



“ASSOCIATION OF CHOLELITHIASIS, CHOLEDOCHOLITHIASIS AND HYPOTHYROIDISM IN PREGNANCY-A PROSPECTIVE STUDY”

General Surgery

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ABSTRACT

Introduction: Thyroid disorder is a prevalent condition among adult population; however, it is frequently overlooked. Hypothyroidism causes low bile flow and sphincter of Oddi dysfunction and hence promotes gall stone formation. This study was done to substantiate the need for evaluating the thyroid status in patients presenting with cholelithiasis/ choledocholithiasis. **Aims:** To study the prevalence of hypothyroidism in patients presenting with Cholelithiasis/ Choledocholithiasis in pregnancy. To assess if thyroid profile is indicated in patients with biliary lithiasis in pregnancy. **Materials And Methods:** This is an observational and prospective study. Method of sampling was non-random, purposive. 68 patients with USG evidence of cholelithiasis/ choledocholithiasis, were evaluated with basic investigations and additionally thyroid function test was performed. The operation procedure and related per operative factors were observed directly and recorded. **Results:** The operation procedure and related per operative factors were observed directly and recorded in the data collection sheet instantly. Age of these selected patients ranged from 20- 50 yrs, with mean age being 47.14 yrs. Pregnant Females were the predominant group. Thyroid function test was performed in all 68 patients out of which, 18 patients (26.4%) were found to have hypothyroidism and the rest i.e. 50 patients were euthyroid. Of these 18 patients only 2 were known hypothyroid, rest 16 patients were newly diagnosed hypothyroid patients. Of these 18 patients, 16 patients were females rest were males. 50-70 yrs were the predominant group. More than 70% of the patients with hypothyroidism belong to this group. **Conclusion:** Evaluation of thyroid profile in pregnancy should be a part of general workup in patients with both cholelithiasis and choledocholithiasis especially in females above the age of 40yrs and patient should be treated with appropriate thyroid medications.

KEYWORDS

Hypothyroidism, Cholelithiasis, Choledocholithiasis, Pregnancy

1 INTRODUCTION

Gallstones are the most common biliary pathology, can be divided into three main types: cholesterol, pigment (black, brown) or mixed stones. In the USA and Europe, 80% cholesterol or mixed stones, where as in Asia, 80% are pigment stones. Cholesterol or mixed stones contain 51 – 99 % cholesterol plus admixture of calcium salts, bile acids, bile pigment and phospholipids. Gallstones may be single or multiple, large or small those containing calcium salts are radio-opaque. Single stones are uncommon but usually consist mainly of cholesterol and arise due to a disorder of the physio-chemical equilibrium which normally maintains cholesterol in micellar form in the bile.

Many studies were done to identify risk factor for biliary lithiasis in the west have focused on supersaturation of cholesterol in bile in nucleation process a critical step in the genesis of bile stone.

Thyroid disorder is a prevalent condition in pregnancy among adult population; however, it is frequently over looked. For decade, there has been a discussion, whether thyroid disorders could cause gallstone disease. Particularly, there are several explanations for a possible relation between hypothyroidism and gallstone disease; these explanations include the known link between thyroid failure and disturbances of lipid metabolism

that may consecutively lead to change of composition of the bile. Recent studies also demonstrated low bile flow in hypothyroid subjects.

Furthermore, the sphincter of oddi expresses thyroid hormone receptors and thyroxine has a direct prorelaxing effect on the sphincter. Both low bile flow and sphincter of oddi dysfunction are regarded as important functional mechanisms that may promote gallstone formation.

The prevalence of previously undiagnosed thyroid function abnormalities has never been studied in gallstone patients before. If an increased prevalence of thyroid disorders will be found, it might have an effect on the diagnostic and therapeutic work up of patient with gallstone.

Hypothyroidism is the most common cause of secondary

hypercholesterolaemia, patients with hypothyroidism have serum level of cholesterol approximately 50% higher than level in euthyroid patients and 90% of all hypothyroid patients have elevated cholesterol level.

1.2 OBJECTIVES

The purpose of this study is

1. To study the prevalence of hypothyroidism in patients presenting with cholelithiasis/choledocholithiasis in pregnancy.
2. To assess if thyroid profile is indicated in patients with biliary lithiasis in pregnancy.

The effects of thyroid hormones in pregnancy:

The thyroid gland secretes both T4 and triiodothyronine (T3) into the circulation. "In extrathyroidal tissues, T4 is converted to T3, assumed to be the major active TH. Characteristic of THs is the multiplicity of the cellular functions they regulate in virtually every type of vertebrate tissue. The diverse responses to TH can be divided into two major categories:

- Regulation of metabolic activity, energy consumption and muscular activity in adult mammals, and
- Regulation of postembryonic or perinatal growth and development. Most actions of THs can be explained by their interaction with nuclear receptors. THs bind to specific intranuclear TH receptors (TR), TR1, TR1 or TR2. This ligand-receptor complex binds to TH response elements in the target genes to regulate the rate of synthesis of specific messenger RNAs. This results in a change in the amount or activity of the cognate proteins, which in turn alter the rate of the metabolic process. The TRs are expressed in a tissue- and development-stage-specific fashion. For example, TR1 is known to be highly expressed in brain, muscle and fat, and has been identified in frog, chicken, rat, mouse and humans; TR1 is highly expressed in liver and kidney, and has been demonstrated in frog, chicken, rat, mouse and humans. TR2, again, is highly expressed in the pituitary, and has been demonstrated in rat and mouse. The expression of TRs in the SO has not been studied. The genomic effects of THs necessarily require a finite period of time for protein synthesis and for the biological response. Acute response of a cell to THs is unlikely to

- involve a transcriptional mechanism but is rather a result of nongenomic mechanisms involving extranuclear sites of action. Extranuclear sites of TH action include the cell membrane, the cytoskeleton, the sarcoplasmic reticulum, the cytoplasm, the mitochondria, and in vascular smooth-muscle cells presumably the contractile elements." For example, THs mediate sugar uptake, adenylate cyclase, and Ca^{2+} -ATPase activity directly at the level of the plasma membrane of various tissues. The second messengers associated with the extranuclear actions of the THs are not yet known.

Mechanism of Formation of Gallstones in Hypothyroidism in a pregnant female:

In general, the pathogenesis of gallstones is a complex process involving mechanisms affecting bile content and bile flow. There are several factors that may contribute to the formation of gall stones in hypothyroid patients. Based on the investigations currently available, it cannot be concluded whether hypothyroid individuals develop isolated gall stones or present with CBD stones in addition to gallbladder stones. "However, based on what is known about the effects of hypothyroidism on the formation of gallbladder and CBD stones, it seems likely that in hypothyroidism both the risk for gallbladder-originated as well as for de novo CBD stones is increased." In hypothyroidism, the lack of thyroxine

- decreases liver cholesterol metabolism resulting in bile cholesterol supersaturation, which in turn impairs the motility, contractility, and filling of the gallbladder, contributing to the retention of cholesterol crystals and to the nucleation and growth of gallstones.
- diminishes bile secretion from hepatocytes resulting in impaired clearance of precipitates from the bile ducts.
- reduces SO relaxation resulting in delayed bile flow and thus the formation and accumulation of CBD stones.

THs regulate multiple functions in virtually every type of vertebrate tissue. Most actions of THs can be explained by their interaction with nuclear receptors, which are expressed in a tissue- and development stage-specific fashion. In human, the SO expresses both TR β 1 and β 2. Any acute-type response of a cell to THs is unlikely to involve a transcriptional mechanism but is rather a result of nongenomic mechanisms involving extranuclear sites of action. In general, thyroid hormone actions are largely intracellular events that require transport across the plasma membrane. Recently, several active and specific thyroid hormone transporters have been identified, including monocarboxylate transporter 8 (MCT8), MCT10, and organic anion transporting polypeptide 1C1 (OATP1C1).

MATERIALS AND METHODS

3.1 Type of study: Prospective and observational study

3.2 Study Place: MKCG Medical College & Hospital, Berhampur

3.3 Inclusion Criteria:

- Patients in age group of 18-50 yrs and pregnant.
- Patients with USG proven cholelithiasis/ choledocholithiasis

3.4 Investigation

- USG abdomen, UPT Test
- T3, T4, TS

3.7 Study procedure:

Method of sampling was non-random, purposive. After admission short history was taken and physical examination was conducted on each patient admitted in surgery department with features suggestive of extrahepatic biliary lithiasis. Baseline investigations, as routinely required, were done, followed by imaging studies. Patients were then explained about their disease process and the possible line of management. All the necessary information regarding the study was explained to the patients or their valid guardian. Informed written consent was taken from the patients or their guardian willing to participate in the study. Detailed history was taken from the study group to establish proper diagnosis. Thorough physical examination was done in each case. Data collection sheets were filled in by the investigator himself. All of the preoperative factors related to the patient were noted down in the data sheet. After proper evaluation and preparation, patients who required surgical management were taken up for surgery. Strict aseptic precautions were followed during the operation. Meticulous techniques were practiced as far as possible. The operation procedure and related pre operative factors were

observed directly and recorded in the data collection sheet instantly. After completing the collection of data it was compiled in a systematic way.

3.8 Operational definitions:

Cholelithiasis: a condition marked by presence of calculi in the gallbladder

Choledocholithiasis:

a condition marked by presence of calculi in the common bile duct **Hypothyroidism:** abnormally low activity of the thyroid gland develops when the thyroid gland fails to produce or secrete as much thyroxine as the body needs.

Data analysis

Data analysis was done both manually and by using computer. Calculated data were arranged in systemic manner, presented in various table and figures and statistical analysis was made to evaluate the objectives of this study with the help of Statistical Package for Social Science (SPSS)

RESULTS

A prospective study was performed to determine the incidence of hypothyroidism in patients having cholelithiasis and choledocholithiasis. 68 patients were studied who fulfilled the inclusion criteria. All these patients were taken from the surgery department of MKCG Medical College,. All patients were evaluated clinically and only essential investigations were performed before surgery, in addition patients underwent the thyroid function test. The results obtained are as follows.

Table 1: Percentage of patient with co- morbidities

Co- Morbidity	Number	Percentage
Diabetes Mellitus	11	16
Hypertension	14	20.5
Both DM and HT	6	8
No co morbidity	49	72.05

Hypertension was the predominant co- morbidity in this study- in 20% of the patients.

Table 2: USG / CT findings of patients

USG / CT Findings	Number	Percentage
GB- Single stone	20	29.4
GB- Multiple stones	46	67.64
CBD Stones	5	27.3
Both GB and CBD stone	3	4.4

Table 3: Management profile of gall stones

Surgery Performed	Numbers	Percentage
Open cholecystectomy	30	44.11
Lap Cholecystectomy	36	52.94
CBD exploration	4	5.8
Conservative	2	2.9
Lap Converted to open	4	5.8

36 Patients underwent laparoscopic cholecystectomy out of which 4 patients were converted from lap to open procedure.

Table 4: Thyroid Profile of the patients

	Numbers	Percentage
Hypothyroid	18	26.47
Euthyroid	50	73.52

p value <0.05 and it is statistically significant.

26% of patients with cholelithiasis/ choledocholithiasis had hypothyroidism in pregnancy.

p value is <0.05 and it is statistically significant.

Surgeries Performed	Numbers	Percentage
Open Cholecystectomy	7	38.88
Lap Cholecystectomy	7	38.88
CBD exploration	3	16.66
Lap to Open	0	0
Conservative	1	5.5

Both laparoscopic and open procedures were performed in hypothyroid patients.

DISCUSSION

This prospective study was conducted 68 selected patients with evidence of cholelithiasis or choledocholithiasis in Department of General Surgery, MKGG Medical College, Berhampur. The study was carried out with a view to determine the prevalence of hypothyroidism in patients with extra hepatic biliary lithiasis in view of determining its importance as a causative factor and to include thyroid function tests as part of routine workup in gallstone patients.

Age of these selected patients ranged from 20- 50 yrs, with mean age being 47.14 yrs..Pregnant Females were the predominant group. On analysing the co- morbid factors HT was the predominant co- morbid factor followed by Diabetes. HT was found to be a co- morbid factor in 14 patients (20%). DM was found to be a co- morbid factor in 11 (16%). 6 patients had both DM and HT.

On evaluation of patients with USG and CT, 46 patients (67.4%) had multiple stones, and 20 patients (29.4%) had single stone. 5 patients had CBD stones and 3 patients had both CBD and GB stones. The size of the stones ranged from 4- 18mm.

Patients were managed with both laparoscopic and open procedures. 36 patients underwent laparoscopic cholecystectomy out of which 4 patients were converted from lap to open procedure. The reasons for conversion were bleeding, adhesions and technical difficulties. Open procedure was done in 30 patients and 4 patients underwent CBD exploration in addition to cholecystectomy.

Thyroid function test was performed in all 68 patients out of which, 18 patients (26.4%) were found to have hypothyroidism and the rest i.e. 50 patients were euthyroid. Of these 18 patients only 2 were known hypothyroid, rest 16 patients were newly diagnosed hypothyroid patients.

Of all the hypothyroid patients, 14 had multiple stones and 4 had single stone, one patient had CBD stone and one patient had both CBD and GB stone.

7 patients underwent open cholecystectomy and 7 underwent laparoscopic cholecystectomy. In 3 patients CBD exploration was done. Post operative and intraoperative periods were uneventful in all these patients.

Summary

Cholelithiasis and Choledocholithiasis are one of the commonly encountered diseases in a general surgery department. Multiple risk factors have been attributed to the development of gallstones which include age, female gender, obesity, high fat diet, family history etc. Patients usually present with right hypochondrial pain, dyspepsia, vomiting and occasionally fever or jaundice. Management includes diagnostic imaging studies followed by surgery, if indicated. Hypothyroidism is not an accepted or proven risk factor for gallstones as of yet. Several studies have postulated the possible pathophysiology behind the role of thyroxine in the normal physiology of the biliary system. No concurrence has been established

Co Morbid Factors:

Hypertension and Diabetes Mellitus were the prevalent comorbid factors as cholelithiasis like previously told is a disease of the elderly. None of these seemed to have a significant correlation with the disease process.

Diagnostic Studies:

USG was sensitive in detecting stones in nearly all patients with CECT abdomen and MRCP required only in few cases.

Management:

Laparoscopic and open Cholecystectomy were both performed. Conversion to open was seen in 4 patients. This can be attributed to technical problems and as the study was done in a teaching institute and a good percentage of surgeries was done by trainees.

Hypothyroidism and gallstones in pregnancy:

Eighteen patients in our study had gallstones showing a prevalence of nearly one fourth of the patients being affected. All these indicated a

pathophysiological role of thyroxine in gallstone formation, apart from the supposed lipid metabolism abnormalities. This has been substantiated by physiological studies in animal models by Johanna Laukkarinen et al.

CONCLUSION

This prospective observational type of study was conducted in Department of General Surgery, MKCG Medical College. It can be concluded from the findings of the study that hypothyroidism is a highly probable risk factor for development of hypothyroidism especially for middle aged females. Undetected and untreated hypothyroidism in such patients will result in persistence of the basic pathophysiology responsible for the initial disease process resulting in recurrence and complications. So, it can be assumed that patients at risk of forming gall stones due to hypothyroidism will benefit from early treatment. Most importantly, when treating patients with cholelithiasis or choledocholithiasis, clinicians should be aware of the possible hypothyroid background and consider examining the thyroid function, at least in pregnant female patients over 40 years of age, in which group the prevalence of clinical and subclinical hypothyroidism is the highest.

Recommendations

On the basis of the findings of the study, the following recommendations can be made:

1. Evaluation of thyroid profile should be a part of general workup in patients with both cholelithiasis and choledocholithiasis especially in pregnant female patients.
2. Proper evaluation and preoperative preparation in patients with hypothyroidism, anticipating complications.
3. The patients with clinical hypothyroidism in pregnancy should be started with appropriate thyroid medications.

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