Middle East Fertility Society Journal 22 (2017) 269–272

Contents lists available at ScienceDirect

Middle East Fertility Society Journal

journal homepage: www.sciencedirect.com

Original Article

Assessment of anti-Mullerian hormone level in reproductive age group women with diabetes mellitus type one

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ARTICLE INFO

Article history:
Received 5 December 2016
Revised 7 March 2017
Accepted 10 April 2017
Available online 15 May 2017

Keywords:
Type I diabetes mellitus (TIDM)
Anti-Mullerian hormone (AMH)
Hemoglobin A1C Test (HbA1c)
Fertility
Menarche

ABSTRACT

Objective: To assess the levels of anti-Mullerian hormone in women with type I diabetes mellitus during their reproductive age period.
Background: Reproductive impairment in poorly controlled type one diabetes mellitus results from perturbations at different levels of the gonadotropic axis, including the hypothalamus/pituitary and the ovary.
Methods: This study was designed as a case-control study. We evaluated anti-Mullerian hormone serum level in a female with type I diabetes mellitus (N = 60) who attended the Diabetes and Endocrine Center in Merjan Medical city in Babylon, from November 2015 to April 2016. These patients were compared with a healthy fertile female (N = 80) as a control group. The female's age ranges from 13 to 40 years for the two groups. Body mass index was calculated and serum samples for anti-Mullerian hormone serum levels were estimated.
Results: There was a significant difference between patients and control group regarding body mass index, residence, educational level, fertility, and menarche. Anti-Mullerian hormone level is significantly lower in patient group when compared with the control group ($p = 0.000^*$). HbA1c level is significantly higher in a patient group when compared with the control group ($p = 0.000^*$).
Conclusion: The results suggest that type I diabetes is an independent risk factor for decrease of anti-Mullerian hormone level in reproductive age group women.

1. Introduction

Diabetes mellitus (DM) is a syndrome of impaired carbohydrate, fat and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of tissues to insulin [1]. Diabetes mellitus type 1 (also known as type 1 diabetes) is a form of diabetes mellitus in which not enough insulin is produced and the lack of insulin results in high blood sugar levels [2–4]. The cause of TIDM is unknown; however, it is believed to involve a combination of genetic and environmental factors [5,6]. TIDM is associated with an increased risk of microvascular and macrovascular complications [7].

Several studies have shown an increased prevalence of menstrual cycle abnormalities in adult women with TIDM [8,9]; these have shown that menstrual cycle irregularities are especially prevalent in young women and that these abnormalities decrease with advancing age [8,10].

Anti-Mullerian hormone (AMH), also known as Mullerian-inhibiting substance, is a member of the transforming growth factor-β (TGFβ) superfamily and it is very important biomarkers in ovarian reserves [10,11]. A decrease in AMH levels above the age of 33 compared to healthy controls was found to be associated with poorly controlled TIDM [12,13]. The real cause of this association still remains unexplored [14,15]. The negative effects of diabetes on kidneys, nerves, and vessels are well established; however, the effect of diabetes on reproductive function is less well understood, but it is important to characterize, given the increasing numbers of young women with diabetes [16].

2. Aim of the study

The aim of the study was to assess serum levels of AMH in women with TI DM during their reproductive age period.

Peer review under responsibility of Middle East Fertility Society.
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http://dx.doi.org/10.1016/j.mefs.2017.04.004
1110-5690/

3. Subjects and methods

This study was designed as a case-control manner. Approved by the Medical Ethical Committee of the College of Medicine/University of Babylon, informed written consent has been signed by the participant before enrollment in this study. Anti-Mullerian hormone serum levels were evaluated in female with TIDM (N = 60), and they were selected from 220 diabetic females who attended the Diabetes and Endocrine Center in Merjan Medical city in Babylon, from November 2015 to April 2016.

3.1. Exclusion criteria

1- Woman who took any hormone therapy within previous three months of hormonal assays.
2- Women age less than 13 years or more than 40 years.
3- Menopause state.
4- Hysterectomy or oophorectomy.
5- Other endocrine disorders.

Selected female was compared with healthy fertile female (N = 80) as a control group. A standard questionnaire was used for collecting demographic data (age, menarche, residence, educational level, fertility, menstrual cycle history (regularity, duration), assessment of Anthropometric data such as height and weight) to calculate body mass index (BMI).

3.2. Hormonal and biochemical analysis with sample collection

Blood samples were collected between 8:30 and 10:00 a.m. from the two groups for Anti Mullerian Hormone (AMH) serum level. These women should be fasting to estimate the fasting blood sugar, HbA1c. Samples were collected by venipuncture into 2 ml (ml) glass tubes. These samples were left to stand at least for 15 min at room temperature which then were centrifuged at 3000 rpm (rpm) for 3 min to separate the serum. Serum aliquots were obtained, and stored at −20 °C for later measurement (AMH). Serum samples for AMH were examined by sensitive Enzyme Linked Immuno Sorbant Assay method (ELISA) and the kit used was from Beckman coulter; USA in one run within about four months of collection. The lower limit of AMH (ng/ml) is 1 and the upper limit 4. Blood for HbA1c was collected in Vacuum blood collection tube glass (2 ml) and Jordan kit (Bio-rad; France) was used for HbA1c analyses. Lower limit of HbA1c (mmol/l) is <36 and upper limit is 48.

3.3. Statistical analysis

Statistical analysis of the data was performed using SPSS version 17 for Windows (Statistical Package for Social Science; SPSS, Inc., Chicago, IL). Continuous variables were expressed as the mean ± standard deviation (SD) and range; categorical variables as percentages. Between-group differences were tested by comparing means–independent samples *t*-test for continuous parameters, and Chi–square test was used for categorical variables; Pearson's correlation was used to examine the relation between continuous variables (AMH and HbA1c). A p value of <0.05 was considered significant for all analyses.

4. Results

4.1. Comparison between patients and control groups

There were significant differences between patients and control group regarding BMI, residence, educational level, fertility, and menarche (Table 4.1).

Table 4.1
Comparison of demographic data of patient and control group (values are mean ± SD or percentages).

Parameter	Patient group N = 60	Control group N = 80	P value
Age (years)	24.87 ± 8.47	25.91 ± 8.29	0.659
BMI (kg/m^2)	25.17 ± 5.43	22.94 ± 2.38	0.001*
Residence (N)			
Rural	(35) 58.3%	(59) 73.8%	0.000*
Urban	(25) 41.3%	(21) 26.3%	
Educational level (N)			
Illiterate	(18) 30.0%	(32) 35.5%	0.000*
School	(10) 16.7%	(30) 30%	
Higher degree	(32) 53.3%	(18) 34.5%	
Fertility			
Fertile	(31) 51.7%	(80) 100.0	0.000*
Infertile	(29) 48.3%	0	
Menstrual cycle regularity (N)			
Regular	(58) 96.7%	(80) 100%	0.10
Irregular	(2) 3.3%	0	
Menarche (year)	12.82 ± 0.75	12.16 ± 0.58	0.001*

BMI - Body Mass Index.
* Significant different from the corresponding value.

Table 4.2
Hormonal level and biochemical test of control and patient group (values are mean ± SD).

Parameter	Patient group	Control group	P value
AMH (ng/ml)	(2.82 ± 1.27)	(3.79 ± 1.91)	0.000*
HbA1c (%)	(8.73 ± 2.80)	(4.82 ± 0.39)	0.000*

AMH: Anti-Mullerian Hormone, HbA1c: Hemoglobin A1C Test.
* Significant difference from the corresponding value.

4.2. Comparison between patients and control group regarding AMH level and HbA1c

Table 4.2 shows AMH level of patients and control group regarding AMH and HbA1c. AMH serum level is significantly lower in patient group when compared with control group (p = 0.000*). HbA1c level is significantly higher in patient group than control group (p = 0.000*).

4.3. Correlation of anti-Mullerian hormone with HbA1c in patient and control group

In patient group, there was insignificant negative correlation between AMH and HbA1c (r = −0.931, P = 0.20). In control group there was insignificant negative correlation between AMH and HbA1c (r = −0.076, P = 0.50), Fig. 4.1.

4.4. Binary logistic regression analysis for patients as the dependent variable

To examine the relationship of measured factors with diabetes in women, a binary logistic regression analysis was performed. In this analysis, AMH, HbA1c, residence, BMI and education level were significantly associated with diabetes. AMH, HbA1c, residence, BMI and low education were associated with increased odds ratio in diabetic patients, see Table 4.3.

5. Discussion

There was a higher significant difference in BMI of patient vs control groups (25.17 ± 5.43 vs 22.94 ± 2.38) kg/m^2, as shown in Table 4.1. This result is similar to many research works which

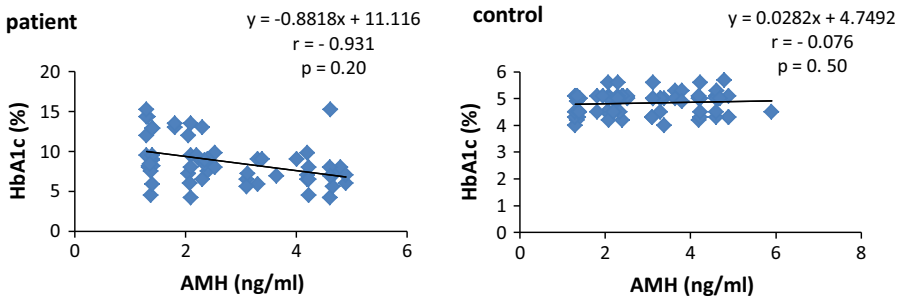

Fig. 4.1. Correlation between anti-Mullerian Hormone and HbA1c in patient and control group.

Table 4.3
Binary logistic regression analysis for patients as the dependent variable.

	Parameter	P value	Odds ratio	Lower bound	Upper bound
Patients	AMH	0.000	1.494	1.170	1.907
	HbA1c	0.000	15.204	4.908	47.098
	BMI	0.002	1.174	1.051	1.312
	Low/high Education	0.473	1.127	0.813	1.563
	Residence Rural / urban	0.000	3.933	1.924	8.04
	Age of menarche	0.000	2.300	1.407	3.761
	Menstrual cycle regularity	0.15	6.418E−8	6.418E−8	6.418E−8

had concluded same results as our [17,18]. Obesity increases the risk of comorbidities among individuals with TIDM, especially metabolic syndrome, and macrovascular and microvascular diseases [19].

Higher significant percentage of patient live in urban place than control group (41.8% vs 26.3%); this may be due to the fact that migration exerts both direct and indirect effects on urban population growth as many people in rural area migrate to urban area for better chance of living, work and education [20,21]. In a large study conducted in north of Iran, which included 1,600,000 population, 43.9% and 56.1% are living in urban and rural areas, respectively which is the same as our results [22].

The patient group have significantly higher educational level than control group, this can be explained by the fact that a high percentage of patients live in urban places, where colleges are available, or it may be due to social consideration that those who live in rural areas don't agree to send their daughters to the center [23].

Regarding fertility, Table 4.1 shows the significant lower percentage of patient fertility vs control group (51.7 vs 100%). In diabetic females, disruption of positive-feedback effects of estradiol, delayed or absent pre-ovulatory LH surges and anovulation are observed [24–30]. These abnormalities are at least partially reversed after insulin administration [29,30]. Compelling evidence suggests that some of the reproductive deficits associated with TI DM may stem from alterations in the ovarian physiology. There are abnormalities in follicular growth and survival, including increased follicular and granulosa cell apoptosis, as well as impairment of oocyte-to-granulosa communication, oocyte maturation and ovarian follicular development which is demonstrated in animal models of TIDM [31,32]. Perturbation of ovarian steroidogenesis and ovulation was also observed in diabetic female mice. In addition, insulin deficiency has been associated with defective ovulation, which can be reversed by insulin treatment in diabetic rodents [33,34].

The mean age at menarche was significantly higher in the patient compared to the control (12.82 ± 0.75 vs 12.16 ± 0.58) in year, as in Table 4.1. This result is in accordance with many research works, who have also reported a delay of 1 year in menarche in TIDM as well as a later menarche among those with an earlier age at the onset of TIDM and revealed that menarche occurs earlier or at the same time as in controls if diabetes occurs prior to the onset of puberty [35–38]. Griffin et al., stated that diabetes onset before puberty may disrupt the hypothalamic pituitary-gonadal axis and may delay ovarian maturation and sex hormone production and/or cause weight loss, decreasing body fat that is important for menarche to occur [39].

AMH level was significantly lower in the patient than the control group (2.82 ± 1.27 vs 3.79 ± 1.91) ng/ml. The first phase of ovarian folliculogenesis, involving the noncyclic recruitment of primordial follicles up to the small antral stage (2–5 mm), is gonadotrophin independent [40,41]. After the onset of puberty, the second phase of folliculogenesis, the cyclic recruitment stage, occurs under the control of gonadotrophins and other metabolic signals. Insulin acts as a co-gonadotrophin, stimulating the recruitment and growth of larger follicles [42–44], which only secrete a small amount of AMH [40,41].

There is significantly higher difference in the HbA1c level of the patient vs control groups (8.73 ± 2.80, 4.82 ± 0.39)% as shown in Table 4.2. This result is similar to many research works which have concluded the same results as our [45–48]. Since HbA1c reflects diabetic glycaemic control so it will be higher.

In the present study HbA1c, residence, age of menarche, BMI were significantly associated with diabetes as shown in Table 4.3. These results are similar to many research works which have concluded the same results as our [17,18,20,22,37,38]. The odds ratio (OR) for AMH is (1.494), CI:[1.907–1.170]. The negative effect of diabetes on ovarian reserve is still unexplored, and Diamanti-Kandarakis & colloquies claimed glycotoxins end products to have a negative effect on theca and granulosa cell functions in rat models [49]. De kat and team underscore previous findings of early vascular damage in DM-1 and suggest that there is no relationship between vascular function and ovarian reserve, so the exact cause is still in need for further elaboration [15].

6. Conclusions

The results suggest that type I diabetes mellitus is an independent risk factor for decreasing AMH level in reproductive age group women.

Suggestion

1. Larger sample multicenter study is needed to confirm these preliminary results.
2. An animal model study to explore the real cause of ovarian dysfunctions.

Limitation

Period of the study is time limited and the sample size was small, and we couldn't follow the patients for a long period.

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