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THE EFFECT OF THYROID DYSFUNCTION ON ANTI-MOLLURIAN HORMONE CONCENTRATION IN THE INFERTILE WOMEN AT THE FERTILE AGE

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ABSTRACT
In the present study was an attempt to describe the complex relationships that link thyroid dysfunction and hypothyroidism with female infertility defined as the inability of a couple to achieve pregnancy over an average period of one year (in woman under 35 years of age) or 6 months (in a woman above 35 years of age) of unprotected sexual intercourse. The study was conducted in the infertility center of Al-Batoul teaching hospital in Diyala, age matching 100 patients and 50 control group, was selected for this study during the period from February 2014 to June 2014.The age of infertile and fertile women was ranged from 16 to 35 years. The study was conducted to find out the effect of thyroid disorders on serum anti-Mullerian hormone concentration in infertile women at reproductive age, and to find the correlation between anti-Mularian hormone (AMH) and the level of thyroid stimulating hormone (TSH), total thyroxin hormone (T4), triiodothyronin (T3), thyroglobulin (TG), follicular stimulating hormone (FSH) and luteinizing hormone (LH). The results are analyzed statistically among the control and infertile groups using (SPSS12) system and significant difference were considered when the p value exceeds 95%, $p<0.05$. There was a significant increase in the level of BMI, LH, TSH, AMH and TG while T3 and FSH level show significant decrease in serum concentration of infertile group than the control group (table -1) ($P\leq0.05$). While thyroxin hormone (T4) show no significant difference in the levels among patients and control groups.

KEYWORD: fertile and infertile women, Anti-Mullerian Hormone, Thyroid hormone function, FSH, LH, TG.

INTRODUCTION

Infertility defined as the inability of a couple to achieve pregnancy over an average period of one year (in woman under 35 year of age) or 6 months (in a woman above 35 years of age) of unprotected sexual intercourse. Infertility can be due to the woman, the man, or both: primary or secondary. For instance, if you or partner has a known fertility problem, you probably should not wait an entire year before seeking treatment. However, once you begin to explore your medical options, you'll find that fertility treatments offer more hope for a successful pregnancy than ever before. The vast majority of patients who seek care from a fertility specialist reach goal of becoming pregnant[1-3]. Infertility may be caused by an underlying medical condition that may damage the fallopian tubes, interferes with ovulation, or causes hormonal complication. These medical conditions include pelvic inflammatory disease, endometriosis, polycystic ovarian syndrome, premature ovarian failure, uterine fibroids and environmental factors. Other causes of infertility in females include ovulation problems, tubal blockage, age-related factors, uterine problems, previous tubal ligation and hormone imbalance while the main cause of male infertility is poor[4-5]. Ovarian dysfunction could be caused by weight loss and excessive weight gain with body mass index (BMI) greater than 27 kg/ m2. Excess weight has also been found to have effect on treatment efficacy and outcomes of assisted reproductive[6]. Fertility declines with age, and its peak between the ages of 18 and 24 years, while, it begins to decline after age 27 and drops at somewhat greater rate after age 35, so age is the most important factor in female infertility[7]. Infertility resulting from ovarian dysfunction may be due to absence of eggs in the ovaries or due to a complete blockage of the ovaries. Polycystic ovaries syndrome (PCOs) is usually a hereditary problem and accounts for up to 90% of cases of an ovulation[8]. In PCOS the ovaries produce high amounts of androgens, particularly testosterone and thus amenorrhea or oligomenorrhea is quite common. The increased androgen production in PCO results in high levels of luteinizing hormone (LH) and low levels of follicle-stimulating hormone (FSH), so that follicles are prevented from producing a mature egg [9,10]. The hypothalamus, through the release of gonadotropin releasing hormones, controls the pituitary gland which directly or indirectly controls most other hormonal glands in the human body thus, alterations in the chemical signals from the hypothalamus can affect the pituitary gland, ovaries, thyroid, mammary gland and hence, hormonal abnormalities. Hormonal imbalance is an important cause of an ovulation. Women with hormonal imbalance will not produce enough follicles to ensure the development of an ovule [9,11].

Anti-Mullarian Hormone (AMH)

Anti-Mullerian hormone (AMH) is a dimeric glycoprotein belonging to the transforming growth factor-beta (TGF-β) super family, which acts on tissue growth and differentiation[12,15]. It is produced by the granulosa cells

from pre-antral and small antral follicles. Together with two other factors, it inhibits the initiation of premature follicle growth and decreases the sensitivity of follicles to FSH[16]. AMH levels decline with age from adult hood toward menopause reflecting the size of the ovarian follicle pool[17]. Several studies have shown that serum AMH measurement is more accurate than serum FSH, inhibin B or estradiol in predicting ovarian response [18]. Furthermore, AMH levels appear to remain constant throughout the menstrual cycle and thus can be reliably measured at any time unlike FSH, LH, estrodiol and other hormone markers that must be measured in the early follicular phase [19,20].

Follicle stimulating hormone (FSH)

Human Follicle Stimulating Hormone (FSH) is a glycoprotein (M.W. approximately 30000D). FSH is secreted by basophilic cells of the anterior pituitary. FSH is responsible for the proliferation of the follicular cell, for the development of the griffin follicle and for ovum maturation[21]. FSH is needed to protect a portion of the follicles in the growing follicle pool from Atresia, stimulate the follicles to grow, and to select the highest quality follicle from its cohort to begin ovulation. Low levels of FSH are found during follicle development and high levels during ovulation. As the granulosa cells enlarge, the level of AMH is diminished, and the follicles enter the growing pool and become regulated FSH [18].

Luteinizing hormone (LH)

Known as Lutropin is a hormone produced by the anterior pituitary gland. In females, an acute rise of LH called the LH surge triggers ovulation and development of the corpus luteum[10]. In conditions with high LH and normal or low FSH levels, as in PCOS, AMH concentrations are positively correlated with LH concentrations, while they are not negatively correlated with FSH[15]. Furthermore, an independent positive correlation between AMH and LH levels has also been found[16]. Also shown that normal-weight women with PCOS presented higher LH values than overweight and obese women with the syndrome[22]. Thus, the lower LH concentrations observed in obese women may be attributed to the increased aromatization of androgens to estrogens which takes place in the peripheral fat tissue, resulting in the suppression of LH. Therefore, higher AMH levels seen in normal-weight women with PCOS compared to obese women[22,23].

Thyroid Function and Human Reproductive Health

Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction. In both genders, change in sex hormone binding globulin (SHBG) and sex steroids are a consistent feature associated with hyper- and hypothyroidism and were already reported many years ago[24]. In females, thyrotoxicosis and hypothyroidism can cause menstrual disturbances. Thyrotoxicosis is associated mainly with hypomenorrhea and polymenorrhea whereas hypothyroidismis associated mainly with oligomenorrhea [26].Thyroid dysfunction can lead to menstrual disturbance, anovulatory cycles, and decreased fecundity. Proper management of thyroid dysfunction can result restoration of normal fertility. Therefore it is very important to screen thyroid abnormalities among women with infertility [7].

MATERIAL & METHODS

The study was carried out in Diyala City in Al-Batoul Teaching Hospital the data were collected from (100) women as referred by Gynecologist for infertility investigation their average age 27 years (infertile women were visit the infertility unit for treatment and follow up). Additionally 50 normal fertile women (control group) their average age was (27) years, came from different residence. The study was conducted from February- 2014 till June - 2014. The inclusion criteria for the selection of cases were diagnosis of primary infertility, age under 30 years and duration of marriage more than one year. The exclusion criteria that were adopted during case selection were male factor infertility and amongst the female factors were tubal factor, any congenital anomaly of the urogenital tract, or any obvious organic lesion. 10 ml of venous blood was drown from those two groups at early follicular phase (day 2-3 of menstrual cycle) the serum was separated by centrifuge and divided in the eppendrof tubes and stored in deep freezing (-36C°). ELISA kit method was utilized to measure Anti-Mullerian hormone (AMH) and thyroglobulin hormone (TG) (auto-antibodies) in both groups, while follicular stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4) were determined by immune-radiometric assay method.

Body mass index is a number calculated from a person's weight and height. BMI provides a reliable indicator of body fatness for most people and is used to screen for weight categories that may lead to health problem.

$$BMI = \text{weight (KG)} / \text{height (m}^2\text{)}$$ ([26]).

Serum anti-mullerian hormone level & thyroglobulin (auto-anti-bodies) were determined quantitatively using a commercial kits obtained from CUSABIO BIOTECH CO[26], using the ELISA method, and immuno-radiometric assay was used for determination of FSH, LH, TSH, T3,and T4[27].

Statistical analysis

Statistical package for social sciences version 12 (SPSS v. 12) was used for data input and analysis. Continuous variables presented as mean ± Standard deviation (SD). Correlation for normally distributed data was tested by Pearson correlation test while Spearman correlation test was used for abnormally distributed data. Findings with P value less than 0.05 were considered significant.

RESULTS

Baseline characteristics

The results of all infertile women (n=100) in this study showed significant increase in the level of the body mass index (BMI), leutial hormone (LH), thyroid stimulating hormone (TSH), anti-mularian hormone (AMH) and thyroglobuline hormone (TG) table (1) except triiodothyronin (T3) & follicular stimulating hormone (FSH), show significant decrease than that of the control group (n=50) ($p \leq 0.05$),while thyroxin hormone(T4) level show no significant difference in its concentration , table (1). ($P \leq 0.05$).

TABLE 1: comparison among different parameters between patients group and control group

Parameter	Patients(n=100)	Control(n=50)	P value
Age	27.55 ± 5.95	27.55 ± 4.01	0.995
BMI	26.94 ± 4.18	24.96 ± 2.65	0.004
FSH	4.21 ± 1.57	7.13± 1.68	0.000
LH	5.29 ± 2.21	3.98± 0.92	0.000
TSH	2.4 ± 2.31	1.71 ± 0.29	0.05
T3	1.8±0.23	2.235±0.82	0.001
T4	93.56 ± 18.26	94.98± 7.67	0.657
AMH	21.33 ± 12.06	5.93 ± 3.18	0.000
TG	215.87± 711.8	51.56 ± 34.4	(0.000)

The correlation of different laboratory parameters with AMH among patients

There was a negative relationship between age and serum anti-Mullerian hormone concentration, while a positive correlation is present between BMI and serum AMH level (0.119), table (2). Also table (2) show negative correlation between AMH and serum level of FSH, TSH, LH, T4, T3, and TG, while (fig from.1--4), show no significant correlation between anti-Mullerian hormone (AMH) and thyroid hormones (TSH,T3,T4,TG)

TABLE 2: Correlation of different parameters of patients with AMH

Parameters	Correlation coefficient	P value
Age	-0.109	0.367
BMI	0.119	0.327
FSH	-0.276	0.021
LH	-0.358	0.002
TSH	-0.016	0.898
T3	-0.146	0.229
T4	-0.145	0.232
TG	-0.201	0.095

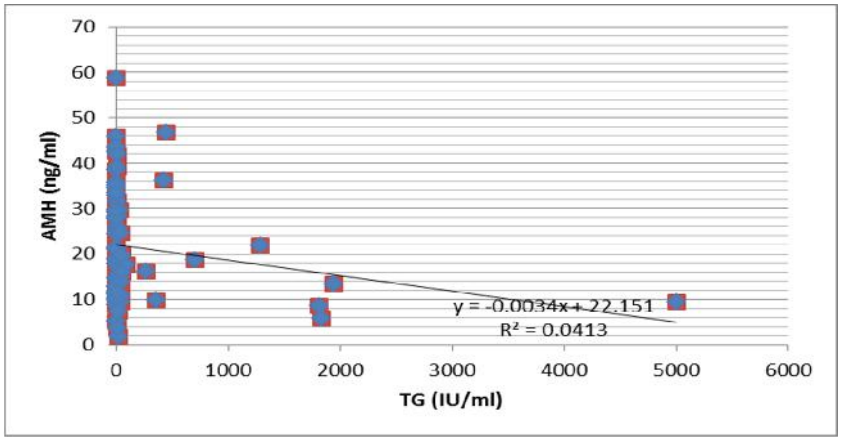

FIGURE 1-Correlation curve of the concentration of TG (IU/ml) and AMH (ng/ml)

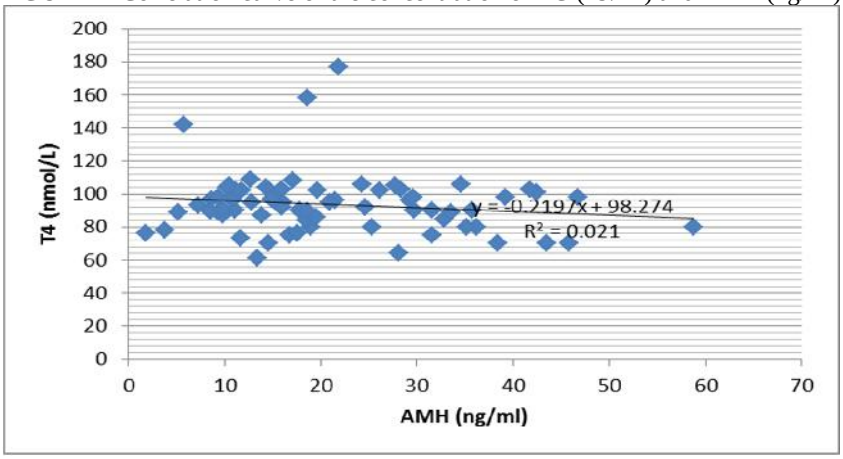

FIGURE 2- Correlation curve of the concentration of T4 (nmol/ml) and AMH (ng/ml)

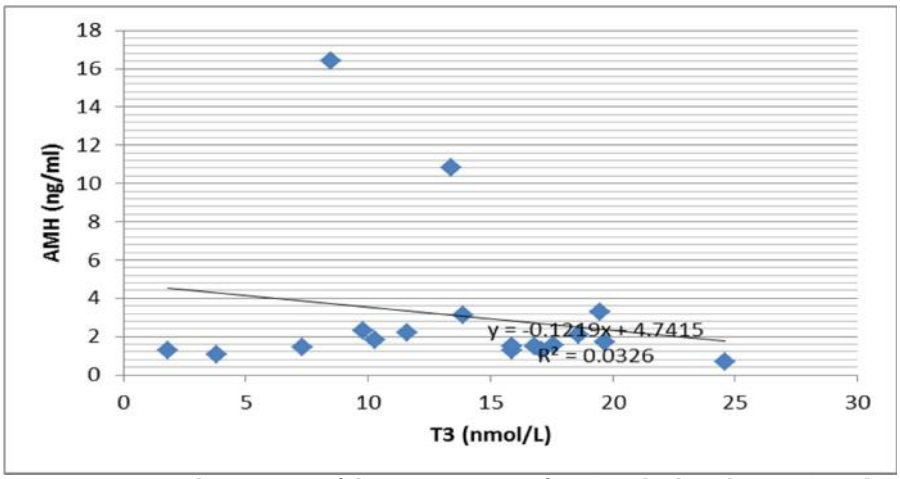

FIGURE 3-Correlation curve of the concentration of T3 (nmol/ml) and AMH (ng/ml)

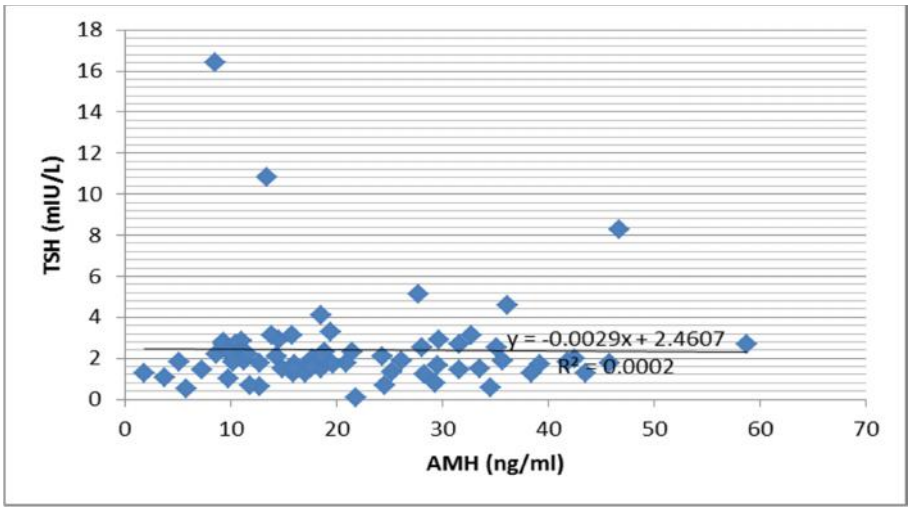

FIGURE 4-Correlation curve of the concentration of TSH (/ml) and AMH (ng/ml)

DISCUSSION

Via its interaction in several pathways, normal thyroid function is important to maintain normal reproduction. In both genders, changes in sex hormone binding globulin (SHBG)and sex steroids are a consistent feature associated with hyper- and hypothyroidism and were already reported many years ago[28]. In females, thyrotoxicosis and hypothyroidism can cause menstrual disturbances. Thyrotoxicosis is associated mainly with hypomenorrhea and polymenorrhea, whereas hypothyroidism is associated mainly with oligomenorrhea [29]. In the present study show that disturbance in thyroid function lead to menstrual cycle abnormalities and increase in the concentration of AMH in all infertile women (table-1), that show an increase in TSH concentration and decrease in T3 concentration (P≤ 0.05 ,0.001 respectively). So thyroid dysfunction has been linked to reduce fertility. Data listed in table (1) showed that there were significant increase in TSH and TG levels (P≤0.05, & P≤0.000 respectively), and a significant decrease in T3 levels (P≤0.001) compared with control groups, while there were no significant differences in T4 levels. Both the thyroid and ovarian are part of the endocrine system and belong to a common hormonal axis consisting of hypothalamus-pituitary-thyroid-ovarian[23],and according to recent studies, many evidences showed that women who suffered from PCOs present in most cases thyroid disorders which is often associated with hypothyroidism or at risk of future hypothyroidism[30]. The hypothyroidism may lead to lower sex hormone binding globulin (SHBG), which in turn leads to high concentration of testosterone, one of the factors that contribute to the onset of some symptoms of PCOs such as infertility [31,32]. While, the correlation between AMH and thyroid disturbances, there is a negative correlation (table-2) in patients. Hypothyroidism is associated with a broad spectrum of reproductive disorders ranging from abnormal sexual development through menstrual irregularities to infertility. The impact of hypothyroidism on the menstrual cycle has been identified since the 1950s and leads to changes in cycle length and blood flow[33,34]. Joshi et al found 68% of menstrual abnormalities in 22 women with hypothyroidism compared to only 12% in 49 controls [35]. In the study by Krassas et al, the prevalence of menstrual irregularities (mainly oligomenorrhoea) reached 23% among 171 hypothyroid patients, while being only 8% in 214 controls. The a authors also showed an association between the severity of menstrual abnormalities and higher serum TSH levels[36], which are in agreement with our study (P≤0.05). Severe hypothyroidism is commonly

associated with ovulatory dysfunction due to numerous interactions of thyroid hormones with the female reproductive system. Thyroid responsibility by the ovaries could be explained by the presence of thyroid hormone receptors in human Oocytes[37]. Thyroid hormones also synthesize with the FSH-mediated LH/hCG receptor to exert direct stimulatory effects on granulosa cell function [38], and in vitro studies effects on differentiation of the trophoblast have been shown[39]. Another pathway through which hypothyroidism may impact on fertility is by altering the peripheral metabolism of oestrogen and by decreasing SHBG production; both pathways may result in an abnormal feedback at the pituitary[40]. Several previous investigations cast serious doubts on the theory that thyroglobulin in a secluded antigen confined to thyroid gland[41,42]. In recent years data showing the presence of thyroglobulin in blood were extended to studies in patients with various pathologic states of the thyroid gland[43,44]. Although the mechanism of the release of this thyroidal protein into the circulation is presently unknown, profound architectural and biological changes of the thyroid gland which a ccompany neoplastic growth, could be responsible [45].The present study investigates the levels of thyroglobulin in the circulation of most women with different causes of infertility show highly increase than that of control groups (table-1,) ($P \leq 0.05$).

CONCLUSION

AMH is highly predictive for the time interval until the occurrence of menopause. Using age and AMH, the age range in which menopause will occur can be individually predicted. There is no significant correlation between AMH serum level and thyroid hormones (TSH, T3, and T3& TG) serum level. There is a negative correlation between BMI and AMH concentration for control group while a positive correlation is present between BMI and AMH concentration for patients group (table, 3-2 and 3-3 respectively. A full thyroid evaluation is essential, and should be done as soon as possible for any woman who wants to get pregnant, especially if she has been:

1-Has been trying unsuccessfully to get pregnant for more than 6 months.
2-Has had two or more miscarriages
3-Has an irregular menstrual cycle
4-Has any family history of thyroid problems.

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