an increase in stromal elemental rough fibers, fibroblasts and histiocytes [21].

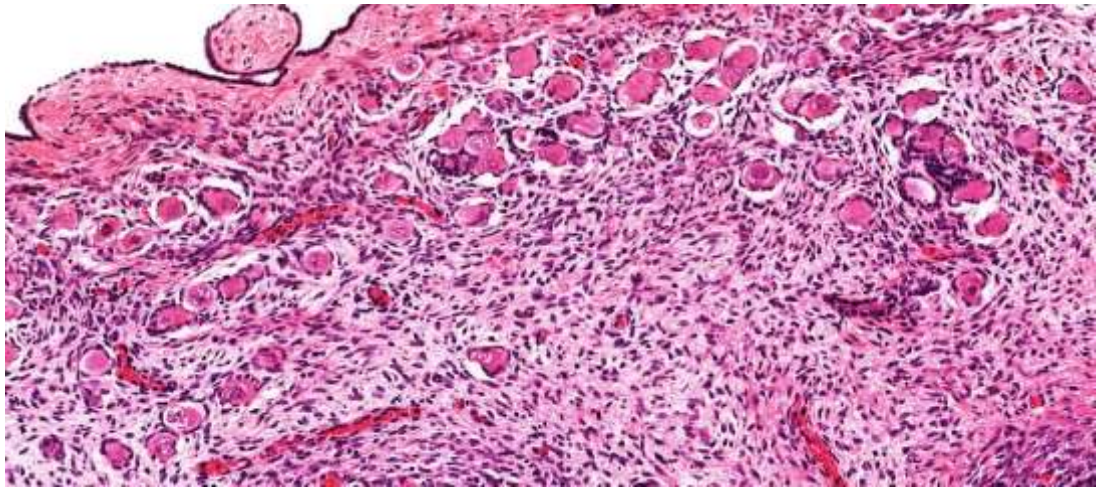

Figure 4. Ovary against the background of hypothyroidism. In the medullary layer, vascular congestion is developed (1), perivascular edema is identified around the vessels (2), a massive pale pink color of granulosa cells in the stroma, and

swelling of fibrous structures is identified (3). Paint G.E. Size 4x10.

A high prevalence of atretic follicles was observed in the ovaries, accompanied by hyperchromasia of the nuclei of primary follicles, a reduction in the number of nutritive structures surrounding the oocyte, and the appearance of predominantly chromophobic inclusions. The ovarian stroma demonstrated an increased abundance of fibrous connective tissue elements. This phenomenon may be attributed to reduced metabolic activity, enhanced collagen synthesis by fibroblasts, and the predominance of tissue hypoxia.

An increase in collagen and elastic fiber deposition within the ovarian stroma was identified, together with enhanced apoptotic activity in the theca and granulosa cells. In contrast, proliferative activity was predominantly observed in mesenchymal cell populations. As is well known, apoptosis in each cell type is regulated by a balance between specific inducers and inhibitors.

The findings of the present study demonstrated that hypothyroidism is associated with hypoplasia of morphofunctionally active ovarian cells, transformation of stromal elements into coarse fibrous structures, the appearance of a myxomatous stromal pattern, and a marked reduction in parenchymal cell populations.

The remaining parenchymal cells exhibited prominent atrophic changes. These alterations indicate a high probability of subsequent ovarian sclerosis and structural deformation.

Furthermore, within the ovarian medulla, only one or two incompletely developed follicles were identified per ×200 microscopic field. The theca cells and granulosa epithelial cells arranged concentrically around the follicles also demonstrated degenerative changes. These findings suggest impaired follicular stimulation and delayed postnatal ovarian development.

Along the perimeter of the ovarian cortex, the central structures of primordial follicles were often indistinct and exhibited a pale eosinophilic appearance. Traces of mucoid material were detected within the follicular cavities. The surrounding flattened epithelial and granulosa cells showed a significant decrease in both number and size. Blood vessels in these regions demonstrated persistent irregular vascular congestion, while most exhibited perivascular edema accompanied by pronounced interstitial swelling.

Following the primordial follicle stage, primary, secondary, and tertiary follicles failed to demonstrate the expected progressive increase in size. Morphologically, many follicles remained small and elongated toward the medullary layer. The structural components of tertiary follicles were incompletely developed, indicating delayed folliculogenesis compared with the ovaries of the age-matched control group.

Conclusions

1. Systemic Hypoplasia and Metabolic Disturbances

Under hypothyroid conditions, all morphofunctional components of the ovary exhibit delayed development. These alterations reflect systemic ovarian hypoplasia and suppression of tissue metabolic activity.

2. Stromal Remodeling and Sclerosis

Increased proliferative activity of mesenchymal cells and accumulation of coarse fibrous stromal structures were observed within the ovarian stroma. These changes may contribute to the future development of ovarian sclerosis and structural deformation.

3. Disruption of Folliculogenesis

Hypothyroidism is associated with atrophy of primordial follicles, increased numbers of atretic bodies, and failure of mature follicles to develop. These pathological processes are accompanied by hydropic degeneration and enhanced apoptosis of ovarian cells.

4. Hemodynamic and Extracellular Matrix Alterations

Persistent vascular congestion and perivascular edema were evident in ovarian tissues. Accumulation of mucopolysaccharides within the extracellular matrix increased oncotic pressure and promoted the

movement of fluid from blood vessels into the interstitial space, thereby contributing to tissue edema and impaired ovarian function.

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