



## Assessment of Gonadotropins Level and Their Ratio In Gallstone Patients In Kolkata: A Cross-Sectional Study

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### ARTICLE INFO

### ABSTRACT

Gallstone disease (GSD) is a worldwide disease ranging from 10% to 20% of the global population and four times higher in women than in men. Several studies have proclaimed that risk of developing cholesterol gallstones is increased by pregnancy, contraceptive steroids and conjugated oestrogens suggesting that oestrogen could be an important risk factor in forming cholesterol gallstones by increasing the cholesterol saturation index, altering bile salt and promoting nucleation of cholesterol into crystals. To evaluate gonadotropin (FSH and LH) level and their ratio including their correlation with study variables among gallstones patients in Kolkata. 46 subjects were enrolled during a period of April to June, 2022 in West Bengal. Serum level of FSH and LH and its ratio were measured using sandwich ELISA. The data was analysed using statistical package of social science (SPSS) and results was expressed as percentage (%) and mean  $\pm$  SD, and significance difference was considered as  $P < 0.05$ . Analyses of frequency showed that GSD is more common in premenopause (76.1%) than post-menopause (23.9%). Independent t-test revealed that, FSH/LH ratio is significantly increased in gallstone patients in comparison with control group ( $P < 0.048$ ). In addition, Pearson's correlation results noted positive correlation between both FSH and FSH/LH ratio with BMI while significant negative correlation in between LH and BMI. The data suggests that obese premenopausal women are much more susceptible to gallstones and FSH/LH ratio specifically is for all intents and purposes higher in gallstone patients, which specifically is fairly significant.

**Keywords:** GSD (Gallstone Disease), FSH (Follicular Stimulating Hormone), LH (Luteinising Hormone), oestrogen, postmenopausal woman, obese individual, gallbladder, cholesterol.

### Introduction

Gallstone disease stands as the primary gastrointestinal ailment affecting the biliary system, stemming from the development of solid deposits comprised of cholesterol or bilirubin. These deposits manifest as hardened accumulations within the gallbladder, exhibiting diverse sizes and configurations, ranging from minute particles resembling grains of sand to substantial entities akin to golf balls (Chen *et al.*, 2006). Traditional factors contributing to gallstone disease (GSD) are often summarized in the widely recognized mnemonic '4 F's': female gender, obesity or excess body fat, forties age group, and fertility potential. However, additional risk factors encompass the use of oral contraceptives, pregnancy, a familial history of gallstones, obesity, diabetes, liver disease, and rapid weight loss (de Bari *et al.*, 2015). In 2013, approximately 104 million individuals, equivalent to 1.6% of the global population, experienced gallbladder and biliary system-related disorders, leading to 106,000 deaths. The prevalence of these conditions ranged from 10% to 20% worldwide, with women facing a fourfold higher risk compared to men (Idris *et al.*, 2013). Various research inquiries have identified estrogen hormone as a contributing factor in the development of gallstones, evident in the

alterations in the regulation of gonadotropin hormones and their relative proportions. With the rising incidence of gallstone cases, particularly among women across different age groups, including postmenopausal women, understanding the implications of these circumstances on daily life becomes increasingly crucial (Kharga *et al.*, 2016; Pak and Lindseth, 2016). Therefore, to assess this influence, it is essential to measure the levels of FSH/LH hormones. The gender-based difference in the occurrence of cholelithiasis begins during puberty and persists throughout the childbearing years. Multiple studies have indicated that factors such as pregnancy, contraceptive steroids, and conjugated estrogens heighten the likelihood of developing cholesterol gallstones (Russo *et al.*, 1993). These observations suggest that estrogen, a prominent female sex hormone, may play a pivotal role as a risk factor in the development of cholesterol gallstones. It accomplishes this by increasing the cholesterol saturation index, altering bile salt composition, and facilitating the nucleation of cholesterol into crystals. Consequently, ongoing research is investigating the impact of estrogen on gallstone formation, discernible through changes in its regulation of gonadotropic hormones. These alterations may, in turn, have significant implications for fertility and various other biological functions. In light of this context, the primary objectives of this research are to analyze the levels of gonadotropins in individuals with gallstones and to determine whether the ratio of FSH to LH could serve as an indicator for gallstone disease.

### Materials and Methods

This cross-sectional study was conducted in West Bengal, India, from April to June 2022, focusing on female participants aged 30 to 50 years diagnosed with gallstone disease through ultrasonography. The participants were selected from various outpatient departments of hospitals and primary healthcare centres. Male subjects were not included in this research. Exclusions criteria comprised individuals without abdominal ultrasonography, those with recent viral hepatitis (within the last 5 years), recipients of hormone replacement therapy, and those outside the age range of 30 to 50 years. The study enrolled a total of 48 female participants with gallstone cases and 38 healthy female controls, all of whom provided their consent. Participants completed a questionnaire covering aspects such as age, marital status, menopausal status, alcohol consumption (within the past year), and smoking history (within the past year). Additionally, all participants underwent a physical examination, including measurements of weight (in Kg) and height (in cm). The Body Mass Index (BMI) was calculated using the formula: weight [kg] / height [m<sup>2</sup>]. Serum FSH and LH levels were determined through specific ELISA kits (BioVision, USA) after an overnight fast (5–10 days post-menstrual bleeding for premenopausal subjects). The LH/FSH ratio for each participant was computed as LH (mIU/mL) divided by FSH (mIU/mL). Statistical analysis was conducted using GraphPad PRISM. Continuous variables (age, height, weight, BMI, FSH, LH, and FSH/LH ratio) are presented as means with standard deviations. Group differences for quantitative variables were assessed using Student's t-test. Pearson's correlation was employed to measure association of LH, FSH and LH/FSH ratio with BMI

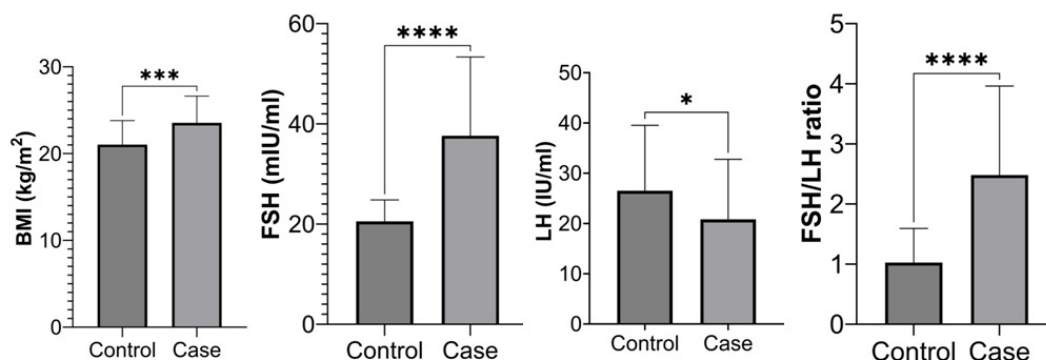
### Results:

**Table 1: Demographic variables [Mean±SD] and basic characteristics [n and percentage (%)] of study population**

Parameters	Control [n=38]	Gall stone disease [n=46]
Age (Years)	39.12±5.32	35.0±2.53 <sup>NS</sup>
Body weight (Kg)	58.5±2.47	68.8±4.33 <sup>*</sup>
Height (cm)	164.45±3.86	159.37±4.87 <sup>NS</sup>
Alcohol consumption		
n	0	04
%	0	8.70
Smoking history		
n	3	5
%	7.89	10.87
Premenopausal		
n	30	35
%	78.9	76.1
Postmenopausal		
n	8	11
%	21.1	23.9
Married		
n	35	44
%	92.10	95.65

**\*Significance level based on Student's t-test (P<0.05), NS - Not significant**

Demographic characteristics of study participants are presented in Table 1. Mean age (years) and height (cm) were found statistically insignificant in between control subjects and gall stone disease subjects. However, weight (Kg) and BMI (Kg/m<sup>2</sup>) were found to be significantly higher among participants having gall stone disease as compared to control subjects. Further categorical variable like menopausal status, marital status, alcohol consumption and smoking history are also presented in Table 1.



**Figure 1:** (a) BMI (Kg/m<sup>2</sup>), (b) FSH (mIU/ml), (c) LH (mIU/ml) and (d) FSH/LH Ratio among control subjects and gall stone disease subjects (Case). \*Significance level based on on Student's t-test \*P<0.05, \*\*\*P<0.001, \*\*\*\*P<0.0001

**Table 2: Correlation of BMI with FSH,LH and FSH/LH ratio among individuals with gallstone disease**

Variables	Pearson's r	P-value
BMI vs FSH	0.66	0.001
BMI vs FSH/LH	0.71	<0.001
BMI vs LH	0.46	>0.05

This study was mainly focused on measuring FSH, LH, and the FSH/LH ratio. Although, FSH, LH and FSH/LH ratio all were found to be altered in gall stone disease population, but FSH and FSH/LH ratio were found to have maximum switching towards higher value in gall stone disease subjects. Further, Pearson's r calculation revealed that BMI is significantly correlated with FSH/LH ration and FSH. Although, LH level is negatively correlated with BMI but that did not reach statistical significance.

## Discussion

Gallstone disease (GSD) poses a significant global health concern, necessitating surgical intervention due to its widespread prevalence. Multiple studies have highlighted the risk associated with estrogen hormone as a contributing factor to gallstone development. This risk manifests through alterations in the regulation of gonadotropic hormones, potentially impacting fertility and various biological functions. In this initial cross-sectional study, we demonstrated that the levels of gonadotropins (FSH and LH) and their ratio show promise as predictors for gallstone disease. Moreover, we emphasized the link between gallstone disease and the risk posed by estrogen. Specifically, female sex hormones, particularly estrogen, have been suggested as substantial contributors to the development of gallstones (Pak and Lindseth, 2016). The connection between gallstone disease and estrogen can be elucidated by considering the interplay between obesity and cholesterol levels, both of which act as precursors for bile salt production. This process disrupts the equilibrium in bile composition, increasing the susceptibility to gallstone formation (Russo *et al.*, 1993). Notably, the risk of symptomatic cholelithiasis shows a direct relationship with an increase in body mass index (BMI) (Simonsen *et al.*, 2013). Participants in the study who had gallstone disease exhibited a significantly higher BMI further emphasizing the association with gallstone disease. However, BMI might have combined effects with other confounding variables on gallstone disease. Earlier studies have proposed that premenopausal women may be more susceptible to developing gallstones, potentially due to prolonged exposure to various risk factors, irrespective of geographical or socioeconomic circumstances (Wang *et al.*, 2020). Correspondingly, the results of our current study indicate that 76.10 % of individuals with gallstones were in the premenopausal stage, while 23.90 % were postmenopausal, aligning closely with the findings of the aforementioned previous study (Wang *et al.*, 2020). Furthermore, our current study revealed that over 76% of individuals with

gallstone disease were in the premenopausal phase, and this group exhibited higher BMI levels. These findings are consistent with previous data suggesting that the risk of gallstone development is significantly higher among overweight premenopausal women (Pak and Lindseth, 2016). However, in contrast to earlier epidemiological findings (Kharga *et al.*, 2016; Pak and Lindseth, 2016; Yuan *et al.*, 2022), the mean age did not differ between the control and case groups in our study, and we adjusted for age in multiple logistic regression analyses.

The present study's results revealed significant differences in the mean levels of both FSH and LH between gallstone patients and the control group. Furthermore, comparative analyses demonstrated a substantial elevation in the FSH/LH ratio among gallstone patients compared to the control group ( $P < 0.0001$ ). As previously observed, alterations in the control of gonadotropic hormones can have significant consequences for fertility and various bodily functions (Russo *et al.*, 1993). Thus, the significant link identified between FSH (Follicle-Stimulating Hormone) and the FSH/LH (Follicle-Stimulating Hormone to Luteinizing Hormone) ratio among individuals with gallstone disease suggests their potential significance in the clinical evaluation of health outcomes in this population. It is essential to note that our study cohort does not use hormonal replacement therapy, known to lower LH levels (Zamani *et al.*, 2014; Zhang *et al.*, 2023). Additionally, postmenopausal estrogen therapy has been associated with an increased risk of gallstone disease (Zhao, 1990). Our findings also serve as a cautionary note regarding the use of oral contraceptive steroids and conjugated estrogens in premenopausal women, as well as hormone replacement therapy in postmenopausal women, as a preventive measure against the development of cholesterol gallstones in these populations.

Therefore, it is advisable to closely monitor FSH and LH levels, as well as their ratios, in individuals with gallstones as an initial measure for detecting potential associated complications. The findings from this study underscore the importance of ongoing monitoring of the FSH/LH ratio in gallstone patients, as this may signal reproductive anomalies within this population. Consequently, further research and increased awareness regarding estrogen hormone levels, lipid profiles, and the potential risks associated with various forms of estrogen administration are recommended. Additionally, attention to nutritional and lifestyle factors is crucial, as they are also recognized as risk factors for gallstone formation.

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