
The Effect of Glycemic Control on Menstrual cycle in Iraqi Diabetic Women

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Abstracts

Objective: - The study was designed to evaluate the importance of glycemic control on menstrual cycle disorders in Iraqi diabetic women.

Setting: - The study was held at Department of Physiology, Medical College of Al-Mustansiriya University in cooperation with the Iraqi National Diabetes Center (NDC) of Al-Mustansiriya University in Baghdad from November 2004 till November 2005.

Outcomes measures: - The glycemic control was assessed by estimation of glycosylated hemoglobin and fasting plasma glucose while the pelvic ultrasound and hormonal measurements were done for detecting menstrual disorders and state of ovarian function. The Follicular Stimulating Hormone FSH, The Lutenizing Hormone LH, Estrogen and progesterone were measured by using Enzyme Linked Fluorescent Assay technique (ELFA).

Results: -The present study showed that menstrual disorders are more common in diabetic than non-diabetic females. Diabetics with menstrual disorders (i.e. amenorrhea or oligomenorrhea) had anovulatory cycles with normal or low gonadotrophine and low progesterone levels, and it is more common in poorly controlled diabetics than those with good glycemic control. The polycystic ovarian syndrome was found to be associated with insulin resistance, obesity and glucose intolerance and is more common in diabetics than non-diabetic women.

Conclusion: - The study revealed that good glycemic control in diabetic women exerts a positive influence on menstrual cycle regulation and on ovarian and gonadotrophic hormones.

Keywords: -Menstrual cycle, ovarian function, glycemic control, polycystic ovarian syndrome.

Introduction

Menstrual disorders, especially irregular cycles, are common in diabetic women, particularly in those with obesity. Before the advent of insulin, women with diabetes often had amenorrhea, which is not surprising in view of their poor general health. Bergquist reported that women with diabetes had delayed menarche and an increased incidence of menstrual disorders throughout their fertile years^[1]. Since then, the general control of diabetes has improved, and there is evidence that these disorders have become less marked, although oligomenorrhea and irregular cycles in particular are more common among diabetic women than in the general population^[2, 3].

Adcock had shown that adolescent girls with diabetes who have irregular cycles are significantly having heavier periods with higher glycated haemoglobin and insulin-like growth factor-1 (IGF-1) concentrations and a higher luteinizing hormone (LH) / Follicle stimulating hormone (FSH) ratio than those with regular cycles^[4].

Also, the polycystic ovarian syndrome (PCOS) is associated with insulin resistance, obesity and glucose intolerance, and is more common in diabetic than non-diabetic women^[5]. PCOS is strongly associated with insulin resistance, which apparently lies at a post-receptor level and is primarily manifested by reduced glucose uptake and metabolism in skeletal muscle and fat; unlike non - insulin - dependent diabetes mellitus (NIDDM), does not appear to have significant impairment of insulin ability to suppress hepatic

glucose output^[6]. The prevalence of impaired glucose tolerance (IGT) and of overt NIDDM are raised amongst young women with PCOS, especially if they are obese, and the long - term risk of developing NIDDM is several - folds higher than in the general population^[7].

Diabetes mellitus, both type 1 and type 2 can cause various endocrine disorders by affecting the secretion, metabolism, clearance or bioavailability of hormones. Diabetes has many effects on the hypothalamo-pituitary- gonadal axis, including impaired gonadotropin release, which may be due to abnormal generation of gonadotropin-releasing hormone (GnRH) pulses in the hypothalamus^[8].

In girls, type 1 DM can delay menarche, and many diabetic women have anovulatory cycles, with oligomenorrhea-or amenorrhea. The prevalence of polycystic ovarian syndrome is increased, and hyperinsulinaemia in these subjects may stimulate androgen production by the ovaries^[9, 4].

Most diabetic women with amenorrhea or oligomenorrhea have anovulatory cycles with low or normal basal gonadotropin levels despite low estrogen levels^[10, 11].

Subjects & methods

A total number of 180 Iraqi women were involved in this study. 50 healthy control subjects versus 80 with type 1 and 50 type 2 diabetic women.

All females were between the age of 16 and 42 years with a mean 30.38 ± 6.22 years.

Fasting plasma glucose was measured by glucinate method; while HbA_{1c} was estimated using (high performance liquid chromatography) (HPLC).

FSH, LH, progesterone and estrogen were measured using enzyme linked fluorescent assay technique. Ultrasound was done to all subjects to detect the dominant follicle and the ovarian morphology.

The degree of glycemic control was assessed using the HbA_{1c} level as follows:-

- Normal range for HbA_{1c} is typically between 4.1 % – 6.7 %.

- Good control: less than 7 %.

- Accepted control: 7 – 8 %.

- Poor control: more than 8 %.

(VariantTM HbA_{1c} program, 2003).

So we depend on the range (7% – 8%) and pass it as accepted diabetic control index. So any value of HbA_{1c} less than 8% was regarded as good control while value more than 8% was included in the poor control category for comparison purpose.

The ultrasonic examination and gynecological checking was performed by specialist in radiology and gynecologist, all females were having normal hepatic and renal function tests.

The statistical analysis was done using the Chi-Square test and the T-test for two independent means.

Results

In the present study, eighty women with type 1 DM were examined, forty five of them have regular menstrual cycles, recurs every 28 days. The rest of type 1 diabetic females were thirty five, all had irregular cycles as shown below (**Table 1**);

- Eighteen of them with oligomenorrhea.
- Fourteen of them with amenorrhea.
- Three of them with metrorrhagia.

Also twenty seven of them (33.7%) having different criteria of PCOS like hirsutism, amenorrhea, infertility and ultrasound findings suggestive of PCOS.

On the other hand ,the examination of the fifty diabetic women with type 2 DM showed that ; thirty two of them have regular menstrual cycles recurs every 28 days. The rest of type 2 diabetic females were eighteen, all having irregular cycles distributed as shown in **Table 1**;

- Sixteen of them have oligomenorrhea.
- Two of them have metrorrhagea.

Also twenty five of them have polycystic ovarian syndrome with different criteria. (50 %).

Table 1 showed the comparison between types 1 and type 2 diabetic subjects for menstrual regularity. There was no significant difference detected between the two groups in menstrual regularity.

Table 1 : The comparison between type 1 and type 2 Diabetic females for menstrual regularity.

		Control	Control	Type 1		Type 2		P-value
		N=50	%	N = 80		N= 50		
				n	%	n	%	
Menstrual Regularity	Normal	46	92%	45	56.2	32	64	0.140
	Metrorrhagia	2	4%	3	3.75	2	4	
	Amenorrhea	0	0%	14	17.5	0	0	
	Oligomenorrhea	2	4%	18	22.5	16	32	

Table 2 showed the comparison between type 1 and type 2 diabetic women for glycemic control and ovulation. There was no significant difference between the two diabetic groups so both were considered as one group for comparison purposes.

Table 3 showed the correlation between glycemic control and ovulation in diabetic women in both groups. There is high significant correlation between glycemic control represented by HbA_{1c}

and ovulation in diabetic women in both types with P – value < 0.001.

Diabetic females with good glycemic control showed ovulatory cycles in 56.65% of them in contrast to 20.8% ovulatory cycles in those with poorly controlled diabetic females .While anovulatory cycles were detected in 43.4% of diabetic females with good glycemic control in contrast to 79.2%in those with poor glycemic

control giving a high value of statistically significant difference between the two groups.

Table 2 : The comparison between type 1 and type 2 Diabetic females for diabetic control and ovulation.

		Type 1 n = 80		Type 2 n = 50		P - value
		n	%	n	%	
Glycemic control	Good	31	38.7	22	44	0.716
	Poor	49	61.2	28	56	
Ovulation	Neg.	50	62.5	33	66	0.722
	Pos.	30	37.5	17	34	

Table 3: Effect of glycemic control on ovulation in diabetic women.

		Ovulation				Total	P-value
		Negative		Positive			
glycemic control (HbA _{1c})	Good	23	43.4%	30	56.6%	53	0.001*
	Poor	61	79.2%	16	20.8%	77	
Total		84	64.6%	46	35.4%	130	

Table 4 showed the level of ovarian and gonadotrophic hormones in relation to glycemic control in our diabetic females with the LH/FSH ratio which is regarded as an important criteria for

diagnosing PCOS. There was significant effect between glycemic control and LH/FSH ratio and progesterone level.

Table 4: Effect of glycemic control on ovarian and gonadotrophic hormones.

	Type 1 DM		Type 2 DM	
	Good control HbA _{1c} <8	Poor control HbA _{1c} >8	Good control HbA _{1c} <8	Poor control HbA _{1c} >8
FSH	5.32.7	5.17±3.2	4.7±2.1	5.1±2.4
LH	12.5±7	13.7±6.7	11.4±8.6	12.7±8.8
LH/FSH	2.35	2.649	2.425	2.49
Estrogen	160±80	155±90.7	110.4±80.2	105±75.7
Progesterone	7.69±5.4	6.2±6.5	9.5±4.7	7.7±5.8

Discussion

In this study; a significant difference between diabetic women and the healthy women was

detected in relation to menstrual regularity (p<0.01) 92% of our healthy women had normal cycles in comparison to 56.2% for type 1 diabetic women

and 64% for type 2 diabetics, emphasizing the hazardous effect of hyperglycemia on menstrual regularity. For type 1 diabetics 3.75% had metrorrhagia, 17.5% had amenorrhea while 22.5% were having oligomenorrhea. Similar results were reported by Janice et al^[12] who reported that women with type 1 diabetes have greater prevalence of menstrual disorders than women without diabetes while Elsa et al^[13] reported that women with type 1 DM are more likely to experience menstrual problems through out their primary reproductive years as compared with their sisters and unrelated female subjects.

Type 2 diabetic women showed 36% abnormality in menstrual cycle comprising 4% with metrorrhagia and 32% with oligomenorrhea, no previous similar study showed this correlation as earlier studies shed light on polycystic ovarian syndrome (PCOS) and its association with type 2 diabetes as PCOS is strongly correlated with insulin resistance with consequent hyperinsulinaemia and obesity. So this study is the first which correlate the glycemic control of diabetic women with menstrual regularity and ovarian hormones in all type 2 diabetic women not only those with PCOS criteria.

Over the past decade studies had shown that women with PCOS have a high prevalence of hyperlipidemia and hyperinsulinaemia^[14] with progression to type 2 diabetes mellitus^[15].

The current study is in agreement with the above explanation since 25 out of 50 diabetic women of type 2 have features of PCOS or one of the diagnostic criteria for PCOS.

Also in this study 27 cases out of 80 women with type 1 DM had history of PCOS with different criteria of the syndrome, the ratio of LH/FSH is equal to 2.8 which is greater than 2; the significant ratio for diagnosis of PCOS.

No significant difference was detected between type 1 and type 2 for menstrual irregularity so both groups were pooled together and delt with as one group for division into categories of glycemic control.

We tried to find the effect of glycemic control expressed by HbA_{1c} and ovulation monitored by ultrasound morphological study of the ovaries at mid cycle. There was no significant difference between the two groups of diabetes for ovulation, so both were considered as one group (n = 130) for comparison purposes, (Table 2)

There was highly significant correlation between glycemic control and ovulation with P – value < 0.001. As shown in table 3, out of the fifty three diabetic women with good diabetic control, thirty of them had either dominant graffian follicle or corpus luteum which is a sign of ovulation. So more than 50 % of those with good glycemic control have positive ovulation. Also out of the 77 females with poor glycemic control, only 16 of them have

positive ovulation and 61 of them have negative ovulation.

There is no exact similar study that correlates between glycemic control and ovulation in both types of diabetes mellitus. Except, there is a study done by Elsa et al^[13] for menstrual cycle and type 1 diabetes, they did not find any differences in menstrual problems related to glycemic control when stratifying by HbA_{1c} at clinic visit, although this may not reflect control over long periods or earlier in the life time.

There was no significant difference between the 2 groups concerning FSH level. In type 1 diabetic females with poor glycemic control, there was slight elevation in LH level. This finding for FSH and LH level is in total agreement with findings reported by Adcock, (4) and Franks, (6) who stated that serum levels of FSH are usually normal, raised LH / FSH ratio was observed, with a high incidence of polycystic ovarian changes diagnosed by ultrasound.

Also there was slight elevation in serum progesterone in type 2 diabetic females with good glycemic control, this is because good control is associated with good ovulation and when there is good ovulation there is elevation in serum PRG at luteal phase, as table 2 showed that 22 women of type 2 D.M. have good glycemic control of diabetes, 17 of them have good ovulation.

We can conclude that good glycemic control of diabetes can exert better influences on female reproductive system by inducing regular periods with ovulatory cycles which may improve both fertility and psychological aspects in diabetic females.

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