

**INCIDENCE OF OVARIAN CYST IN HYPOTHYROIDISM: AN INSTITUTIONAL STUDY**Ramesan C<sup>1</sup>, Unnikrishnan E<sup>2</sup>, Firozbabu K<sup>3</sup><sup>1</sup>Associate Professor, Department of General Surgery, Government Medical College, Kozhikode.<sup>2</sup>Assistant Professor, Department of General Surgery, Government Medical College, Kozhikode.<sup>3</sup>Junior Resident, Department of General Surgery, Government Medical College, Kozhikode.

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**ABSTRACT**

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**BACKGROUND**

Primary hypothyroidism is the decrease in production and secretion of thyroid hormones by the thyroid gland. This is characterised by slackening of metabolism and leading to multiple system impairment. The important aetiological factors for primary hypothyroidism are congenital, iodine deficiency, autoimmune thyroiditis and iatrogenic.<sup>[1]</sup> Ovarian cysts are a common cause for gynaecological surgeries. The aetiology<sup>[2]</sup> of ovarian cysts can vary greatly including benign or malignant tumours, endometriosis and inflammation, etc. However, some cysts are direct result of endocrine disorders and do not require surgery. Hypothyroidism may cause reproductive and endocrinological disorders as well. The aetiopathogenesis is complex. In 1960 Van Wyk and Grumbach first described the relation between ovarian cyst and hypothyroidism. They proposed that there was a hormonal overlap in the pituitary feedback mechanism. It is due to the fact that TSH, GH, FSH and LH are all glycoproteins with a common alpha chain and may thus cross react. High TSH could produce FSH and LH like activity leading to luteinised ovarian cyst. The TRH may also act on pituitary cells to stimulate gonadotropin release and hence FSH and LH. Other postulated mechanisms are increased ovarian sensitivity to gonadotropins, altered metabolism of oestrogen, hypothalamopituitary dysfunction and altered prolactin metabolism.

**AIMS**

To study the percentage of ovarian cyst among the diagnosed cases of primary hypothyroidism and then to find out the association between hypothyroidism and ovarian cyst. To study the relation between level of TSH and size of ovarian cyst. To study the percentage of ovarian cyst among patients with TSH <50 mIU/L between 50-100 and >100 mIU/L separately.

**SETTINGS**

**Study Design: Descriptive:** Cross-sectional study.

**Duration:** One year.

**Period:** March 2013 to February 2014.

**Sample Size:** 100.

**Study Area:** Government Medical College, Calicut.

**INCLUSION CRITERIA**

Female patients of age more than 12 years presenting to Surgery/Medicine/Gynaecology OPD with clinical features of hypothyroidism and biochemical values of TSH >6.0 mIU/L.

**EXCLUSION CRITERIA**

Less than 12 years of age. Fully treated cases of hypothyroidism. Patients on hormonal therapy. Patients who are known cases of PCOS/FSH/LH/GH and GNRH abnormalities. Postmenopausal patients.

**PROCEDURE**

The patients presenting to Surgery/Medicine/Gynaecology Departments with clinical features of primary hypothyroidism and high serum TSH level (TSH>6 mIU/L) are evaluated with USG ABDOMEN AND PELVIS to detect ovarian cysts. After satisfying inclusion criteria, consent is taken and patients are included in the study and statistical analysis done.

**STATISTICAL METHOD**

SPSS 18 software for data analysis.

**RESULTS**

33% of the patients were detected to have various types of ovarian cysts like simple cyst, complex cyst and bilateral multicystic ovaries. Of these, majority was simple ovarian cyst and the complex cysts were seen only in 12% of the study group.

**CONCLUSION**

Most common clinical presentation of patients with primary hypothyroidism is lethargy/fatigue and simple ovarian cyst is the most common type of cyst occurring in association with primary hypothyroidism. The occurrence of ovarian cyst was significantly higher in those patients suffering from severe primary hypothyroidism (p value <0.005).

**KEYWORDS**

Ovarian Cyst, Hypothyroidism.

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**INTRODUCTION:** Primary hypothyroidism is the decrease in production and secretion of thyroid hormones by the thyroid gland. This is characterised by slackening of metabolism and leading to multiple system impairment. Prevalence of hypothyroidism is high in general population and the incidence is higher in females than males with a female-to-male ratio of 10:1.<sup>[3]</sup> The diagnosis and treatment of hypothyroidism is often considered simple and is often carried out in a primary care setting. The diagnosis of primary hypothyroidism is confirmed by the presence of elevated levels of Thyroid-Stimulating Hormone (TSH) and reduced Free Thyroxine (FT4) levels.<sup>[4]</sup> The common clinical features are tiredness, weight gain, dry skin, mild anaemia, cold intolerance, constipation, muscle weakness, puffiness around eyes and hoarseness of voice.<sup>[5]</sup> The important aetiological factors for primary hypothyroidism are congenital iodine deficiency, autoimmune thyroiditis and iatrogenic.<sup>[1]</sup>

Ovarian cysts are a common cause for gynaecological surgeries. Owing to the complexity of ovarian composition and function, the aetiology<sup>[2]</sup> of ovarian cysts can vary greatly including benign or malignant tumours, endometriosis and inflammation, etc. However, some cysts are direct result of endocrine disorders and do not require surgery. Hypothyroidism may cause reproductive and endocrinological disorders as well. Occasionally, concomitant ovarian cyst formation is reported as Van Wyk and Grumbach syndrome<sup>[6]</sup> in juvenile hypothyroidism. The ovarian enlargement could present as a large ovarian cyst or multicystic ovaries in young adults also.

Although, pathophysiology remains unclear, association of multicystic ovarian disease with hypothyroidism has been described in literature.<sup>[7-10]</sup> There is sizeable literature describing the association of ovarian cyst with severe primary hypothyroidism. Case reports published by Hedayati et al,<sup>[11]</sup> Akbay et al,<sup>[12]</sup> Dietrich et al,<sup>[13]</sup> Lussiana et al,<sup>[14]</sup> Edwards et al,<sup>[15]</sup> Borna et al<sup>[16]</sup> and Mousavi et al<sup>[17]</sup> are few among them. In all these case reports, the ovarian cyst was regressed on administration of thyroid hormone.

The aetiopathogenesis is complex. In 1960, Van Wyk and Grumbach first described the relation between ovarian cyst and hypothyroidism. They proposed that there was a hormonal overlap in the pituitary feedback mechanism. It is due to the fact that TSH, GH, FSH and LH are all glycoproteins with a common alpha chain and may thus cross react. High TSH could produce FSH and LH like activity leading to luteinised ovarian cyst. The TRH may also act on pituitary cells to stimulate gonadotropin release and hence FSH and LH.

Other postulated mechanisms are increased ovarian sensitivity to gonadotropins, altered metabolism of oestrogen, hypothalamopituitary dysfunction and altered prolactin metabolism. There are numerous case studies reporting the presence of ovarian cysts in patients with primary hypothyroidism. Some studies have reported regression of the ovarian cysts in young females with primary hypothyroidism on thyroid hormone supplementation. Jing Shu et al published the case study on a patient with ignored adult primary hypothyroidism presenting chiefly with persistent ovarian cysts.<sup>[18]</sup> They also provide an elaborate discussion on the possible pathophysiology of development of patients with primary hypothyroidism. TSH, FSH and their receptors have related structures. Extremely high concentrations of TSH in hypothyroidism maybe sufficient to cause the activation of FSHR. This provides a major potential mechanism for severe hypothyroidism resulting in ovarian hyperstimulation. They conclude that it is necessary to consider hypothyroidism and other endocrine disorders in the differential diagnosis of adult patients with ovarian multiple cyst formation in order to prevent inadvertent ovarian surgery.<sup>[18]</sup>

Prof. Rajiv R Mahendru<sup>[19]</sup> reported a case, which he claims to be apparently the first case of its kind in the medical literature where an 11-year-old prepubescent girl who had co-existent presence of hypothyroidism and multiple large ovarian cysts not only had remarkable improvement in her physical appearance with conservative management with L-thyroxine alone, but also had disappearance of her large ovarian cysts without the need of any surgical intervention, whatsoever. In a case study done by Harpreet Kour Isher et al,<sup>[20]</sup> they reported a 21-year-old unmarried female with large multicystic ovaries. On further evaluation, they found that the patient had severe hypothyroidism. On thyroxine supplementation for a period of 6 weeks, both the ovarian cysts had resolved completely and she attained normal menstrual cycles.

Roghieh Molaei Langroudi et al<sup>[21]</sup> reports a case of ovarian cyst regression with levothyroxine in ovarian hyperstimulation syndrome associated with hypothyroidism. A 15-year-old girl with classical features of hypothyroidism presented with abdominal distention and abdominal pain and was found to have enlarged ovaries with multiple thin walled cysts and mild ascitic fluid. She was diagnosed as ovarian hyperstimulation syndrome. She was started on levothyroxine and followed up with serial ultrasounds. A reduction in size of the ovaries was seen in 6 weeks' time and complete regression of the cysts occurred in 4 months' time. Sharma Y et al<sup>[22]</sup> studied the outcome in ten girls with ovarian cysts and hypothyroidism managed at their hospital with special emphasis on subsequent pubertal development and ovarian imaging. On long-term follow up after starting thyroxine, all patients had normal ovarian size in ultrasound evaluation with six girls progressing to normal puberty. The study emphasises the need to exclude hypothyroidism in young girls with ovarian cysts. In a case study done by Kubota K et al,<sup>[23]</sup> a 21-year-old female who presented with abdominal pain was found to have bilateral enlarged ovaries with multiple cysts.

Further evaluation revealed underlying hypothyroidism due to autoimmune thyroiditis. The cysts regressed on thyroid hormone supplementation thus emphasising the need to properly manage cases of coexistent ovarian cysts and hypothyroidism to prevent unnecessary surgical interventions. Pramila Darmshaktu et al<sup>[24]</sup> reports a case of large ovarian cyst in a 21-year-old woman regressing completely in 4 months after initiation of thyroxine therapy thus saving her from an elective laparotomy she was planned to undergo. This study is to find out the occurrence of ovarian cyst among patients with primary hypothyroidism in our settings so that the association of ovarian cyst with hypothyroidism can be established. Hence, recognising hypothyroidism as an aetiological factor for ovarian cyst could lead to avoidance of unnecessary oophorectomy at least in few cases. Whenever large ovarian cysts are detected in a young females, possibility of hypothyroidism should be considered and conservative management by thyroid hormone replacement can result in regression of cyst and thereby avoidance of unnecessary surgical intervention.

**MATERIALS AND METHODS:** This study was conducted on hundred female patients of age more than twelve years presented with clinical features of hypothyroidism and biochemical values of serum TSH more than 10 mIU/L in the Surgery and Medicine Outpatient Department of Government Medical College, Kozhikode, over a period of one year from March 2013 to February 2014. Those patients who satisfied the inclusion criteria were further evaluated with ultrasonogram of abdomen and pelvis to look for the presence of significant ovarian cyst (>3 cm). The size, side and other characteristics of the ovarian cyst were also assessed as a part of this study.

**RESULTS AND DISCUSSION:** Among the 100 female patients with primary hypothyroidism, the lowest and highest age recorded was 13 years and 48 years, respectively. Mean age of the study group was 31 years. The various clinical presentations of the patients with primary hypothyroidism were lethargy/fatigue, weight gain, cold intolerance, constipation, menstrual disturbance, muscle/joint pain, hair loss, skin changes, depression, pallor, non-pitting oedema and thyroid swelling. Out of the 100 patients with primary hypothyroidism, 66 patients presented with lethargy/fatigue, 51 patients had weight gain and 50 patients had menstrual disturbances. So, lethargy, weight gain and menstrual disturbances together constitute the most prevalent symptoms of primary hypothyroidism among the study group. In a study conducted by Pauden B et al<sup>[25]</sup> in residents of western region of Nepal, the most common symptom complained was lethargy (39%) followed by constipation (37%) and cold intolerance (34%). Considering the age wise distribution of the study group, 76 patients belong to the 3rd and 4th decade of life. In a study conducted by Rajkumar Yadav et al<sup>[26]</sup> in Nepal, majority of patients belong to 4th, 5th and 6th decades of life. Upon categorisation of the patients based on their serum TSH levels, it was found that majority of the patients (60%) had their serum TSH levels <50 mIU/L.

In the study group, 21% of patients had very high serum TSH levels (>100 mIU/L). On evaluation, 33% of the patients were detected to have various types of ovarian cysts like simple cyst, complex cyst and bilateral multicystic ovaries. Of these, majority was simple ovarian cyst and the complex cysts were seen only in 12% of the study group. On reviewing the literature, the exact prevalence of ovarian cyst is unclear due to the lack of consistent reporting and high likelihood of spontaneous resolution. In a cross-sectional study conducted by Christenson et al,<sup>[27]</sup> the prevalence of functional ovarian cyst was reported around 8%. Most US prevalence data indicate a range among the general population of 3% to 15%. But, a large European screening trial revealed 21.2% incidence of ovarian cyst among healthy postmenopausal women.

On considering the relationship between the serum TSH levels and the prevalence of the ovarian cyst, it was found that there was a significantly high occurrence of ovarian cysts in those patients with very high serum TSH levels (>100 mIU/L). In this study, 66.7% of the patients having serum TSH levels >100 mIU/L had ovarian cysts whereas only 21.2% of the patients having serum TSH levels <50 mIU/L had ovarian cysts. Here, in this study, the p value is significant, hence, it can be said that the young females with severe primary hypothyroidism is predisposed to develop ovarian cyst.

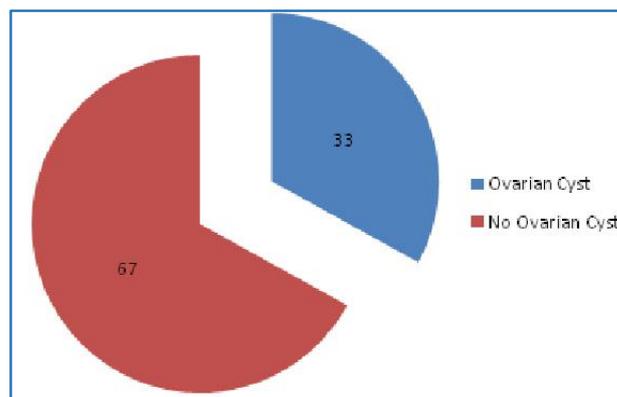
Though literature do not report any prevalence study of ovarian cyst in patients with primary hypothyroidism, many cases are reported from various parts of the world in which hypothyroidism is mentioned as the aetiological agent for the development of large ovarian cysts and multicystic ovarian masses. Van Wyk and Grumbach first described the combination of multicystic ovaries, juvenile hypothyroidism and precocious puberty in prepubertal and adolescent girls. Jing Shu et al,<sup>[18]</sup> Yama Shitha et al,<sup>[28]</sup> Taher BM et al,<sup>[29]</sup> Bassam T et al,<sup>[30]</sup> Kubota K et al<sup>[23]</sup> reported cases of large ovarian cyst in young adult patients with severe hypothyroidism, which regressed in size following thyroid hormone supplementation. It is reported that at times severe primary hypothyroidism can lead to spontaneous ovarian hyperstimulation due to high TSH values.

#### **There are several hypotheses about the ovarian cyst formation in severe hypothyroidism;**

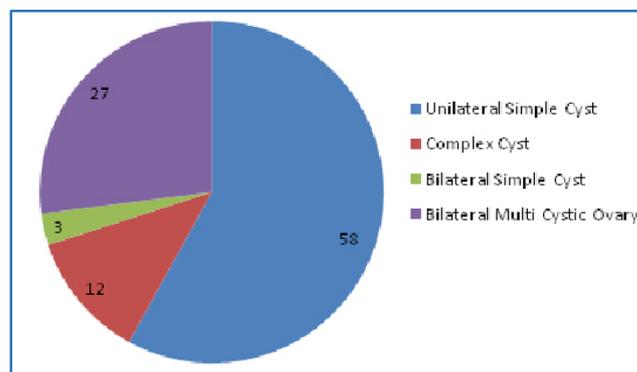
1. There is a hormonal overlap in the pituitary feedback mechanism due to the fact that TSH, GH, FSH and LH are all glycoprotein with common alpha chain and may thus cross react. So, high serum TSH can act like FSH and LH leading to luteinised ovarian cyst.<sup>[18]</sup>
2. A second possible mechanism maybe due to a change in pituitary gonadotropin level. It is suggested that an overlap effect in the negative feedback response occurs. So that, not only TSH, but also gonadotropins are stimulated by extremely high TRH and hence the remarkable high FSH can stimulate ovarian cyst formation.

3. A third possible mechanism has been hypothesised to be due to FSH receptor activating mutation permitting or amplifying the effect of TSH on the follicles.<sup>[13,14,27]</sup>
4. TSH may sensitise the ovaries to gonadotropin stimulation by stimulating the nuclear thyroid receptors in the granulosa cells thereby exacerbating the ovarian hyperstimulation.
5. Myxomatous type of infiltration might also account for the interference of steroidogenesis in the ovary and contribute to ovarian cyst formation.

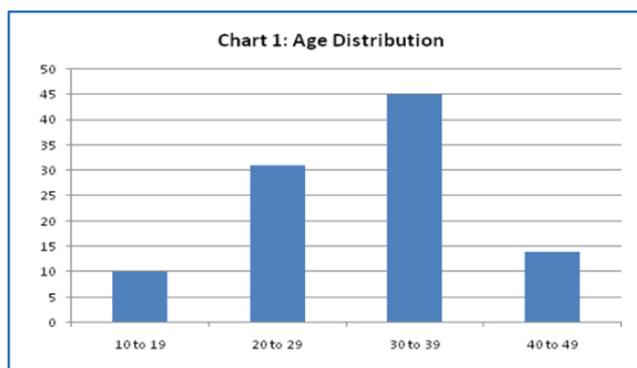
In this study, the occurrence of ovarian cysts among the patients with primary hypothyroidism was significantly (p value - 0.001) higher in those belonging to the second and third decades of their life. Available literature also supports this finding such that the cases reported are in the second and third decades of life.<sup>[28-30]</sup> In this study, on statistical analysis, it was found that there is no significant association between the size of the ovarian cysts and the serum TSH level (p value - 3.0). Ovarian cysts were found to be arising from the right ovary in 17 patients out of the 33 patients with ovarian cysts in this study. On literature review, sufficient data was not obtained enough to support this finding. Hence, this could be an incidental finding.



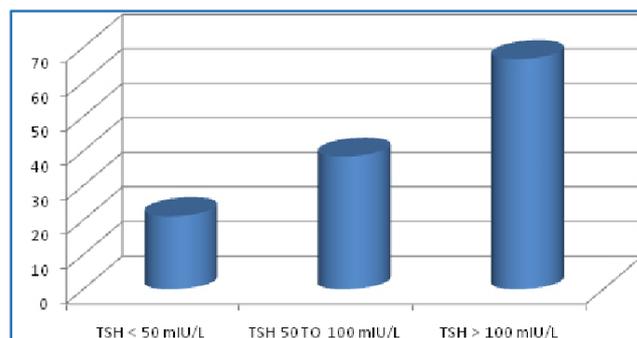
**Chart 3: Distribution of Ovarian Cyst**



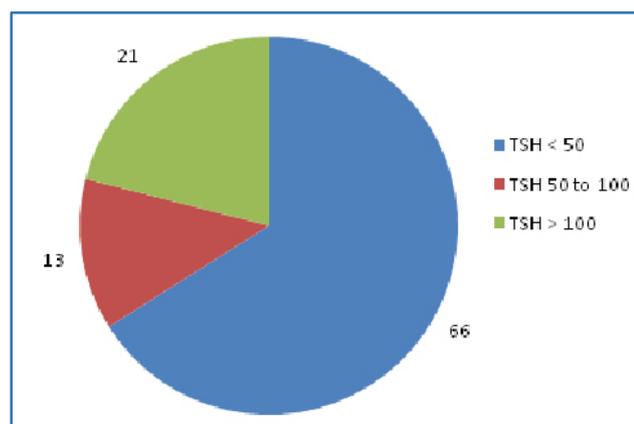
**Chart 4: Distribution of Various Types of Ovarian Cyst**



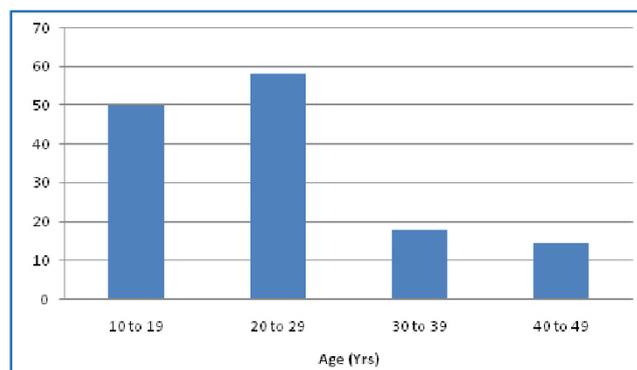
**Chart 1**



**Chart 5: Frequency of Ovarian Cyst in Relation with Serum TSH Value**



**Chart 2: Distribution of Patients Based on TSH Values**



**Chart 6: Age Wise Distribution of Ovarian Cyst**

**CONCLUSION:** This study is to find out the occurrence of ovarian cyst among patients with primary hypothyroidism in our settings so that the association of ovarian cyst with primary hypothyroidism can be established. Most of the study findings were consistent with the data available in the literature. It is observed that the most common clinical presentation of patients with primary hypothyroidism is lethargy/fatigue and simple ovarian cyst is the most common type of cyst occurring in association with primary hypothyroidism. The occurrence of ovarian cyst was significantly higher in those patients suffering from severe primary hypothyroidism (p value <0.005). Also, it is noticeable that among the patients with hypothyroidism, the young females belonging to their 2nd and 3rd decade of life had a significantly greater predilection for the development of ovarian cyst (p value <0.005).

Hence, recognising hypothyroidism as an aetiological factor for ovarian cyst could lead to avoidance of inadvertent oophorectomy at least in few cases. Whenever large ovarian cysts are detected in a young females, possibility of hypothyroidism should be considered and conservative management by thyroid hormone supplementation can result in regression of cyst and thereby avoidance of unnecessary surgical intervention. So, it is advisable to screen all young females with ovarian cyst for underlying primary hypothyroidism. In addition to the small sample size and limited ethnic and geographic coverage, this study had another limitation of being a cross-sectional study. Sufficient data was not available to substantiate the finding of greater predilection for the ovarian cysts to arise from the right ovary. Finally, since no long-term follow up has been undertaken, delayed onset of development of ovarian cysts and their consequences have not been covered in this study. Thus, this study opens a new arena of opportunities to carry out a lot of elaborate studies in this field. A larger comprehensive study also focusing on the response of ovarian cysts to thyroid hormone supplementation can be entertained so that the causality assessment can also be incorporated to make this study more specific.

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