Determination of inhibin B levels in hypothyroidism infertile Iraqi women.

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Received: 18/9/2019 Accepted: 26/11/2019 Published: 2020

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Abstract:

Thyroid disorders known to have an impact on the fertility for both males & females. The disturbing in thyroid hormones is usually linked with the decreasing of the reproduction chances. Inhibin B also have an important role in the fertility, and it have been linked with infertility of males. This study has designed to investigate the changing in inhibin B levels in hypothyroidism females with fertility problems. The study revealed a significant difference in inhibin B levels in hypothyroidism females when compared with healthy group (p-value= 0.05), without a significant correlation to the patients age, or the body mass index. The value of 156.35 pg. /ml gives a sensitivity of 95% and specificity of 86% in the infertile women.

Objective: To evaluate inhibin B in women with hypothyroidism and infertility. To investigate the body mass index for the studied groups, searching for possible correlation between body mass index and the inhibin B levels, and testing inhibin B results for sensitivity and specificity.

Design: Cross-sectional, controlled study.

Setting: Baghdad, Iraq.

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Patients: A group of infertile women with hypothyroidism (n= 50). A group of apparently healthy women (n = 40) served as controls.

Interventions: venous blood samples were drawn in the cycle day 3 for patients and controls.

Result(s): A significant difference in inhibin B levels has been found in hypothyroidism females when compared with healthy group (p-value= 0.05), without a significant correlation to the patients age, or the body mass index. The value of 156.35 pg. /ml gives a sensitivity of 95% and specificity of 86% in predicting the patients group.

Conclusions: The infertile women with hypothyroidism have a declining level of inhibin B, and a higher body mass index than healthy women. Inhibin B levels show a high rate of sensitivity and specificity in hypothyroidism females with fertility problems.

Key words: Thyroid disorders, hypothyroidism, inhibin B, infertility, females.

Introduction:

Infertility (synonyms: sterility, infecundity) is commonly defined as the incapability to gain a natural gestation after one year of regular sex without any contraception use. The centers of disease control and Prevention (CDC) refer to that any woman under 35 years old, have a regular sexual intercourse, and didn't get pregnant even without any use of contraceptives, should start to check with an infertility specialist [1, 2].

A recently study has shown that Iraqi women have a total fertility rate of about 4.5 children per woman, this study revealed that the maternal fertility have been declined in Iraq before 2003, and the war conditions have accelerated this declining –in 2003 the multi-national force take down the Iraqi regime, this war has been followed by a great chaos and lawlessness including the 2005-2006 events of sectarian violence. The decline was mostly

concentrated among the less-educated women and was likely to have been poverty-driven [3]

The ovulatory dysfunction accounts for a high number in female infertility. The female reproductive system basic functional units are the follicles. Their development begin in the fetal life. The primordial germ cells (PGCs) formation is the first stage in the follicle formation, then meiotic initiation. These two stages happen in the fetus ovary, and finally folliculogenesis where the follicle counties it's maturation in order to be ovulated in the puberty and through the female reproductive life [4, 5].

The primordial follicle will remain dormant until puberty, when the folliculogenesis starts by recruiting follicles under the hormonal control to resume their development. The ovarian reserve of the woman and her age affect this process [6]

This recruitment of follicles is dependent on the gonadotropin hormones stimulation especially the follicular stimulation hormone FSH. The higher estrogen producer follicle will be selected. In addition, the follicles will produce inhibin which selectively suppress the FSH secretion without affecting the luteinizing hormone. [7] Inhibins are heterodimer peptide, which is part of the transforming growth factor (TGF)-β superfamily with two isoforms, inhibin A and inhibin B (identical α-subunits, different β-subunits) [8]

The elevated TSH level in both clinical and subclinical hypothyroidism have been connected with decreasing the possibility of pregnancy, decreased ovarian reserve, when Hiraoka and colleagues investigate the conception rate in three years retrospective study on females with fertility issues [9].

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This study have been planned to find the possible correlation between the inhibin B levels and the infertility of the hypothyroidism females.

Material and methods:

This study was performed in the period between December 2016, and May 2017 in Al-Yarmuk teaching hospital in Baghdad, the laboratory tests has been performed in the Biochemistry and hormones department in the same hospital. The study included a 90 subjects:

- 50 infertile women with hypothyroidism.
- 40 apparently healthy fertile women, as a control group.

Criteria of patients inclusion was:

- Primary infertile female.
- Not using any kind of hormonal treatment.
- Normal male factor. (The patient's partner have no fertility problem)
- Normal tubal factor. (No deformation or obstruction in the fallopian tube)
- Normal cervical factor.
- No history of current or past infection of a sexually transmitted disease.
- Polycystic ovarian syndrome patients have been excluded.

Criteria of the control group inclusion was:

- No thyroid disorder.
- At least one previous complete pregnancy.
- Non-hormonal contraception.

The mean age of the infertile females was 30.5 ± 5.0 years, and the healthy females mean age was 28 ± 5.0 years. All the infertile group has elevated TSH, and struggling with minimum 1 year, and maximum 16 years of infertility (mean 4.8 ± 3.9 years). Both of the patient and the healthy control

group were blood checked to investigate the thyroid stimulating hormone TSH, and the inhibin B levels by using the enzyme-linked Immunosorbent assay (ELISA) manufactured by Human, Germany. The study also involve measuring the high and the weight for the both studied groups to calculate the body mass index BMI.

Statistical analysis:

All the statistics analysis was done by using computer through SPSS program (version 22).

Results:

The finding of this study (Table 1): Imply a significant difference between the studied groups in weight to high categories (i.e. body mass index), the infertile female patients tend to be over weighted more commonly than the control fertile group.

Body Mass Index groups*	**Groups**			
	Patients		**Control**	
***according to WHO index for Asian.**	**No.**	**%**	**No.**	**%**
Under weight	**2**	**4%**	**3**	**7.5%**
Normal weight	**12**	**24%**	**26**	**65%**
Over weight	**26**	**52%**	**10**	**25%**
Obese	**10**	**20%**	**1**	**2.5%**
Total	**50**	**100%**	**40**	**100%**
P value = 0.05 (Significant)				

*non parametric test (Mann Whiney test)

Table 1: The body mass index (BMI) distribution between the two studied groups.

The results also revealed a significant difference between the studied groups regarding the results of inhibin B. (Table 2)

This result agrees with a recent study by Sallmén and colleagues, which investigate the relationship between BMI and both male and female fertility in new married couples in Palestine: there was a significant association between high BMI, and less probability of conceiving in females [10].

The results also agree with an Iraqi study on infertile females in Baghdad, which found a significant association between female infertility, and high score of BMI in 600 infertile female [11].

This study also agrees with another Iraqi study by Al- Rubae'I, who found a highly significant association between infertility and higher IBM, and higher waist to hip ratio [12].

A Turkish study presented by Dağl and Dilbaz, explained some reasons why the higher BMI, the less fertility outcomes. They provide several mechanisms in order to explain the reason based on the fact that obese women, gonadotropin secretion is affected because the hyper-insulinemia in obese women. However, the exact pathophysiology is not clearly understood yet [13].

More recent study that tried to explain the effect of obesity was focused on leptin; which is an adipokines produced by the adipose tissue, and seems to be responsible for weight regulation. A highly positive linear correlation was found between BMI and serum leptin in infertile obese female than in the fertile control group [14].

This is mainly related to the disturbing metabolism resulted from hypothyroidism. Hypothyroidism, reduced thyroid known to reduce the metabolism rate leading to increase the patients' weight [15].

Tests		Age of the patient	Body mass index
Inhibin B level	r*	-.192	.138
	P-value	.181	.338

Table 2: Inhibin B correlation with age of patients and their body mass index.

r = correlation coefficient.

As demonstrated in **table 3**: inhibin B levels didn't seem to have a significant corelation with the age of paitents, or with the body mass index. In 2006 a study showed a decreasing of inhibin B in obese female even without fertlity issues, but also didn't found a significant correlation between inhibin B and body mass index or waist circumference. [16] The decreasing levels of inhibin B as shown in **Table 2** in infertilile and hypothyroidism female, have been seen in already in hypothyroidism males which found to be approximately half that of normal males. These results are agree with our study results, even with the difference in the gender of patients [17]. Inhibin B, showed a significant decrease infertile women when compared with the control group, even in non-hypothyroidism patients [18].

An Indian research on infertile female without thyroid dysfunction has found that Serum Inhibin B levels was significantly decreased by aging. These results agree with our finding in this study [19]. By calculating receiver operating characteristic (ROC) using SPSS software, for sensitivity and specificity to check the most useful value to predict the patients' results. Inhibin B was known to be the best parameters because the area under the curve was the largest among all the parameters Inhibin B value of 156.35 gives a sensitivity of 95% and specificity of 86% in predicting the patient

group as shown in figure 1.

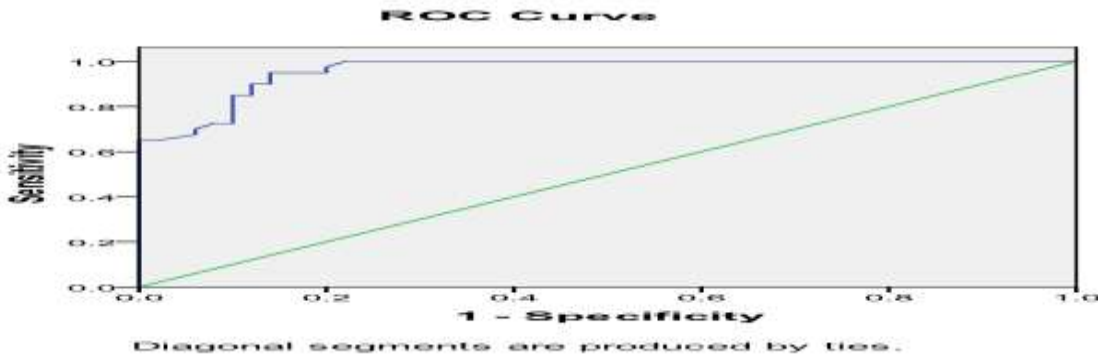

Figure 1: The ROC for inhibin B, calculated using SPSS.

Conclusions:

The infertile women with hypothyroidism have a declining level of inhibin B, and higher tend to obesity than healthy women. Inhibin B levels have a good sensitivity and specificity, which may be consider to investigate in the fertility clinic more often.

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تقدير مستويات هرمون الانهبين ب لدى النساء العراقيات المصابات بالعقم وخمول الغدة الدرقية.

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المستخلص:

من المعروف أن اضطرابات الغدة الدرقية لها تأثير على الخصوبة لكل من الذكور والإناث. عادة ما يرتبط الاضطراب في هرمونات الغدة الدرقية بانخفاض فرص التكاثر. يلعب هرمون الانهبين ب دورًا مهمًا في الخصوبة كذلك، وقد تم ربطه بالعقم عند الذكور. صممت هذه الدراسة للتحري عن التغير في مستويات الانهبين ب في الإناث المصابات بقصور الغدة الدرقية المترافق مع مشاكل الخصوبة. وقد كشفت الدراسة عن وجود فرق معنوي في مستويات الانهبين ب لدى الإناث المصابات بقصور الغدة الدرقية عند مقارنتها بالمجموعة السليمة (القيمة الاحتمالية = 0.05)، دون وجود ارتباط معنوي بعمر المرضى أو مؤشر كتلة الجسم. قيمة 156.35 ببيكوغرام/ مل أظهرت دقة حساسية بمقدار 95٪ ونوعية 86٪ عند النساء المصابات بالعقم.

الهدف من الدراسة:

تقدير مستوى الانهبين ب عند النساء المصابات بقصور الغدة الدرقية والعقم. من أجل فحص مؤشر كتلة الجسم للمجموعات المدروسة، والبحث عن ارتباط محتمل بين مؤشر كتلة الجسم ومستويات الانهبين ب، واختبار نتائج الانهبين ب عبر فحص الحساسية والنوعية.

التصميم: دراسة مقطعية محكمة.

المكان: بغداد، العراق.

المرضى: مجموعة من النساء المصابات بالعقم المصابات بقصور الغدة الدرقية (ن = 50). عملت مجموعة من النساء اللواتي يبدو أنهن يتمتعن بصحة جيدة (ن = 40) كعناصر للمجموعة الضابطة.

الإجراء: تم سحب عينات الدم الوريدي في اليوم الثالث من الطمث للمرضيات والمجموعة الضابطة.

نتيجة البحث: تم العثور على فرق كبير في مستويات الانهبين ب في الإناث المصابات بقصور الغدة الدرقية عند مقارنتها بالمجموعة السليمة/الضابطة (القيمة الاحتمالية p= 0.05)، دون ارتباط كبير بعمر المرضى، أو مؤشر كتلة الجسم. وقد وجدت أن قيمة 156.35 ببيكوغرام/ مل يعطي حساسية 95٪ وخصوصية 86٪ في التنبؤ بمجموعة المرضى.

الاستنتاجات: يبدو أن لدى النساء المصابات بالعقم المصابات بقصور الغدة الدرقية انخفاض في مستوى الانهبين ب، ومؤشر كتلة جسم أعلى من النساء الصحيحات. تُظهر مستويات الانهبين ب معدلًا عاليًا من الحساسية والخصوصية في الإناث المصابات بقصور الغدة الدرقية مع مشاكل الخصوبة.

الكلمات المفتاحية:

اضطرابات الغدة الدرقية، قصور الغدة الدرقية، الانهبين ب، العقم.