Changes in Blood Estrogen Level after Cholecystectomy in Pre-Menopausal Women

Manar G. Sabbagha, MSc* Saad Muwafaq Attash, ABHS ** Heba Khaled Hatem, MSc ***, Ruba A. Mahmood, F.I.B.M.S ****

ABSTRACT

Estrogen is the main female sex hormone. Estrogen is largely metabolized in the liver via several routes, enabling the body to eliminate and detoxify estrogen. Gallbladder stones are a commonly encountered problem in our local society and Cholecystectomy is one of the most frequently performed surgical procedures. The link between estrogen level and gallstone formation has been studied before but, the changes in blood estrogen levels in pre-menopausal women after cholecystectomy were rarely mentioned in research articles. The study aims to examine the changes in blood estrogen levels in pre-menopausal women post-cholecystectomy. A prospective - observational study, assessing the estrogen levels of 77 pre-menopausal women before and one month after cholecystectomy.

Inclusion Criteria: Pre-menopausal women who have gallstones and require cholecystectomy and with a regular menstrual cycle. Exclusion Criteria: Patients who are pregnant or with irregular cycles, who have diabetes, hypertension, thyroid disorders and those on hormonal therapy (HRT) like oral contraceptive pills (OCP) and contraceptive patches. Patients with ovarian, uterine and breast cancer, adrenal gland tumors, polycystic ovary syndrome (PCOS) and endometriosis. We found that the levels of estradiol (E2 (one month after cholecystectomy were higher in concentration. A statistically significant disparity in the magnitude of estradiol (E2) was found prior to and during 1-month period after gallbladder removal in pre-menopausal women.

Keywords: Estradiol, estrogen metabolism, post-cholecystectomy, pre-menopausal women

INTRODUCTION

Estrogen is a vital steroid hormone that exerts diverse physiological effects within the human body, particularly in females. As the predominant female sex hormone, it plays a central role in the regulation of reproductive functions, including the development, maturation, and maintenance of the reproductive system. Beyond its reproductive significance, estrogen also contributes to the establishment and preservation of secondary sexual characteristics such as breast development and fat distribution. Furthermore, it influences various non-reproductive systems, including bone metabolism, cardiovascular health, and cognitive function, underscoring its widespread impact on overall physiological homeostasis[1]. Estrogen levels exhibit variability across individuals. They also vary throughout the menstrual cycle and throughout a woman's lifespan[1,2].

In females, the ovaries synthesize estrogen in response to stimulation by luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There are three principal endogenous estrogens: estrone (E1), estradiol (E2), and estriol (E3). Among these, estradiol (E2) serves as the dominant sex hormone during the reproductive years, playing a crucial role in fertility and overall reproductive function. Estriol (E3) levels increase significantly during pregnancy, whereas estrone (E1) becomes the predominant estrogen in postmenopausal women. These hormonal variations reflect the dynamic endocrine changes occurring across different life stages[3].

The reference ranges for estradiol:

- Day1-14(Follicular phase): 72-529 pmol/L
- Day 14(Ovulation): 235-1309 pmol/L
- Day 14-28(Luteal phase): 205-786 pmol/L[1, 2]

Progesterone and estrogen function in a delicate balance, often counteracting each other's effects to maintain hormonal equilibrium. Estrogen dominance, a state in which estrogen levels exceed those of progesterone, can arise from various physiological and environmental factors. While the removal of the gallbladder has been suggested as a potential contributor to this imbalance due to its role in bile mediated hormone elimination there is currently no direct scientific evidence confirming a link between cholecystectomy and altered estrogen levels[4].

Bile plays a crucial role in the elimination of hormones, including estrogen. Under normal physiological conditions, bile binds to estrogen in the bowel, preventing its reabsorption into the bloodstream and facilitating its excretion in an inactive form. [4,5] However, impaired bile function, as often observed following cholecystectomy, can lead to reduced efficiency in hormone elimination. This diminished clearance may contribute to an accumulation of estrogen in the body, potentially resulting in symptoms associated with estrogen dominance, such as abdominal cramping, breast tenderness, fluid retention, and acne[5,6,7].

* Assistant Lecturer, Department of Medical Physiology, College of Medicine, Ninevah University, Mosul, Iraq, Manar.abdulahad@uoninevah.edu.iq

** Assistant Professor, Department of Surgery, College of Medicine, Ninevah University, Mosul, Iraq.

*** Assistant Lecturer, Department of Medical Physiology, College of Medicine, Ninevah University, Mosul, Iraq.

**** Consultant Surgeon, Al-Jamhoory Teaching Hospital, Mosul, Iraq.

MATERIALS AND METHODS

A prospective observational study evaluating estrogen levels in 77 premenopausal women before and one month after undergoing cholecystectomy.

- This prospective observational study was conducted in private clinics in Mosul, Iraq, from March 2023 to October 2023. The study aimed to assess estrogen levels in 77 premenopausal women before and one month after cholecystectomy. Verbal consent was obtained from all participants before enrollment.
- **Inclusion Criteria:** Participants were premenopausal women who:
  - Had gallstones and required cholecystectomy.
  - Had regular menstrual cycles.

- **Exclusion Criteria:** Women were excluded if they:
  - Were pregnant or had irregular menstrual cycles.
  - Had diabetes, hypertension, or thyroid disorders.
  - Were on hormonal therapy (HRT), including oral contraceptive pills (OCPs) and contraceptive patches.
  - Had ovarian, uterine, or breast cancer.
  - Had adrenal gland tumors, polycystic ovary syndrome (PCOS), or endometriosis.

- The patients' ages spanned from (16 to 50 years) with Mean ± SD of 36.51±9.61 years.

All surgeries were performed by the same team of surgeons under general anesthesia in a secondary surgical unit of a private hospital in Mosul. Patients were discharged within four to six hours postoperatively, and all had an uneventful recovery. Blood samples were collected as part of the preoperative evaluation during the follicular phase of the menstrual cycle and again one month after surgery. Using antecubital venipuncture, five milliliters of venous blood were drawn into plain tubes and left to coagulate in a water bath at 37°C. The samples were centrifuged at 5000 rpm for five minutes to separate the serum, which was then stored at -18°C until analysis. Before measurement, the samples were thawed at room temperature for the determination of serum estradiol (E2) levels.

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS, version 21). Various statistical methods were employed to assess differences in estrogen levels before and after surgery. The data were represented as the mean ± standard deviation (SD) for quantitative values. The t-test was employed to assess the disparities among the means of a given variable. The effect size was demonstrated using Cohen's D equation, which involved calculating the value of Cohen's d and the effect-size correlation, rY⁰, using the means and standard deviations of the two readings (before. and post. operation).

$$\text{Cohen's } d = M_1 - M_2 / \sigma_{pooled}$$

$$\text{where } \sigma_{pooled} = \sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}$$

$$r_{Y\lambda} = d / \sqrt{(d^2 + 4)}$$

Statistical significance was for all tests at $p < 0.05$.

RESULTS

The pre-operative levels of E2 were measured as 78.92 pg/ml with a standard deviation (SD) of 69.08 pg/ml (95% CI for mean = 63.14 to 94.71 pg/ml). The levels ranged from 2.90 to 309.00 pg/ml. The post-operative levels of E2 were measured as 100.16 pg/ml with a standard deviation (SD) of 89.91 pg/ml (95% CI for mean = 79.61 to 120.71 pg/ml), with values ranging from 2.40 to 471.00 pg/ml (Table 1).

Table 1. Levels of E2 before and after cholecystectomy

E2, pg/ml	Mean ±SD	95% CI for mean	Mean difference ±SD	95% CI of the difference	P-value
Pre-Op	78.92± 69.08	63.14-94.71	-21.23-±52.100	(-33.14) – (-9.33)	0.001
Post-Op	100.16±89.91	79.61-120.71			

DISCUSSION

Bile acids, synthesized in the liver and stored in the gallbladder, play a crucial role in fat absorption, metabolism, and endocrine regulation. Beyond their digestive functions, bile acids act as signaling molecules that influence metabolic pathways, including estrogen metabolism, through nuclear receptors such as the foresaid X receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5)[8,9]. Bile serves as

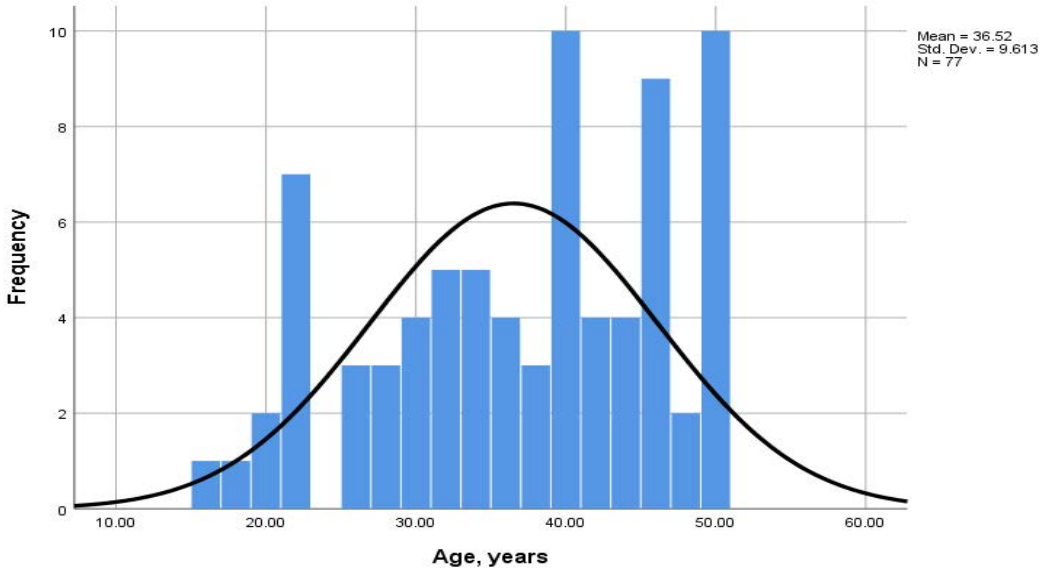

Figure 1. Patients age in the collected sample.

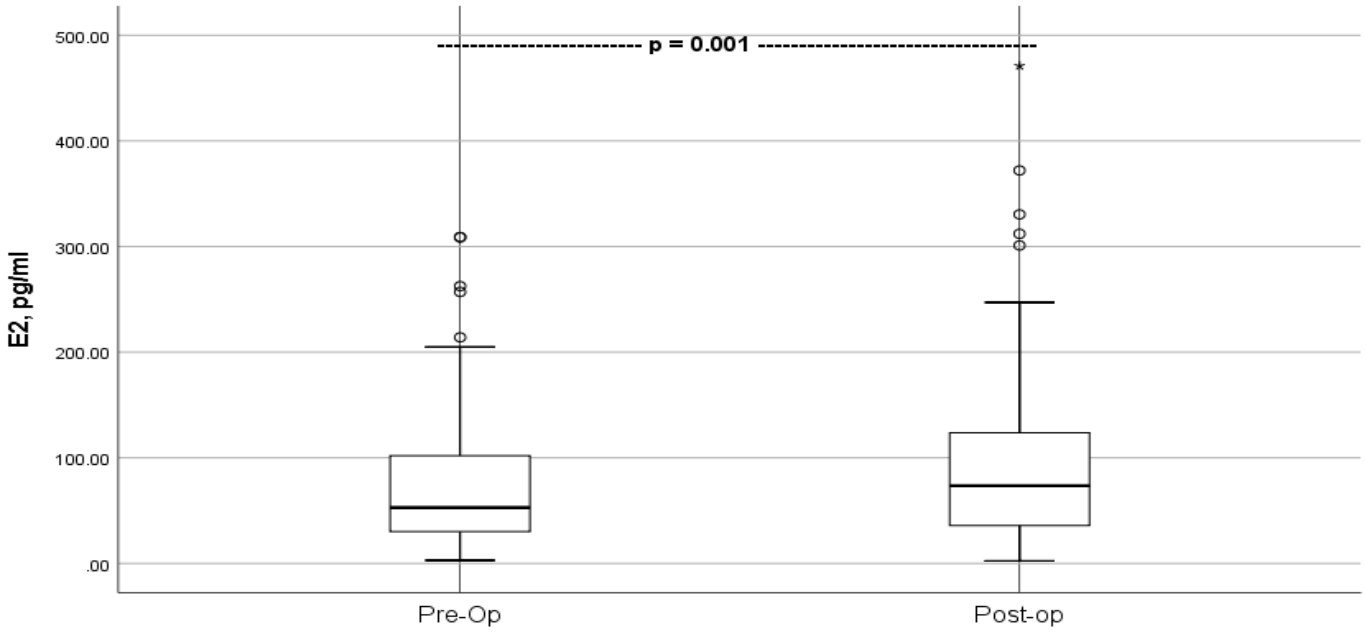

Figure 2. Level of E2 before and after cholecystectomy

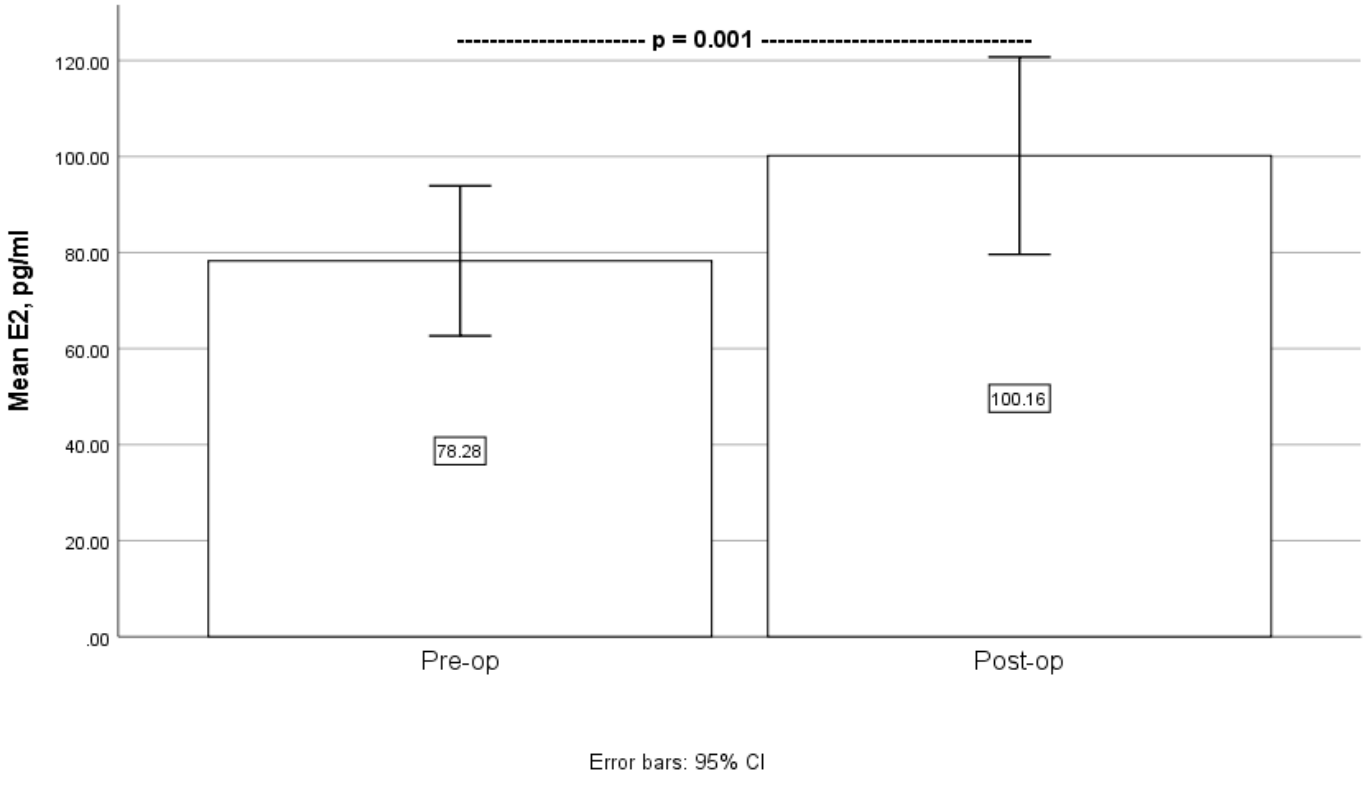

Figure3. Level of E2 before and after cholecystectomy (Via Cohen's d equation) * Cohen's $d = 0.26$, effect size $r = 0.13$

a primary route for estrogen excretion, and disruptions in bile acid homeostasis may impact estrogen clearance and feedback regulation[10] (Figure 1).

While various treatments exist for gallstone disease, cholecystectomy remains the most effective and widely utilized intervention[11]. The removal of the gallbladder alters the normal cycle of bile acid circulation in the body, which can disturb hormonal signaling pathways responsible for metabolic stability[12]. This disturbance may have consequences for estrogen metabolism, potentially causing hormonal shifts that affect different physiological functions (Figure 2).

This study aimed to evaluate the short-term impact of cholecystectomy on estrogen levels, specifically examining changes within the first month after surgery. Since limited research has explored this area, the study sought to contribute to a broader understanding of the endocrine effects associated with gallbladder removal.

The results revealed a significant rise in estradiol (E2) levels within one month following cholecystectomy. Before surgery, E2 concentrations ranged from 2.90 to 309.00 pg/mL, with a mean ± SD of 78.92 ± 69.08 pg/mL (95% CI: 63.14–94.71 pg/mL). After surgery, levels ranged from 2.40 to 471.00 pg/mL, with a mean ± SD of 100.16 ± 89.91 pg/mL (95% CI: 79.61–120.71 pg/mL). These findings suggest that cholecystectomy may influence estrogen metabolism, potentially affecting hormonal balance in premenopausal women.

Existing research on this topic has produced mixed results. Some studies, such as research conducted in Misan City, Iraq, reported a decrease in estrogen and progesterone levels following gallbladder removal, particularly in non-pregnant women who were not using contraceptive therapy[13]. This contrasts with the present study, which observed an increase in estradiol levels postoperatively. Differences in study design, patient demographics, dietary patterns, and metabolic responses to surgery may explain these inconsistencies.

Several potential mechanisms could account for the observed rise in estrogen levels after cholecystectomy. The disruption of bile acid balance may slow down estrogen clearance by affecting the liver's ability to metabolize and eliminate the hormone. Additionally, changes in the way estrogens recirculate through the digestive system might increase the reabsorption of estrogen metabolites, leading to higher overall estrogen levels[14,15]. Another factor could be changes in dietary fat intake after surgery, as dietary lipids influence bile acid production and hormonal regulation[16].

To validate these findings, future research should involve larger sample sizes and long-term follow-up to determine whether estrogen levels remain elevated beyond the initial postoperative period. Additionally, studies assessing symptoms associated with high estrogen levels—such as irregular menstruation, polycystic ovary syndrome (PCOS), weight gain, and headaches—over a period of 6 to 12 months could offer deeper insight into the clinical significance of these hormonal changes. Controlling factors like diet, body mass index (BMI), and pre-existing metabolic conditions would further strengthen future analyses.

CONCLUSION

This study suggests that gallbladder removal (cholecystectomy) might affect how the body processes estrogen. Researchers found a noticeable rise in estradiol (E2) levels within a month after surgery, which raises questions about its potential hormonal effects, especially in premenopausal women. However, previous research has produced mixed results, making it clear that more studies are needed. Future research should involve larger groups of participants and extend over a longer period to get a clearer picture. Factors like body weight, diet, and existing metabolic conditions should also be considered to fully understand the long-term hormonal changes and their medical relevance.

Authorship Contribution: Manar G. Sabbagha: Methodology, Conceptualization, Software, Investigation, Resources, Data Curation; Saad Muwafaq Attash: Methodology, Validation, Formal Analysis, Investigation, Supervision, Project Administration; Heba Khaled Hatem: Methodology, Validation, Writing – Original Draft, Writing – Review & Editing, Project Administration; Ruba A. Mahmood: Methodology, Validation, Visualization, Formal Analysis

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 15 April 2025

REFERENCE

1. Delgado BJ, Lopez-Ojedo W. Estrogen. Treasure Island (FL): StatPearls Publishing; 2019;
2. Bjune J, Strømland PP, Jersin RÅ, et al. Metabolic and epigenetic regulation by estrogen in adipocytes. Front Endocrinol (Lausanne) 2022;13.
3. Thomas MP, Potter BV. The structural biology of oestrogen metabolism. J Steroid Biochem Mol Biol 2013;137:27–49.
4. Palmisano BT, Zhu L, Stafford JM, et al. Role of estrogens in the regulation of liver lipid metabolism. Adv Exp Med Biol 2017;1043:227–56.
5. Fleishman JS, Kumar S. Bile acid metabolism and signaling in health and disease: molecular mechanisms and therapeutic targets. Signal Transduct Target Ther 2024;9(97).
6. Patel S, Homaei A, Raju AB, et al. Estrogen: the necessary evil for human health, and ways to tame it. Biomed Pharmacother 2018;102:403–11.
7. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991;324(16):1073–8.
8. Chiang JY. Bile acid metabolism and signaling. Compr Physiol 2013;3(3):1191–212.
9. Thomas C, Pellicciari R, Pruzanski M, et al. Targeting bile-acid signalling for metabolic diseases. Nat Rev Drug Discov 2008;7(8):678–93.
10. Zhang Y, Edwards PA. FXR signaling in metabolic disease. FEBS Lett 2008;582(1):10–8.
11. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver 2012;6(2):172–187.
12. Houten SM, Watanabe M, Auwerx J, et al. Endocrine functions of bile acids. EMBO J 2006;25(7):1419–25.
13. Aati EK, Mohammed HJ. Estimation of the levels of progesterone and estrogen after cholecystectomy in women at Misan City, Iraq. J Biosci Appl Res 2024;10(3):375–84.
14. Russell DW. The enzymes, regulation, and genetics of bile acid synthesis. Annu Rev Biochem 2003;72(1):137–74.
15. Lefebvre P, Cariou B, Lien F, et al. Role of bile acids and bile acid receptors in metabolic regulation. Physiol Rev 2009;89(1):147–91.
16. Hegyi P, Maléth J, Walters JR, et al. Guts and gall: bile acids in regulation of intestinal function in health and disease. Physiol Rev 2018;98(4):1983–2023.