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Estimation of the levels of progesterone and estrogen after cholecystectomy in women at Misan City, Iraq

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Abstract:

Cholecystectomy, the most popular surgical procedure worldwide, is carried out laparoscopically in more than 90% of cases and is considered as "gold standard" for the surgical treatment of gallstones. **Aim of the study:** Our research set out to determine whether women's levels of estrogen and progesterone hormones were related to cholecystectomy. **Methods and Materials:** 40 women, 20 of whom had undergone cholecystectomy and 20 as a control group and were aged 30-45, participated examined Al-Sadr Teaching Hospital and a few laboratories in Misan City between November 2023 to February 2024. The participants gave up 5 ml of their whole blood via a medical syringe. The blood sample was put in a gel tube and placed at room temperature for 20 min to allow for clotting and centrifuged for 10 minutes at 3000 rpm to collect serum to test the hormones Estro and Progs. **Results**. When compared to the patients' Progesterone decreased significantly ($p \leq 0.050$) in the patients' group (0.41 ± 0.40 ng/mL) compared with the control group (1.75 ± 0.95 ng /mL). When compared to patients(5.54±4.49), the Estro findings in the control group(45.68±23.88) were considerably higher($p \leq 0.05$).**Conclusion:** In the present study we can conclude the levels of progesterone and estrogen decreased in cholecystectomy women because the women that choices in our study were nonpregnant and did not use contraceptive therapy**,** and the risk of cholecystectomy increased after 6 months of gallbladder removal, and it increased in pregnant women more than nonpregnant women.

Keywords: Cholecystectomy, estrogen, progesterone, endometrium, and ovarian cancers.

Introduction

Bile flows through bile ducts from the liver to the intestine, where it is collected by the gallbladder. Gallbladder stones are caused by bile stasis within the gallbladder, and they have the potential to develop into severe jaundice or gallbladder carcinoma (1). In the US, 10-15% of adults suffer from gallbladder disease (2). Most gallstones are clinically "silent," and 50–75% of people don't have symptoms such as cholangitis, pancreatitis, biliary colic, or acute cholecystitis (2). Nevertheless, a higher total mortality rate from cancer as well as cardiovascular disease is linked to gallstones, both asymptomatic and symptomatic (3,4). Cholesterol gallstones, especially progesterone, are more common in females than in males and are predominantly associated with sex steroids. (5-12). The most frequent reason for non-obstetric hospitalizations throughout the first year postpartum has been observed to be gall bladder diseases (13). Pregnancy is linked to a significant risk for gallstones, according to epidemiologic research

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(14). There is a substantial correlation between the frequency and number of pregnancies and an increased risk of gallstones or biliary sludge (10,11,15,16). Gallbladder motility and bile composition change throughout pregnancy, which encourages the production of gallstones (7,8,9). In addition to altering the lipid composition of bile, progesterone prevents intracellular calcium mobilization inside gallbladder smooth muscle cells, resulting in gallbladder relaxation and decreased gallbladder motility. Women with biliary sludge are typically asymptomatic. Yet, individuals who have stones may experience discomfort or severe problems including cholecystitis, and pancreatitis, or which may have a high rate of mortality or morbidity for both the mother and fetus (17,18). Gallstones are more common in females than in males, which may indicate that sex steroid hormones contribute to gallbladder cancer and gallstones development (19,20). Progestins decrease gallbladder emptying, which causes bile stasis, while estrogens increase the secretion of cholesterol and decrease the secretion of bile salt, which contributes to the development of gallstones (2). Exogenous sources of those sex hormones, MHT (i.e., menopausal hormone therapy), have been linked to gallstones, according to many observational studies conducted throughout the 1970s and 1980s (21). Women's Health Initiative (WHI) (22) observed higher risks of self-reported gallstones, and the Heart and the Estrogen/progestin Replacement Study (HERS-II) (23) reported a higher incidence of cholecystectomy. MHT was administered to women at random. MHT use was linked to a higher 5 and a lower gallbladder cancer risk (24, 25), where the main risk factor is gallstones (2). A cholecystectomy, or surgical removal of the gallbladder, is mostly indicated by cholelithiasis, or symptomatic gallstones, and the repercussions that follow. Due to the high prevalence of gallstones and their continued rise, cholecystectomy is a very common surgical procedure (26,27). There are several known risk factors for gallstone development. Depending on age, women are two to three times more likely than males to develop gallstones, making gender one of the main risk factors (28, 29). Among the major risk factors shared by gallstone disease, endometrial, breast, and ovarian cancer are obesity, overweight, and exposure to the female sex hormones (30, 31). The use of oral contraceptives, parity, and low socioeconomic status are all associated with gallstones and cervical cancer. However, despite these common factors of risk and some claims that cholecystectomy is related to increased endometrial and breast cancer risks, the relationship between female cancer risk and cholecystectomy hasn't been extensively studied (32, 33). Since symptomatic gallstones only make up a small percentage of gallstone patients, previous studies of menopausal hormone therapy (MHT) and gallstones that used symptomatic gallstone indicators, like cholelithiasis, diagnosed cholestasis, or cholecystectomy, are hampered by bias of detection (34). Confounding by contraindication could happen in the case where the patients most at risk for the outcome are least possibly to be prescribed the studied treatment, whereas confounding by indication could happen in the case when the indication for treatments is a factor of risk for outcome (major depressive disorder amongst the users of the antidepressants) (35, 36). It's possible that doctors prescribed MHT less frequently to women who were at risk for gallstones (for example, because of high parity, obesity, family history, etc.) (35,37).

Materials and Methods

Forty women, twenty of whom had undergone cholecystectomy and twenty of whom were in the control group and were aged 30-45, participated in the study. The women examined Al-Sadr Teaching Hospital and a few laboratories in Misan City between November 2023 and February 2024. Each participant (both controls and patients) gave five milliliters of their entire blood via syringe. Test tubes have been used for collecting venous blood samples while adhering to aseptic procedures. The

blood sample was placed in a gel tube at the temperature of the room for the clotting and after that centrifuged at 3000rpm for 10min to collect serum to analyze hormones Progesterone and Estrogen with the use of a Cobas e 411 equipment.

Statistical analyses

The values have been expressed in the form of mean ± SD. Statistical analyses of data have been carried out to know the significant differences using analysis of T- test by (SPSS) to show the important statistics and significant differences limited on P<0.05 of probability (38).

Results

1-Progesterone Hormone

The values of Progesterone decreased significantly (p ≤0.050) in the patients' group (0.41 ± 0.40 ng/mL) compared with the control group (1.75 ± 0.95 ng /mL).

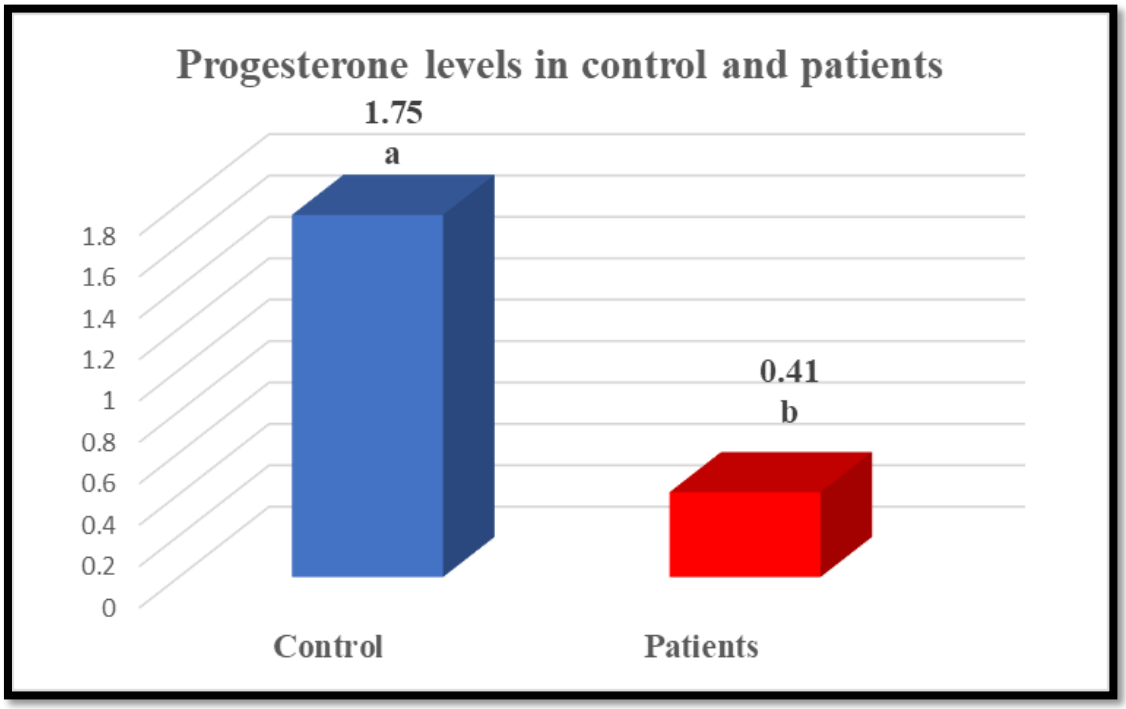

Figure (1): The progesterone levels in patients and control women

- Value represent mean± SD
- Different letters indicate significant differences between the groups at level (P≤0.050)

2-Estrogen Hormone

The values of Estrogen decreased significantly ($p \leq 0.05$) in the patients' group (5.54 ± 4.49 Pg/mL) compared with the control group (45.68 ± 23.88 Pg /mL)

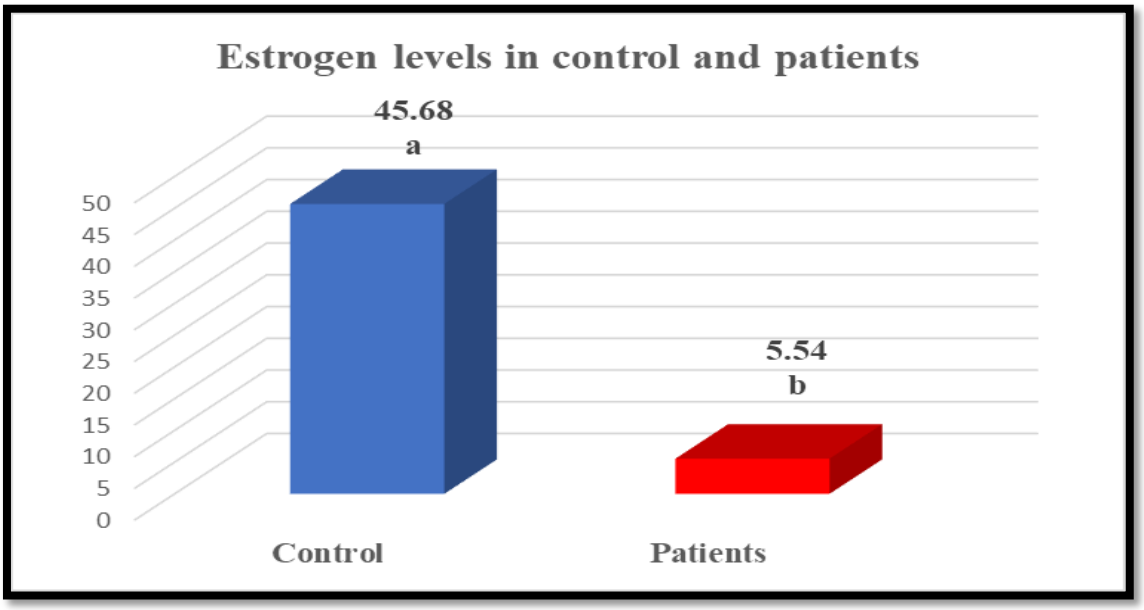

Figure 2: The Estrogen levels in control and patients' women

- Value denotes the mean ± SD
- Different letters indicate significant differences between the groups at the level ($P \leq 0.05$)

Discussion

In this study, we chose women who diagnosed had gallstones or problems in the gallbladder identified by abdominal ultrasonography and made cholecystectomy to evaluate the reproductive hormones (progesterone and estrogen) to find the association between cholecystectomy and these hormones. Our findings demonstrate that, when compared to the control group of healthy women, the patients (women who had cholecystectomy) had lower levels of Progesterone and Estrogen. Theoretically, cholecystectomy could affect hormone levels by many different mechanisms, such as modifications to the enterohepatic circulation, adjustments to the absorption of fat, disruptions to metabolic processes, or disruptions to hormonal feedback pathways. It's still unknown, though, what precise processes could underlie any potential variations in progesterone and estrogen levels. Hormone regulation is one of the signaling pathways that bile acids are known to affect. These feedback mechanisms might be interfered with in the absence of the gallbladder, which could affect hormone synthesis, secretion, or receptor sensitivity (39).

Through the hepatic feedback mechanisms, estrogens become significant regulators of bile acid

synthesis and metabolism. According to a hypothesis, following a cholecystectomy, a decrease in bile acid pool size and an increase in the enterohepatic circulation frequency tend to lower lipid levels through lowering both total and low-density lipoprotein (LDL) cholesterol levels (40). Ovarian hormones regulate the gene expression of various endometrial cell types throughout the menstrual cycle (41). Estrogen is the hormone that controls the endometrium's proliferative phase, which promotes the growth of uterine glands, stromal cells, and a noticeable elongation of the spiral arteries. The rise in postovulatory progesterone (P4) causes the endometrium to take on a receptive phenotype that allows blastocyst implantation, it promotes the proliferation of stromal cells and stimulates glandular secretory activity, and it decreases the proliferation regarding epithelial cells while inducing their differentiation. The "window of implantation" (WOI) is the term used to describe this endometrial receptivity phase. This implantation window opens on the 19^{th} or 20^{th} day for women who are on a 28-day cycle, and it closes once P4 reaches peak serum concentrations, which is just 4–5 days later (42). Progesterone (P4) is a steroid hormone that plays a significant role in both normal and induced cycles by implantation in an estrogen-primed endometrium. Its concentration is low throughout the first half of the normal ovulatory cycles, but it gradually increases 12–24 hours before the luteinizing hormone (LH) surge begins (43).

The sequence of events that was postulated as a possible explanation for increased cancer risk following the cholecystectomy includes metabolic hormone level changes and bacterial microbiota, which could result in inflammation following surgical removal of the gallbladder (44,45,46). The finding that, in females who have a history of cholecystectomy and gynecological cancer types, approximately 30% to 63% of the cholecystectomy cases have been carried out after gynecological cancer diagnosis and not surgical gallbladder removal in particular, supports the idea that increased breast and endometrial cancer risks after the cholecystectomy are potentially a result of the common factors of risk. A portion of the correlation between cholecystectomy (which is most frequently recommended due to cholelithiasis) and breast cancers (particularly post-menopausal type), endometrial cancer, and ovarian cancers might be explained by dietary practices (particularly high consumption of fats and refined carbohydrate products), obesity, and ensuing metabolic and hormonal changes (47,48,49,50).

Since the women who participated in our trial were not pregnant and had not used contraceptive medication, we were able to determine that women who had cholecystectomy had lower levels of estrogen and progesterone. Pregnancy is known to cause physiological changes that enhance the formation of an optimal environment for gallstone development. Specifically, high levels of estrogen stimulate cholesterol secretion, while progesterone leads to decreasing the secretion of bile acid and delays the gallbladder's emptying. Those changes result in excessively saturated bile with cholesterol as well as a predisposition to gallstone formation (51, 52). Based on the data that was gathered, the incidence of gallstone symptoms among the 2814 pregnancies that were registered in one research was (4%). The majority of those occurrences occurred during the first trimester of pregnancy, then the third trimester. Accordingly, some studies discovered that a significant percentage of pregnant women experienced gallstones. Cholecystectomy is the second most frequent surgery performed on expectant mothers. Gallstones can affect up to 7% of the nulliparous females and up to 20% of the multiparous ones (53). Gallbladder hypomotility brought on by physiological and hormonal changes throughout pregnancy leads to the production of bile sludge in 31% of cases and gallstones in 2% of cases (54,55,56,57). Presenting it, though, does not mean that action is highly important. Patients asymptomatic throughout the pregnancy need no medical attention; nevertheless, cholecystectomy

can be necessary in the first year after giving birth due to recurrent acute illnesses or their consequences (58).

By encouraging hepatic secretion of biliary cholesterol (59,60,61), estrogen raises the risk of developing cholesterol cholelithiasis (62, 63, 64). These changes then trigger gallbladder stasis and a sharp rise in bile's cholesterol saturation, which further promotes cholelithogenesis (65,66,67,68), discovered that in mice given high doses of 17E-estradiol, the hepatic estrogen receptor D (ERD), yet not the estrogen receptor E (ERE), is mostly responsible for the development of cholesterol gallstones (69). According to a novel concept, high estrogen levels encourage cholesterol gallstone formation in the liver through the ERD signaling cascade, and women are more likely than men to develop gallstones because of variations in the way their livers respond to estrogen (70). Hepatic secretion regarding biliary cholesterol is known to significantly rise throughout pregnancy when estrogen levels are increased. Bile subsequently becomes more lithogenic and supersaturated with cholesterol. Furthermore, elevated levels of estrogen and progesterone may hinder the smooth muscle contractile action of the gallbladder, resulting in gallbladder stasis (71,72). In pregnant women, these anomalies significantly increase the risks of gallstones and biliary sludge production. The final two trimesters of pregnancy seem to have a higher disease incidence. Yet around one-third of pregnant women with gallstones are symptomatic (73,74,75). The most typical clinical manifestations in pregnant women who do have symptoms include acute cholecystitis, jaundice, biliary colic, and gallstone pancreatitis (76).

Conclusion

In the present study, we can conclude the levels of progesterone and estrogen decreased in cholecystectomy women because the women that choices in our study were nonpregnant and did not use contraceptive therapy, and the risk of cholecystectomy increased after 6 months of removal of gallbladder and it's increased in pregnant women more than nonpregnant women, other factors can increase the risk of cholecystectomy like age, obesity, changes in hormones and lifestyle.

Ethical approval

The study ethics approval was obtained from Al-Sadr General Hospital and some medical laboratories (and participants before enrollment, all participants have provided written informed consent.

Conflict of interest

The authors declare no conflicts of interest.

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