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Impact of Hormones Level and Fertility Status of Iraqi Subfertile Women

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ABSTRACT

Background: *To successfully conceive a child, a healthy egg must be produced by the woman, while the man produces healthy sperm which then fertilize the egg. For a baby to develop, the fertilized egg must then settle in the uterus. However, if anything goes wrong at any point in this process, subfertility can occur. Women's reproductive life was assessed in a study that focused on hormone levels. Hormones secreted by the anterior pituitary gland and the ovaries, such as FSH, LH, TSH, Prolactin hormone, and AMH are crucial for follicle development. Low or high levels of these hormones may suggest reduced fertility or infertility.*

Aim: *To assess the effect of hormones level on fertility status among sub fertile women.*

Materials and Methods: *A case -control study carried out in the Iraqi city of Nasiriyah conducted from Junary-2023 to September-2023, at private infertility clinic, the total number of participating women is 163; {sub- fertile women (N=93) and fertile women (N=70)}. A blood serum sample to test the following hormones; FSH, LH, TSH, Prolactin and AMH was measured at day two or day three of menstrual cycle done for all participating women.*

Results: *The studied groups split into two major groups according to age; the first group within age less than 35 years (N=106), while the second group within age more than or equal to 35 years (N=57). The statistical analysis shows significant differences in BMI and hormones level; FSH, LH, Prolactin and AMH, while no significant differences in age and level of TSH for both studied groups.*

Conclusion: *Significant differences in BMI and level of hormones among studied groups except TSH and age.*

Introduction:

Unwanted non conception for an extended period is the essence of subfertility, encompassing various remedial conditions [1]. Research conducted on populations shows that 10-15% of couples worldwide suffer from infertility [2]. The inability to conceive can be either primary or secondary. Primary infertility denotes the incapacity of a female to establish clinical pregnancy

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or carry it to term. Secondary infertility is the most common form among female individual worldwide. Specifically, this pertains to female individuals who have not achieved clinical pregnancy or delivered a live birth within 12 months after their most recent childbirth [3]. Irregular or absent menstrual periods are a sign of ovulatory issues [4], primordial follicle activation plays a key role in folliculogenesis, which selects one oocyte for ovulation. Menopause starts when the quantity of primordial follicles reaches just about one thousand. As humans age, there is a reduction in the quantity of primordial follicles that can develop potential for activation. This decrease in fertility is a direct result of this phenomenon. [5].

Present in the ovarian cortex, the menstrual cycle is divided into three phases, namely, follicular phase, ovulation, and luteal phase [6]. During the middle of the cycle, ovulation occurs due to the collaborative efforts of ovary, hypothalamus and pituitary. In order to release LH and FSH from anterior pituitary gland, the hypothalamus releases GnRH in a pulsatile fashion, which then acts on the ovarian follicle. The ovarian follicle contains crucial components such as granulosa cells, theca cells, and the oocyte. The process begins with the Luteinizing hormone, which influences the theca cells to produce androstenedione. This substance is then transformed into estradiol by aromatase, with its production being stimulated by Follicle Stimulating Hormone (FSH). When a critical concentration of estradiol is reached, the regular negative feedback on LH by estrogen is halted. After this shutdown, the hormone begins to have a positive influence on LH secretion and results in an "LH rise," which serves as the catalyst for ovulation. Post-ovulation, the follicle transforms into a corpus luteum, which functions to secrete progesterone, but only when activated by LH or hCG in case a pregnancy occurs [7].

1. Hormones:

1-Follicle-Stimulating Hormone:

The anterior pituitary gland releases follicle-stimulating hormone (FSH), which is a glycoprotein dimer containing both alpha and beta subunits. Interestingly, the beta subunit is unique to FSH, while the alpha subunit is shared with other hormones like hCG, TSH, and LH. This hormone is released in response to gonadotropin-releasing hormone (GnRH), which is secreted by the hypothalamus. In females, FSH receptors can be found specifically in the ovaries' granulosa cells. [7]. In a myriad of primary ovarian follicles, just one matures into a Graafian follicle, spurred on by the follicle-stimulating hormone released from the anterior pituitary gland. Meanwhile, unlucky follicles undergo atresia. The Graafian follicle that is developing dispenses estrogen into the liquor folliculi, which is responsible for the proliferative phase of the uterine cycle **[**6].

2-Luteinizing Hormone (LH):

The anterior pituitary gland secretes a glycoprotein known as luteinizing hormone (LH), which is typically accompanied by follicle-stimulating hormone (FSH). LH is an integral part of a neurological process that involves the hypothalamus, the pituitary gland, and gonads. This intricately balanced cycle is triggered by GnRH and countered by estrogen in females and testosterone in males. LH is responsible for regulating the length and order of the menstrual cycle, as well as influencing ovulation and implantation of an oocyte in the uterus [8].

3- Thyroid Stimulating Hormone (TSH):

Thyrotrope cells in the anterior pituitary gland produce a glycoprotein hormone, consisting of alpha and beta subunit, that regulates the thyroid gland's endocrine function.

Stimulation of granulosa cells occurred through cAMP activation, specifically via TSH. Dense concentrations of thyroid hormone receptor TRα1, TRß1, and TSH-Receptor were observed in ovarian surface epithelium, as well as primordial, primary, and secondary follicle, endometrial stromal, and Ishikawa cells. Evaluation of the thyroid should be conducted, based on the

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Endocrine Society's recommendations in 2012, specifically through TSH-receptor [9]. Achieving a TSH level below 2.5 mIU/L was suggested as a treatment for women experiencing infertility before becoming pregnant due to thyroid dysfunction.[10,11].

4-Prolactin Hormone:

Lactotrophs in the pituitary gland primarily generate prolactin, while the hypothalamus tonically restrains it. Prolactin, primarily responsible for breast milk production through the activation of prolactin receptors found in numerous tissues, is activated by dopamine. While there are alternate spots outside of the pituitary gland where prolactin may be produced, the 23-kDa isoform is the most prominent and activates through the membrane-based prolactin receptor.

Humans experience reproductive dysfunction due to the interference of high levels of prolactin, a cytokine superfamily member that acts as a receptor [12].

5- Anti-müllerian hormone (AMH):

Prompting the retraction of müllerian ducts is how this hormone earned its name. While also known as a serum marker for ovarian function, AMH has other functions. Granulosa cells of growing follicles express AMH in the ovary, up until the small antral stage. Even after FSH-dependent selection, preovulatory follicles retain expression of AMH in cumulus cells. However, expression disappears in corpora lutea and atretic follicles [13].

Materials and Methods:

Throughout in-depth interviews with 163 women, their age, weight, length, type, and duration of infertility were extensively studied. For both infertility women and controls, every blood serum sample collected from day two to day three of their menstrual cycle was a minimum of 2mL, and subjected to testing by the Full Automated 800 using a Snibe (maglumi) device. Hormonal levels for FSH(mIU/mL), LH(mIU/mL), TSH(mIU/L), AMH(ng/ml), and Prolactin (ng/ml) were simultaneously analyzed..

Statistical analysis

Using the statistical significance software package (SPSS) version 23.0 and Microsoft Excel 2010, we calculated our results and presented them as the mean ± standard deviation (mean ± SD). Our comparison of groups involved utilizing a one-way ANOVA test and we deemed values at $P<0.05$ as statistically significant.

Results:

Table1: Demographic characteristics such as age, BMI, are displayed for studied groups (N=106) within age less than 35 years; patient group(N=60),and control group (N=46) The age difference between the subfertile and control groups was not significant. While significant decrease for BMI shows in control group as compare to subfertile group. According to hormones level, FSH, LH, and Prolactin there is significant difference for subfertile group as compare to control group. Other hormones included in this study such as TSH, and AMH shows no significant differences.

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Variable	Patient(Mean)	SD	Control(Mean)	SD	p-value
Age(year)	34.21	3.33	33.12	4.87	0.234 NS
BMI(Kg/m^2)	28.23	3.45	25.76	3.89	0.001 **
FSH (mIU/ml)	10.45	2.75	16.21	3.11	0.005**
LH (mIU/ml)	13.27	2.31	16.217	6.728	0.030*
Prolactin (ng/ml)	17.28	2.50	14.568	3.17	0.040*
TSH (mIU/ ml)	2.55	0.93	2.618	0.98	0.650NS
AMH (ng/ml)	2.91	0.94	3.55	0.72	0.405NS

Table (1): The statistical analysis of hormones level among studied groups within age < 35 years.

ANOVA test

**** Extremely significant difference (P≤0.01)**

***Significantly different (P≤0.05).**

NS non significant different (P>0.05)

Table2: Demographic characteristics such as age, BMI, are displayed for studied groups (N=57) within age more than or equal to 35 years; patient group (N=33),and control group (N=24). The significant difference between the subfertile and control groups among BMI,FSH,LH, and AMH was clarified by table-2-. According to the age and other hormones included in this study such as prolactin, and TSH shows no significant differences.

Table (2): The statistical correlation for hormonal levels among studied groups within age > or equal to 35 years.

Variable	Patients(mean)	SD	Control(mean)	SD	p-value
Age(year)	41.57	4.32	39.34	3.89	0.221NS
BMI(Kg/m^2)	27.33	3.76	26.12	4.53	0.021**
FSH(mIU/mL)	15.12	3.67	20.82	4.29	0.023*
LH(mIU/mL)	10.22	2.32	16.79	2.64	0.013*
Prolactin (ng/ml)	12.26	2.05	14.34	2.75	0.062NS
TSH(mIU/ml)	4.78	1.36	3.30	0.93	0.051NS
AMH(ng/ml)	0.91	0.26	3.03	0.77	0.002**

ANOVA test

**** Highly significant difference (P≤0.01)**

***Significantly different (P≤0.05).**

There was no significant difference in NS (P > 0.05).

Discussion:

The evaluation of a female partner's infertility typically involves assessing the functionality of the ovulatory process as it is the most common cause of the issue[14]. To estimate this important step, certain factors such as ovulation problems - including hyperprolactinemia, hypogonadotropic hypogonadism, Hyper gonadotrophic hypogonadism, and polycystic ovaries - must be taken into account[15]. Oocyte maturation, which culminates in ovulation, is triggered by a surge of FSH and LH during the menstrual cycle in normal physiology. Modulating oocyte maturation during the natural menstrual cycle is a key role played by FSH. Meiosis of the oocyte and cumulus expansion are promoted by the surge of FSH, which also leads to LH receptor formation on luteinized granulosa cells [16]. Despite the age and fertility status of the groups studied, findings reveal no notable variations in TSH levels. Other investigations, however, emphasize the crucial impact of thyroid hormones on implantation and early pregnancy [17,18].

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The menstrual cycle, contrary to popular belief, is a convoluted phenomenon. Among all the different groups studied, the opportunity for an egg to be fertilized by sperm each month occurs during a precisely executed process. However, thyroid issues can disrupt this complex process and lead to an irregular menstrual cycle or amenorrhea. The significance of measuring TSH cannot be overstated, even though it is seldom abnormal, particularly in women with regular cycles [19]. Evidence suggests that hormonal imbalances resulting in menstrual disruption, anovulatory cycles, and reduced fecundity can manifest as infertility due to thyroid dysfunction. Restoration of normal fertility can be achieved through appropriate management of thyroid dysfunction, making it crucial to screen for thyroid abnormalities among women with infertility [20]. While amenorrhea is typically a prerequisite for hyperprolactinemia, Chang and Auchus (2019) indicate that a moderately raised serum prolactin level is present in 8-10% of women with polycystic ovarian syndrome [21]. Hyperprolactinemia may affect the anterior pituitary gland by reducing FSH and LH release after desensitizing it to GnRH effect. Additionally, the ovaries can suffer from direct effects of hyperprolactinemia, which can hinder steroidogenesis [22]. AMH levels remain relatively unaffected by pregnancy, contraceptive hormone usage, and treatment with GnRH-agonist due to its representation of the continuous and non-cyclic development of small follicles. Strangely, this hormone does not appear to be influenced by BMI or smoking status, as studies have shown [23, 24]. Age-related fertility decline is often assessed using endocrine markers such as AMH, as recommended by Hiremath et al. and Meczekalski et al. in their studies [25,26]. It is observed that women with older age experience ovarian reserve decrease, as indicated by increased FSH hormone levels and decreased AMH levels. Conversely, young women with minimal ovarian reserve demonstrate normal FSH levels but lower AMH levels. Studies have further shown that higher FSH levels are a late indicator of reduced ovarian reserve [27].

Conclusions:

The current study clarified that no significant differences among age and level of TSH among all studied groups included in this study. Significantly differences in BMI, level of FSH, LH among studied groups. AMH significantly differ in studied groups within age more than or equal to 35 years, while prolactin hormone level differs in studied groups within age less than 35 years.

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Consent to Participate: All participants provided written informed consent before participating in the study.

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