

International Journal of Radiology and Diagnostic Imaging



E-ISSN: 2664-4444
P-ISSN: 2664-4436
www.radiologypaper.com
IJRDI 2024; 7(2): 20-28
Received: 17-01-2024
Accepted: 23-02-2024

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Cross-sectional study on the association of ovarian cysts and gall stones

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DOI: <https://doi.org/10.33545/26644436.2024.v7.i2a.379>

Abstract

Background and Introduction: Hypothyroidism is a common condition which causes numerous metabolic derangements. Based on the physiology of TSH and the thyroid hormones, it was hypothesized that there would be an association between hypothyroidism and ovarian cysts and /or gall stones. Ultrasound is a good imaging modality to accurately image both of these pathologies.

Methodology: Ultrasound-based cross-sectional study was conducted with 202 patients recruited from the endocrinology OPD of which half were controls. Their clinical details, data on comorbidities and results of their screening ultrasound were compiled and subjected to statistical analyses.

Results and Discussion: Age group of patients was 19 to 52 years. Hypothyroid patients had a slightly higher BMI and were more likely to complain of easy fatigability (p-value 0.001), constipation (p-value 0.003), weight gain (p-value 0.000), lethargy (p-value 0.041) and menstrual disturbances (p-value 0.002). There was a slight but statistically insignificant increase in the prevalence of diabetes, hypertension and dyslipidemia in hypothyroid patients. There was a statistically significant association of hypothyroidism with gall stones (p-value 0.004), fatty liver (p-value 0.023). And the occurrence of both ovarian cysts and gall stones (p-value 0.009). Slightly increased prevalence of ovarian cysts (p-value 0.138) and polycystic ovarian morphology (p-value 0.121) was seen but it failed to reach statistical significance.

Conclusion: Hypothyroidism has a significant association with cholelithiasis. The study also highlights the association of hypothyroidism with fatty liver and the co-occurrence of both ovarian cysts and gall stones. Recognizing the role that hypothyroidism has in these pathologies can change management and improve overall patient outcomes.

Keywords: Hypothyroidism, ovarian cysts, gall stones

Introduction

Hypothyroidism is characterized by a failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body ^[1]. Hypothyroidism is a common condition affecting up to 11% of females in India ^[2].

It has been hypothesized that abnormalities of thyroid hormone production are associated with gall stones. The mechanisms underlying this are likely related to alterations in lipid metabolism, cholesterol to bile salt ratio and biliary stasis with supersaturation ^[3, 4].

Similarly, hypothyroidism has been linked with the formation of ovarian cysts due to feedback increase in the production of TSH, which has FSH like action on the luteinised ovary, altered metabolism of estrogen, changes in the hypothalamo-pituitary axis and increased sensitivity of the ovaries to gonadotropins. All of these factors may predispose these individuals to develop ovarian cysts ^[5].

Abdominal sonography is the screening investigation of choice in patients with suspected cholelithiasis. Ultrasound is very sensitive in the detection of Cholelithiasis with sensitivity approaching 95-99% ^[6]. Similarly, ultrasound remains one of the best imaging modalities available to evaluate the pelvis. As regards to the utility of ultrasound in the detection of ovarian cysts, the RCOG guidelines state that "A pelvic ultrasound is the single most effective way of evaluating an ovarian mass" ^[7].

Ultrasound scores over the other imaging modalities for these pathologies as it is safe, cheap, widely available, does not have a steep learning curve, does not involve radiation exposure and is adequately sensitive to detect these pathologies ^[8].

Very few studies have been done on the association of hypothyroidism with ovarian cysts and gall stones. By changing how we approach these conditions we can reduce surgical

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morbidity, healthcare burden and positively impact patient care.

Objectives

The primary goal of the study was to assess if there indeed was an association between hypothyroidism and ovarian cysts or gall stones. The secondary objective of the study was to study the symptomatology, the associated comorbidities and assess if there was a relationship between hypothyroidism and conditions such as fatty liver or PCOS morphology on ultrasound.

Materials and Methods

The study was conducted as a cross-sectional cross-sectional study of 202 patients attending our tertiary care hospital. The study included 101 female patients who had been diagnosed with overt hypothyroidism in the endocrinology OPD or in the wards between January 2020 and November 2021. This was compared with a set of 101 euthyroid control patients from the OPD and the wards with normal thyroid function. This study was approved by the institutional ethical review board.

Inclusion criteria

Any female older than 18 years, who has recently been diagnosed with hypothyroidism and was willing to participate in the study were included.

Exclusion criteria

1. Those refusing to consent to the study.
2. Any female with other conditions that increased the risk of gallstones such as Thalassaemia, Sickle cell anaemia or those who were using oral contraceptive pills
3. Males.
4. Fully treated cases of hypothyroidism.
5. Post-menopausal females.
6. Any subject on thyroid altering drugs - anti-thyroid action or thyroid supplements will be excluded.
7. Newly diagnosed hypothyroid patients with a history of cholecystectomy.
8. Pregnant females

After taking informed written consent and confirming the patient conformed to inclusion & exclusion criteria as described above, a brief history regarding symptomatology and duration of disease as well as demographic details were collected from each patient.

Case definitions

Any female with newly diagnosed primary hypothyroidism was defined as a case. Any female with normal thyroid function was defined as a control. Gall stones will be said to be present if the patient has gall stones on ultrasound examination. Any simple (no septae/ solid component) ovarian cyst which was larger than 3 cm.

An ovary was said to have PCOS morphology if it had multiple (at least 10) peripherally arranged follicles (each measuring 2-9 mm) with central echogenic stroma.

Ultrasound evaluation

Patients were imaged using the "GE Logiq P9 R2.5" or the "Samsung RS 80A".

Patient preparation involved an overnight fast of 8 hours and scans were done once the urinary bladder was distended for

evaluation of the pelvis.

The curvilinear transducer (2-5 MHz) was used with the mode set to 'Abdomen'.

Standard views which were obtained for all patients included the longitudinal and transverse views from the sub-costal, epigastric regions and along the intercostal spaces.

The ultrasound protocol we followed in imaging the pelvis included midline sagittal and parasagittal images angled from the midline to the periphery to evaluate both halves of the pelvis.

Statistics

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical variables were determined. Chi-Square test was used to find association between Categorical Variables. Level of Significance was kept at p value of less than 0.05.

Results

- Age Group:** Most patients were in the age group of 30-39 years with the mean age of the case group being 34.9 years and that of the control group being 35.8 years. The findings as regards to the age distribution have been summarised in table 1.
- Body habitus:** Calculated BMI revealed, 46/101 patients in the control group were overweight or obese and 64/101 patients in the case group were overweight/obese as described in table 2.
- Clinical Presentation:** The symptomatology of these patients was assessed and compared to the control group. The respective symptom and its relative usefulness in identifying a patient who may benefit from thyroid function testing, as determined by the chi square test are summarised in Table 3.

The most common presenting symptoms in our study population were unexplained weight gain (51.4%), menstrual disturbances (48.5%) and easy fatigability (42.5%). Other reported symptoms included constipation (33.6%), lethargy (22.7%) and hoarseness of voice (5.9%). The statistically significant features that were found in hypothyroid patients included easy fatigability (p-value 0.001), constipation (p-value 0.003), weight gain (p-value 0.000), lethargy (p-value 0.041) and menstrual disturbances (p-value 0.002). While hypothyroid patients were more likely to complain of cold intolerance (p-value 0.268) and hoarseness of voice (p-value 0.148); these failed to reach statistical significance.

Self-reported prevalence of diabetes, hypertension and dyslipidemia were noted down. In our study, 11.9% of hypothyroid patients were diabetic (p-value 0.396), 14.9% were hypertensive (p-value 0.401) and 30.7% had some form of dyslipidemia (p-value 0.269).

In our study, 5/101 hypothyroid patients and 2/101 control subjects had a family history of thyroid disorder which implied there was no significant association of family history with hypothyroidism. In our study, 20.8% of hypothyroid subjects had gall stones on ultrasound as compared to 6.9% of control subjects. Thus, there was a statistically significant association (p-value 0.004) between

hypothyroidism and gall stones. Selected ultrasound images of cholelithiasis are shown in Figure 1a-1d.

In our study, 11.9% of hypothyroid patients had ovarian cysts as compared to only 5.9% of control individuals. This failed to reach statistical significance (p-value 0.138). Selected ultrasound image of ovarian cyst is shown in Figure 2.

About 4% of hypothyroid patients had the simultaneous occurrence of both ovarian cysts and gall stones which suggests that there is a significant association (p-value 0.009) if there is simultaneous occurrence of both of these conditions.

Of the hypothyroid patients, 14.9% were found to have PCOD morphology on ultrasound as against 7.9% of controls. This failed to reach statistical significance (p-value 0.121). Selected ultrasound image of the same is shown in Figure 3.

A large number of hypothyroid patients i.e., 51.5% had hepatic fatty infiltration on ultrasound as against 35.6% of control subjects. Thus, there was a statistically significant association between hypothyroidism and fatty liver disease (p-value 0.023).

Discussion

1. Age of the patient

Most patients in our study were in the 40-50 years age group but, the age of participants varied from 19 years to 52 years with an average age of 34.9 years. Bipin Sethi, Sumitav Barua *et al.* created a national thyroid registry which compiled the clinical and hormonal data of adult Indians with hypothyroidism [9].

It has been noted that the incidence of hypothyroidism increases with age and hence the threshold for testing must be lowered in elderly women. Studies by Ghadban *et al.* showed that females more than 40 years of age with gall stones were more likely to be hypothyroid [10].

2. Body habitus

There is a known association between thyroid dysfunction and BMI with some studies having gone further to show that normalisation of thyroid function can reduce the BMI [11]. The mean BMI of the hypothyroid group of patients in our study was 26.4 kg/m² which is the same as that found by Sethi *et al.* in the thyroid registry [9].

Fox *et al.* analysed data from the Framingham heart study group and found a positive correlation between increases in Serum TSH on follow up with increases in body weight [12].

However, recent studies indicate that this relationship may not be straightforward as thyroid function is affected by adipokines produced by adipose tissue. Valcavi *et al.* showed that hypothyroid patients have a lower serum Leptin level before thyroid hormone replacement [13]. Some studies have also shown that obese individuals are more likely to develop anti-TPO antibodies and autoimmune thyroid disease [14]. The exact nature of this relationship remains an avenue for research.

3. Presenting complaint

The most common symptoms in our study were weight gain, menstrual irregularities and easy fatigability. The findings of our study with respect to symptomatology and the respective comparisons with the findings of

Sethi, Barua *et al.* and Dutta, Garg *et al.* have been summarised in table 4. Our study had a similar prevalence of most symptoms except weight gain, easy fatigability and menstrual irregularities.

While these symptoms are fairly common and should raise a clinical suspicion of hypothyroidism, it is important to note that they are non-specific. Anaemia for example is far common than hypothyroidism and can cause symptoms such as fatigue and lethargy. Common causes of menstrual irregularities include stress, hormonal fluctuations, oral contraceptive use, smoking, local causes such as infections, fibroids and endometriosis [15].

A study by Allan Carlé *et al.* suggested that none of the individual symptoms of hypothyroidism had a high likelihood ratio or diagnostic odds ratio and suggested that testing was warranted with the slightest suspicion of thyroid disease [16].

4. Comorbidities

The prevalence of Diabetes mellitus and Hypertension in our study was comparable to that found in the study by Sethi, Barua *et al.* as depicted in table 5 [9].

Hypothyroidism causes reduced peripheral glucose assimilation, suppresses liver and muscle gluconeogenesis and glycogenolysis which ultimately leads to insulin resistance [17]. Elderly age, female sex, obesity and TPO antibody positivity are associated with increased risk of developing hypothyroidism in diabetic individuals [17].

In our study, 14.9% of patients with hypothyroidism had coexisting hypertension. Of note, Ittermann *et al.* showed that there was a positive correlation between TSH levels and current hypertension in adolescents and children and the possible mechanisms involved include sympathetic over-activity, endothelial dysfunction due to reduced T3 (due to vasodilatory action) and increased peripheral alpha-adrenergic response-with blunted beta-adrenergic response resulting in increased systemic peripheral vascular resistance [18].

An Indian Council of Medical Research- India Diabetes (ICMR-INDIAB) study found that up to 79% of the Indian population had some form of dyslipidemia as defined by the National Cholesterol Education Programme (NCEP) guidelines [19]. It is likely that the actual prevalence of dyslipidemia in our study, as well as that by the National Thyroid Registry, were much higher but active testing of individuals was not carried out which likely contributed to the differences in prevalence.

Hypercholesterolemia in hypothyroidism is due to a reduction in LDL-receptor activity, reduced T3 mediated HMG CoA reductase activation, altered activity of hepatic lipase, lipoprotein lipase; and altered flow of bile [20].

Numerous studies have shown that thyroid supplementation positively affects the treatment outcomes of these comorbid diseases as elucidated below.

Soňa Stanická *et al.* reported that there was normalisation of insulin sensitivity and the levels of counter-regulatory hormones after thyroid hormone replacement therapy in hypothyroid patients [21].

Dernellis *et al.* studied the coexistence of hypothyroidism with hypertension and reported that

there was increased aortic stiffness in these patients which may contribute to their elevated BP readings. Interestingly, after thyroid hormone supplementation, there was a uniform decrease in aortic stiffness and normalisation of blood pressure readings in half of these patients [22].

Saxena *et al.* conducted a study on Levothyroxine supplementation in subclinical and overt hypothyroid patients and found that there was normalisation of lipid profile in a significant number of patients after therapy [23]. Thyroid hormone supplementation also potentiates the action of hypolipidemic drugs.

5. Family History

Manji *et al.* conducted a multi-centre study in patients with Grave’s disease and Hashimoto’s thyroiditis and found half the patients had a positive family history [24]. Further studies will be needed to assess if this arises from differences in population genetics or if it is due to inadequate testing in the general population.

6. Ultrasound findings

- **Gall stones:** In our study, there was a statistically significant association (p=0.004) between the presence of gall stones and hypothyroidism.

Maji *et al.* evaluated 54 patients with Cholelithiasis of which 30 were female and found that 26.7% of these females were hypothyroid. The statistically significant parameters that were associated with hypothyroidism in patients with gall stones were elderly age, obesity and female gender [25].

Hypothyroidism can trigger or hasten lithogenesis by the decreasing liver cholesterol metabolism, reducing hepatic bile secretion, impairing sphincter of Oddi relaxation and thereby reducing the flow of bile into the duodenum.

Thyroxine has a β receptor-mediated pro-relaxant action on sphincter of Oddi at physiological levels of serum T4. Thus in hypothyroidism there is decreased motility and prolonged stasis of bile. This leads to retention of cholesterol crystals, with sufficient time for them to enucleate and grow into mature gall stones. (3)

- **Ovarian Cysts:** All the cysts detected on ultrasound were simple, unilateral and barring two cases were between 3-5 cm.

Shu *et al.* reported a young hypothyroid female who presented with large ovarian cyst which resolved with thyroxine supplementation [26]. The co-existence of hypothyroidism and ovarian cysts was first observed in young girls who presented with precocious puberty which was dubbed the van Wyck and Grumbach syndrome [27]. The possible mechanisms that may play a role in the co-existence of ovarian cysts with hypothyroidism include [28]. Extremely high concentrations (several log doses greater than normal physiological FSH concentration) of TSH in hypothyroidism may be sufficient to cause the activation of FSH receptor due to receptor similarities.

Altered pituitary gonadotropin levels with relatively high FSH and low LH. It may be that in patients with hypothyroidism, there are slow pulses, favouring the production and secretion of FSH over LH and hyperprolactinemia in these patients (which is triggered by TRH) blunts the LH response to GnRH pulses.

TSH may stimulate nuclear thyroid receptor in the granulosa cells of the ovary sensitising the ovaries to gonadotropin stimulation with ovarian hyperstimulation. Myxoedematous infiltration of the ovaries can alter steroidogenesis and result in the formation of ovarian cysts.

It is uncertain why hypothyroidism is so common while concomitant ovarian hyperstimulation is so rare. Reported cases of ovarian hyperstimulation are associated with severe hypothyroidism with TSH of more than 100 mU/l and is only seen in girls or young women. It is possible that the gonads of young females are particularly susceptible to stimulation by TSH or FSH [26].

- **Gall stones and Ovarian cysts**

As an extension, we investigated the occurrence of both ovarian cysts and gall stones in patients with hypothyroidism and found a statistically significant correlation (p=0.009) between the two.

- **Polycystic Ovarian Morphology**

In our study, 15 of the 101 hypothyroid patients had polycystic ovarian syndrome morphology on ultrasound as compared to 8 of euthyroid control patients. However, this did not reach statistical significance (p=0.121).

Thyroid hormone deficiency may affect the ovaries causing delayed puberty, anovulatory cycles and infertility. Subclinical hypothyroidism can cause weight gain, increased conversion of androstenedione to testosterone, aromatization to estradiol and increase in sex hormone-binding globulin (SHBG).

Du *et al.* conducted a meta-analysis of 6 studies and concluded that the prevalence of autoimmune thyroid dysfunction, elevated serum TSH, anti-TPO and anti-Tg were all significantly higher in PCOS patients than those in control groups and suggested that autoimmunity may be involved in the pathogenesis of PCOS [29].

- **Fatty liver**

In our study, 51.5% of hypothyroid patients had fatty infiltration on ultrasound as compared to 35.6% of euthyroid subjects with a statistically significant association between the two (p=0.023).

Pathik Parikh *et al.* conducted a study on the prevalence of hypothyroidism in NAFLD patients and found that a significantly higher proportion of patients with NAFLD had hypothyroidism as compared to control subjects (p-value <0.001) [30]. Patients with NAFLD have a higher risk for both liver and cardiovascular related morbidity and mortality.

Table 1: Age-wise distribution of the study population

Age (In Years)	No of patients in case group	No of patients in control group
0-9	0	0
10-19	2	2
20-29	27	23
30-39	41	44
40-49	27	30
>50	4	2

Table 1a: Age-wise distribution of the study population

BMI	Case group	Control group
<18	5	1
18-25	31	53
25-30	41	37
>30	24	10

Table 2: Shows the range of BMI in the control and case groups of the study

		Group				Total				
		Case		Control		Count	% within Group	Pearson Chi-Square Value	DF	P-Value
		Count	% within Group	Count	% within Group					
Fatigue	Present	43	42.6%	21	20.8%	64	31.7%	11.070 ^a	1	.001
	Absent	58	57.4%	80	79.2%	138	68.3%			
Cold Intolerance	Present	14	13.9%	9	8.9%	23	11.4%	1.227 ^a	1	.268
	Absent	87	86.1%	92	91.1%	179	88.6%			
Constipation	Present	34	33.7%	16	15.8%	50	24.8%	8.612 ^a	1	.003
	Absent	67	66.3%	85	84.2%	152	75.2%			
Weight Gain	Present	52	51.5%	22	21.8%	74	36.6%	19.193 ^a	1	.000
	Absent	49	48.5%	79	78.2%	128	63.4%			
Lethargy	Present	23	22.8%	12	11.9%	35	17.3%	4.182 ^a	1	.041
	Absent	78	77.2%	89	88.1%	167	82.7%			
Hoarseness	Present	6	5.9%	2	2.0%	8	4.0%	2.082 ^a	1	.149
	Absent	95	94.1%	99	98.0%	194	96.0%			
Menstrual Abnormality	Present	49	48.5%	28	27.7%	77	38.1%	9.255 ^a	1	.002
	Absent	52	51.5%	73	72.3%	125	61.9%			
Pain Abdomen	Present	20	19.8%	7	6.9%	27	13.4%	7.225	1	0.007
	Absent	81	80.2%	94	93.1%	175	86.6%			
Family History	Present	5	5.0%	2	2.0%	7	3.5%	1.332	1	0.248
	Absent	96	95.0%	99	98.0%	195	96.5%			

Table 3: Mentions the group-wise break-up of symptomatology with the respective number of patients showing each symptom and the respective p value

DM	Present	12	11.9%	8	7.9%	20	9.9%	.888 ^a	1	.346
	Absent	89	88.1%	93	92.1%	182	90.1%			
HTN	Present	15	14.9%	11	10.9%	26	12.9%	.706 ^a	1	.401
	Absent	86	85.1%	90	89.1%	176	87.1%			
Dyslipidemia	Present	31	30.7%	24	23.8%	55	27.2%	1.224	1	0.269
	Absent	70	69.3%	77	76.2%	147	72.8%			
Gallstones	Present	21	20.8%	7	6.9%	28	13.9%	8.126	1	0.004
	Absent	80	79.2%	94	93.1%	174	86.1%			
Ovarian cysts	Present	12	11.9%	6	5.9%	18	8.9%	2.196	1	0.138
	Absent	89	88.1%	95	94.1%	184	91.1%			
Calculus+Cyst	Both	4	4.0%	0	0.0%	4	2.0%	9.389 ^a	2	.009
	Either One	25	24.8%	13	12.9%	38	18.8%			
	Nil	72	71.3%	88	87.1%	160	79.2%			
PCOS	Present	15	14.9%	8	7.9%	23	11.4%	2.404 ^a	1	.121
	Absent	86	85.1%	93	92.1%	179	88.6%			
Fatty Liver	Present	52	51.5%	36	35.6%	88	43.6%	5.155	1	0.023
	Absent	49	48.5%	65	64.4%	114	56.4%			

Table 4: Comparison of the symptom spectrum between our study and similar studies

Chief complaint	Prevalence in our study (%)	Prevalence(%) as per the Thyroid Registry: Sethi, Barua <i>et al.</i> (84)	Prevalence(%) as per the Dutta, Garg <i>et al.</i> in the overt hypothyroidism group (32)
Easy fatigability	42.5	60.17	68.4
Cold intolerance	13.8	15.2	18.4
Constipation	33.6	18.15	--
Weight gain	51.4	36.2	40
Lethargy	22.7	19.8	25.3
Hoarseness	5.9	8.7	16.9
Menstrual irregularities	48.5	100	28.4

Table 5: Describes the prevalence of comorbidities in this population and compares the data to the Thyroid registry compiled by Sethi, Barua *et al.*

Comorbidity	Prevalence in our study (%)			Prevalence (%) as per the Thyroid Registry: Sethi, Barua <i>et al.</i>
	Case	Control	P-value	
Diabetes mellitus	11.9	7.9	0.346	13.5
Hypertension	14.9	10.9	0.401	11.3
Dyslipidemia	30.7	23.8	0.269	4.27

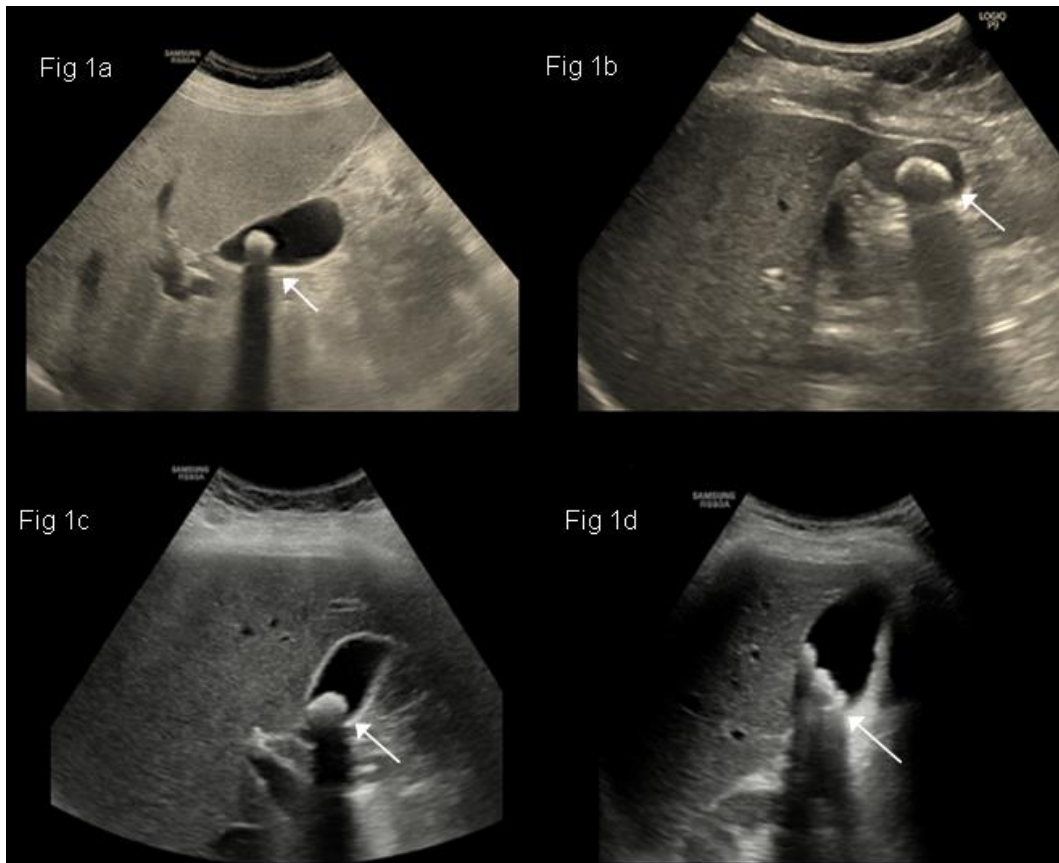


Fig 1a-1d: Gall bladder calculi (white arrows) as seen in different patients in our study have been shown. Gall bladder calculi appear as mobile echogenic foci within the gall bladder which show posterior acoustic shadowing

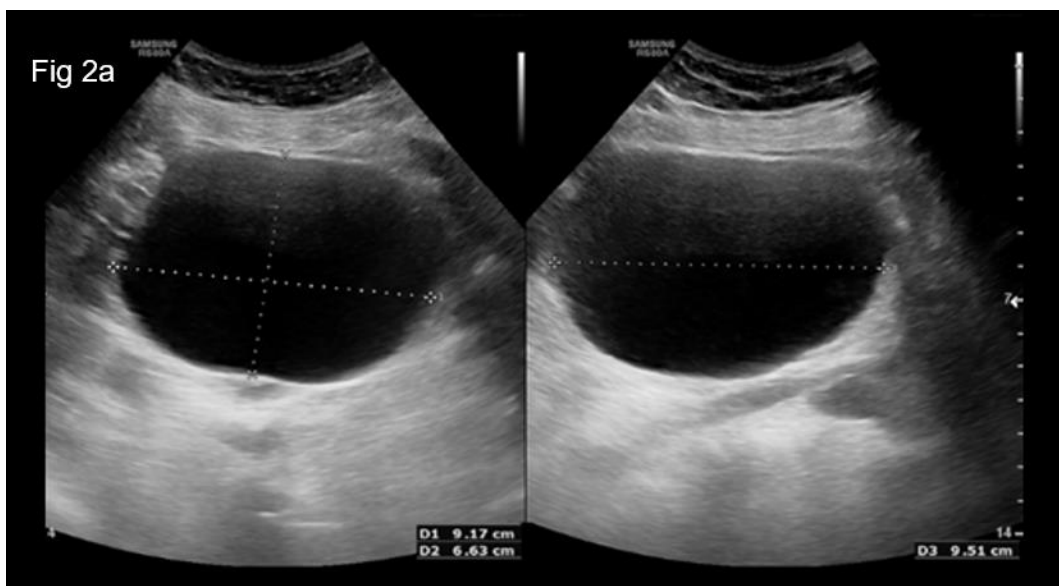


Fig 2a: Shows a large anechoic cystic lesion (white arrow) as seen in the axial and sagittal planes on trans-abdominal ultrasound

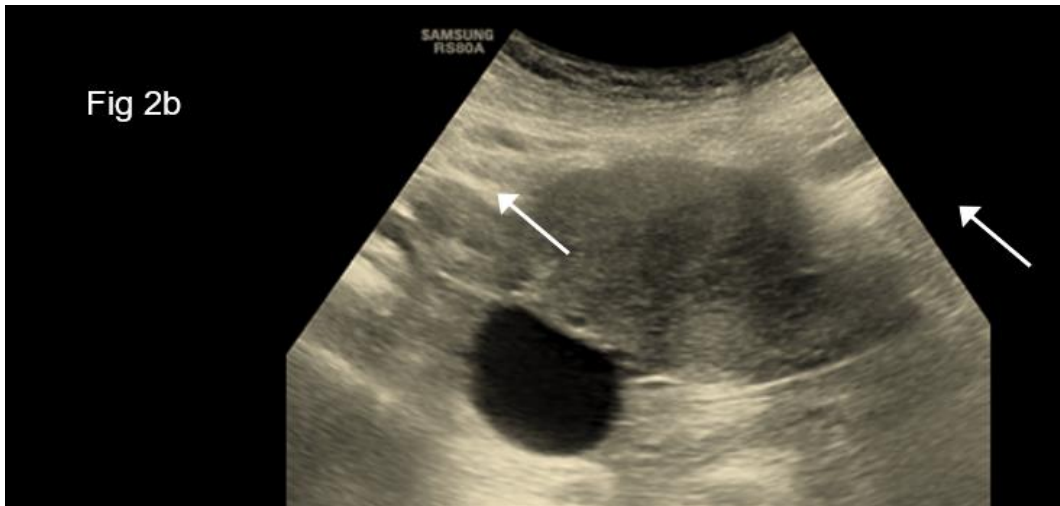


Fig 2b: Shows a cystic lesion (white arrow) in the right adnexa with the right ovary not seen separately from it with no septae/solid component

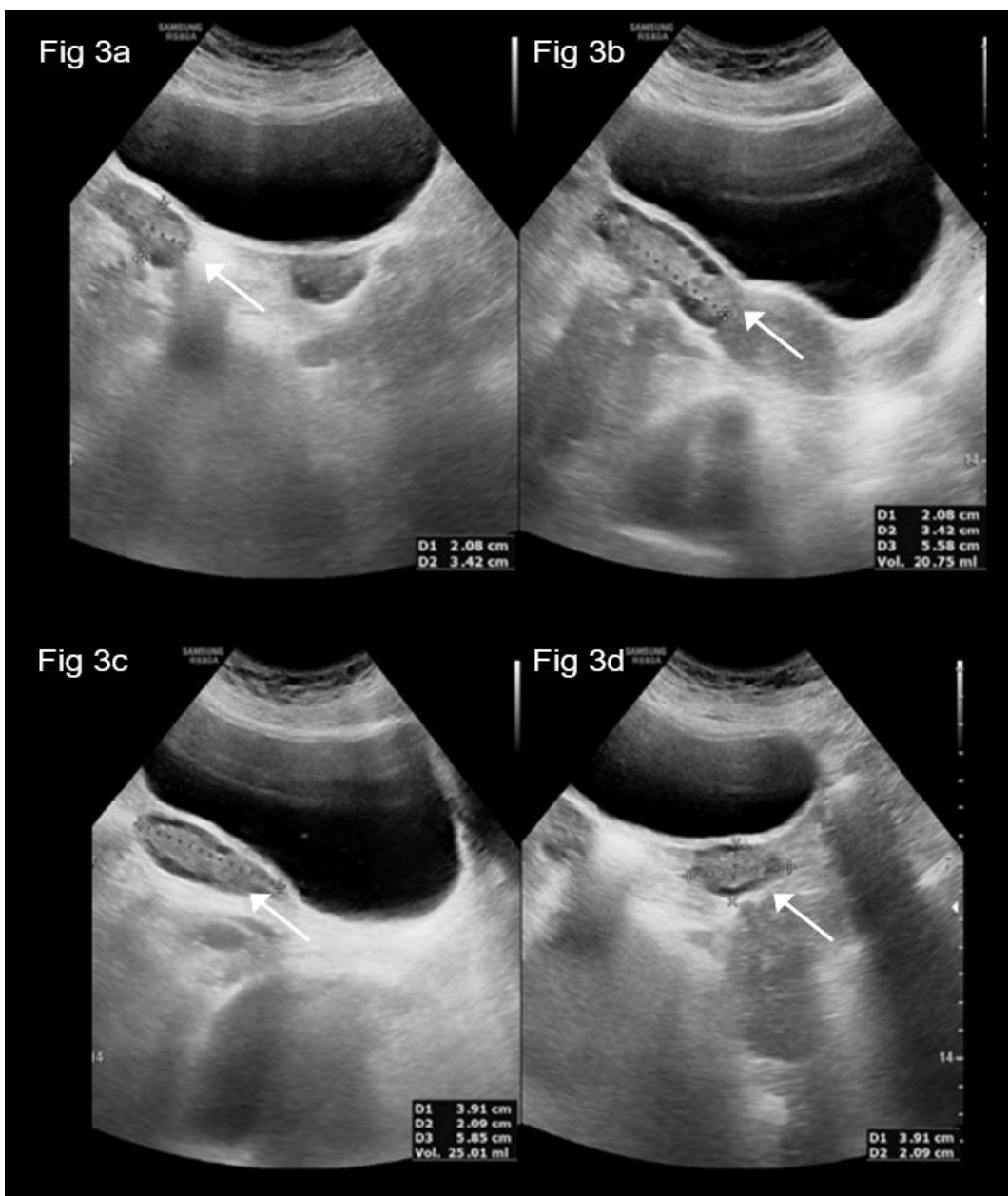


Fig 3a and 3b: Show the right ovary(white arrow) in transverse and sagittal planes. Fig 3c and 3d show the left ovary(white arrow) in the sagittal and transverse planes respectively. The bilateral ovaries in this patient appear bulky with central echogenic stroma and multiple tiny peripherally arranged follicles, giving a string of pearls appearance, suggestive of PCOS morphology.

Conclusion

We conducted an ultrasound-based cross-sectional study on the association of hypothyroidism with ovarian cysts and gallstones. In our study, most female patients were middle aged and had a slightly higher BMI. We found that certain symptoms such as unexplained weight gain, menstrual irregularities and easy fatigability should prompt evaluation for hypothyroidism. In our study, there was a slight, statistically insignificant increase in the prevalence of diabetes, hypertension and dyslipidemia in hypothyroid patients as compared to the control group. Early screening and institution of hormone replacement therapy can improve outcomes of these comorbidities.

In our study, there was a statistically significant association of hypothyroidism with gall stones, fatty liver and the occurrence of both ovarian cysts and gall stones. While there was a slightly increased prevalence of ovarian cysts and polycystic ovarian morphology in these individuals, they failed to reach statistical significance.

Gallstones are often treated with upfront surgery and although there are fewer complications with the advent of minimally invasive surgery, it does still take a toll on the patients and the healthcare system. Ovarian cysts, especially those that are large and complex are often treated with surgery. Recognising the role that hypothyroidism has in the development of these pathologies can alter treatment regimens and improve overall patient outcomes.

Acknowledgement

Not available.

Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

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How to Cite This Article

Rai P, Joshi AR. Cross-sectional study on the association of ovarian cysts and gall stones. *International Journal of Radiology and Diagnostic Imaging*. 2024;7(2):20-28.

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