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NOVEL BIOCHEMICAL STUDY OF THE IMPACT OF CHOLECYSTOKININ HORMONE IN INFERTEREty PATIENTS

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Abstract
Infertility is a common hormonal condition in women and men of reproductive age, characterized by metabolic and hormonal disorders. This study investigated the relationship between cholecystokinin (CCK) and reproductive hormones in 90 infertile patients of both sexes of reproductive age and 90 healthy controls of both sexes. This study assessed levels of CCK, estrogen, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and testosterone (TST), as well as lipid profiles and body mass index (BMI) for both groups. The first group, both sexes, showed hormonal imbalance and CCK deficiency compared to the control group, as well as significantly higher levels of lipid profile and obesity compared to the control group. Finally, the study demonstrated that CCK is a novel indicator of increased risk of infertility and has potential as a diagnostic and therapeutic indicator for both sexes.
Keywords: *Gonadotropins Hormone, Cholecystokinin Hormone, Females Hormone, Testosterone, Infertility.*

INTRODUCTION

Infertility is a global problem with a significant impact on families and societies, affecting both sexes. Millions of people of reproductive age worldwide are affected by infertility, impacting their families and communities. Statistics indicate that between 48 million couples and 186 million individuals suffer from infertility worldwide (Sharma and Shrivastava, 2022, ALjader & Aljawadi, 2021, Al-Ttaie & Aljawadi, 2021). Female infertility is a complex condition, with causes including impaired ovarian follicle development, ovulation, fertilization, or implantation. In women, it is a complex condition caused by multiple biological factors (Mustafa et al., 2023, Al-Jawadi & Al_taie, 2025). In men, it includes low sperm count, poor sperm motility, azoospermia, or a combination of these conditions, along with potential contributing factors (congenital malformations of the urinary tract) (Leslie et al 2024).Cholecystokinin (CCK) or CCK-pancreozymin (CCK-PZ) has been identified. It was discovered in 1928 based on the ability of intestinal extracts to stimulate gallbladder contraction (Rehfeld, 2017). It is an enteric neurohormone associated with the digestive system, consisting of 33 amino acids (Asim et al., 2024). It is secreted by enteroendocrine cells (EECs) after eating (Atanga et al., 2023). Recent studies indicate that CCK not only regulates appetite and digestion but also affects physiological functions associated with both sexes (Al-Talib & Al-Jawadi, 2024). Women have been observed to exhibit a greater response to the appetite-suppressing effect of CCK after consuming high-fat meals, compared to men. This is related to the hormone's interaction with hormones such as estrogen, which enhances the expression of CCK receptors in the brain (Wan et al., 2023). The purpose of this study is to investigate how CCK affects the early diagnosis of infertility.

MATERIALS AND METHODS

Sample Collection:
Samples were collected from January 22, 2024, to July 30, 2025, at Al-Batoul Teaching Hospital/Fertility and IVF Center in Nineveh Governorate, after obtaining ethical approval for sample collection from the relevant committee of the Nineveh Health Directorate, Iraq, for this study in accordance with the standards of the Declaration of Helsinki.
Infertility Patient Group: This study included 90 infertile female patients, aged 18–43.

Control Group: As a control group, 90 women aged 18–49 participated in this study.

Materials and Procedures:

Blood samples were taken in the morning after 12 hours of fasting (day 2 or 3 of the menstrual cycle) to measure levels of sex hormones (estrogen E2), progesterone, testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), cholecystokinin (CCK), glucose, and lipid profiles during the early follicular phase. Progesterone was measured during ovulation (day 13 or 14 of the menstrual cycle) for both groups.

A specialized kit (Bio Merieux kits) from Minividas-France was used to assess contaminants using the ELISA (Enzyme-Linked Immune Sorbent Assay) technique, and the Autolumo A1860 device.

Finally, SPSS version 27 was used to analyze the data, and the results were considered significant at a probability value of less than or equal to 5.

Ethical Approval:

The research was conducted and approved by the author's Institutional Review Board in accordance with all applicable national legislation, institutional policies, and the principles of the Declaration of Helsinki.

RESULTS

Clinical variables for males with infertile illness compared to the control group:

Table (1) showed that infertile men had significantly lower levels of the hormones CCK, progesterone, and testosterone compared to the control group. In contrast, infertile men had significantly higher levels of the estrogen hormones FSH and LH, prolactin PRL, as well as blood sugar GLU.

Table (1): Level of clinical variables for ' infernal disease compared to the control group among male.

Clinical Variables	Male Control Group (Mean±SD)	male Infernal Disease (Mean±SD)	p-value
CCK (pg/ml)	57.6 ± 4.06	32.5 ± 2.82	<0.001***
Estrogen(pg/ml)	65.6 ± 1.88	79.02 ± 3.78	<0.001***
FSH (m IU /ml)	4.8 ± 0.48	8.4 ± 1.6	0.02*
LH (m IU /ml)	4.9 ± 0.4	6.4 ± 1.1	0.01**
LH/FSH	1.1 ± 0.1	1.45 ± 0.2	0.04*
Progesterone(ng/ml)	2.3 ± 0.3	0.84 ± 0.16	<0.001***
Testosterone (ng/ml)	3.5 ± 0.2	1.9 ± 0.2	0.005**
PRL (ng/ml)	8.5 ± 1.7	20.2 ±2.3	<0.001***
GLU (mg/dl)	92.0 ± 4.4	100.8 ± 7.0	<0.001***

Table (2) showed that infertile women had significantly lower levels of cholecystokinin, estrogen, and progesterone compared to the control group. In contrast, the levels of the other variables shown in the table were significantly higher.

Table (2): Level of clinical variables for females' infernal disease compared to the control group

Clinical Variables	Female Control Group (Mean±SD)	Female Infernal Disease (Mean±SD)	p-value
CCK (pg/ml)	57.6 ± 3.9	31.3 ± 2.4	<0.001***
Estrogen(pg/ml)	66.1 ± 1.8	43.1 ± 0.82	<0.001***
FSH (m IU /ml)	5.2± 0.5	6.4 ± 1.1	0.05*
LH (m IU /ml)	5.5 ± 0.7	7.4 ± 0.83	0.04*

LH/FSH	1.08 ± 0.1	1.5 ± 0.2	0.06
progesterone(ng/ml)	1.3 ± 0.16	0.84 ± 0.16	0.05*
Testosterone (ng/ml)	0.33 ± 0.06	1.5 ± 0.2	<0.001***
PRL (ng/ml)	11.5 ± 0.48	35.34 ± 1.15	0.001***
GLU (mg/dl)	98.3 ± 4.3	104.3 ± 1.9	0.05*

Table (3): Level of clinical variables for males' infernal disease compared to the control group male

Clinical Variables	**Control Group (Mean±SD)**	**Infernal Disease (Mean±SD)**	**p-value**
Cholesterol (mg/dl)	168.2 ± 6.07	192 ± 5.8	0.007**
TG (mg/dl)	154.1 ± 13.2	226.5 ± 15.3	<0.001***
HDL (mg/dl)	32.5 ± 2.1	36.4 ± 2.4	0.23
VLDL (mg/dl)	30.1 ± 2.8	40.8 ± 3.6	0.02*
LDL (mg/dl)	99.87 ± 5.01	114.6 ± 9.8	0.17
Atherogenic risk	4.7 ± 0.39	5.5 ± 0.35	0.15
BMI (Kg/m^2)	23.5 ± 1.5	29.2 ± 1.4	0.001***

Table (4): Level of clinical variables for ' infernal disease compared to the control group among female.

Clinical Variables	**Control Group (Mean±SD)**	**Infernal Disease (Mean±SD)**	**p-value**
Cholesterol (mg/dl)	153.8± 3.3	182.9± 6.1	0.004**
TG (mg/dl)	122.0± 6.6	173.7 ± 12.9	0.009**
HDL (mg/dl)	37.72 ± 2.06	41.5 ± 2.0	0.22
VLDL (mg/dl)	30.2 ±1.4	33.7 ± 3.04	0.30
LDL (mg/dl)	116.6 ± 4.6	107.6 ± 5.5	0.27
Atherogenic risk	5.8 ± 0.34	4.7 ± 0.30	0.04*
BMI (Kg/m^2)	23.6 ± 1.6	30.8 ± 5.3	<0.001***

DISCUSSION

Table (1) showed a significant drop in cholecystokinin concentrations in infertile males compared to healthy men. This is because intestinal endocrine cells release CCK in reaction to lipids, carbs, and proteins. The gene expression of nutrient-sensing molecules in I cells is still unknown, owing to the difficulty of separating I cells from intestinal epithelial cells in vivo in this work (Kato et al., 2021). The low levels of CCK could be attributed to sperm cells expressing the CCK gene less than 25% of CCK. Interestingly, CCK peptides in mature sperm are localized in acrosome granules, raising the potential that CCK plays a role in fertilization through the interplay of acrosome expression, as human sperm also expresses its homologue, gastrin. The reason for the dual expression remains unknown (Persson et al., 1989). The results in Table (2) also demonstrated that infertile guys had significantly higher estrogen concentration than healthy males. This rise in estrogen is caused by adrenal gland hyperplasia, early puberty, and some ovarian, adrenal, and testicular cancers, all of which can result in excessive estrogen levels in the male body (Al-Jawadi, & Al_taie, 2025). Neurons convert testosterone to estrogen, which is extremely active in the brain during development. Thus, estradiol appears to govern not just sexual behavior in adult males, but also the early brain's programming of sexual behavior (Mohamed Khie et al., 2024). Table (2) also revealed a significant drop in progesterone concentrations in infertile and fertile guys. Very low levels can result in a testosterone shortfall because progesterone is required for both sperm

creation and maturation, as well as testosterone production. Progesterone is actually a basic structure of testosterone (Cable et al., 2022). Infertile males had a significantly higher prolactin content than healthy men, according to the results in Table (2). A reduction in gonadal function and a drop in testosterone are the ultimate effects of hyperprolactinemia on male fertility. These symptoms show up clinically as sexual dysfunction and a decline in the quantity and quality of semen parameters, which ultimately results in infertility (Green et al., 2020). According to the results in Table (2), infertile males had significantly higher FSH and LH concentrations than healthy males. Elevated LH and FSH levels are associated with a certain degree of spermatogenesis dysfunction, low sperm count, and poor motility in infertile males. This is supported by our findings that FSH and LH levels were significantly higher in the subfertile group (Hayon et al., 2024). Elevated FSH levels indicate pituitary or testicular dysfunction. Inhibin B, a hormone produced by Sertoli cells that normally inhibits FSH secretion and is a positive indicator of spermatogenesis in the seminiferous tubules, is deficient in association with elevated FSH levels (Halidou et al., 2022). The results in Table (2) also demonstrated that infertile males had a much lower testosterone levels than healthy persons. According to our findings, people with defective spermatogenesis have lower serum testosterone levels than people with normal sperm. Compared to controls, our idiopathic infertility patients had significantly higher serum FSH levels, and a FSH/LH ratio. Higher FSH levels can indicate an issue with the spermatogenesis area of the testicle. A low testosterone-to-luteinizing hormone ratio implies a probable impairment in spermatogenesis by verifying the reduced effectiveness of follicle-stimulating hormones on testicular function (Kim & Koo, 2023). The results in Table (2) also demonstrated that infertile men had a much higher glucose concentration than healthy males. According to studies, elevated blood sugar levels can have an effect on male fertility (Maresch et al., 2018) Men with impaired glucose metabolism experienced poor sexual function and difficulty conceiving (Barkabi-Zanjani et al., 2020).

The results in Table (2) demonstrated that infertile women had significantly higher prolactin levels than healthy women. Functional hyperprolactinemia caused by stress may be attributed to neuroendocrine alterations in dopamine and serotonin that affect prolactin secretion. Hyperprolactinemia raises ACTH secretion, which promotes adrenal hyperplasia and enhances adrenal cortical sensitivity. As a result, those who are more sensitive to stress show signs of hyperprolactinemia, this, in turn, may have a direct impact on fertility, as stress-related hyperprolactinemia causes hormonal changes that block the release of gonadotropins and the secretion of estrogen and progesterone from the ovaries. Given the direct and indirect long-term effects of prolactin, it appears that chronic stress-induced hyperprolactinemia can dramatically diminish female reproductive potential (Wdowiak et al., 2020). Table (2) also demonstrated that infertile women had significantly higher levels of LH and FSH than healthy women. This is owing to the fact that LH is an essential component of the menstrual cycle and works in tandem with FSH. High LH levels in infertile women are also connected with polycystic ovarian syndrome (PCOS), a major cause of infertility. This condition causes an imbalance in gonadotropin-releasing hormone (GnRH) secretion, resulting in higher pulses and elevated LH levels, which stimulates the ovaries to secrete androgens and testosterone, interrupting ovulation and causing cyst formation (International Evidence, 2023; Al-Jawadi, 2021). Hormonal imbalance is linked to both chronic disorders and infertility, with infertile women having higher levels of FSH, LH, and prolactin (Alheyali & Al-Jawadi, 2022; Al-Jawadi & Al-Helaly, 2008; Iris et al., 2003). Furthermore, Table (2) of the study showed that the male hormone was substantially more concentrated in infertile women than in healthy women. This is due to the fact that elevated testosterone levels in women can significantly impair fertility and often lead to infertility, as well as interfere with ovulation and the production of healthy eggs. The main reasons of increased testosterone levels in women of reproductive age include hyperandrogenism and irregular menstrual cycles (Sharma & Welt, 2021). The results in table (2) demonstrated that infertile women had significantly higher glucose levels than healthy women. This had a substantial influence on infertility, a measure of insulin resistance (IR), which was significantly higher in the infertile group than in the non-infertile group (Zhuang et al., 2024). Possible explanations for this relationship include ovarian theca cells, which create androgens, triggering hyperinsulinism and impairing FSH-dependent aromatase action, resulting in excessive androgen production and infertility. Furthermore, elevated glucose levels can impair egg quality by interfering with

mitochondrial activity (Zeber-Lubecka et al., 2023). IR also impairs endometrial tolerance and exacerbates androgen excess, which leads to ovulation issues (Lei et al., 2024).

The results in Table (3) showed a significant increase in the concentration of cholesterol and triglycerides, atherosclerosis factor in infertile men compared to fertile men, as hyperlipidemia and an abnormal body mass index (BMI), which is a major risk factor for infertility in men, lead to lower testosterone levels. Obesity in men is likely to be associated with lower fertility rates (Ding & Wang, 2022; Al-Taie & Al-Jawadi, 2019). Obese men had significantly lower semen volume, sperm count, and motility than men of normal weight (Abayomi et al., 2018).

According to the results shown in Table (4), infertile women had higher levels of cholesterol, triglycerides, atherosclerosis factor, and body mass index (BMI) compared to healthy women. This is due to the fact that obesity may lead to ovulation dysfunction and irregular menstrual cycles, as obese individuals have more adipose tissue, which is necessary for steroid metabolism and increased estrogen production. Menstrual irregularities can take various forms, and the main reason for this increase is the activity of the aromatase enzyme in adipose tissue, which converts androgens into estrogen. Hormonal imbalance resulting from elevated estrogen levels associated with obesity may be a factor in menstrual irregularities (Fielder et al., 2023; Al-Jawadi & Altalib, 2000).

CONCLUSION

The study concluded that CCK provides a unique diagnostic tool for early detection of infertility in both sexes, especially in young obese women, and could be an effective therapeutic target by monitoring its levels in patients with infertility in both sexes.

CONFLICT OF INTEREST:

There are no conflicts of interest in this study.

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