

Pubertal Development and Gonadotrophic Hormones among Girls with Type 1 Diabetes Mellitus

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Abstract

Background: As a chronic disease occurring in childhood, type 1 diabetes is a factor potentially affecting the pubertal development, including age at menarche.

Aim of study: To investigate the effect of type 1 diabetes on pubertal development among adolescents; and to investigate their gonadotrophic hormonal profile.

Subjects and Methods: Nineteen Egyptian girls aged (13.8- 21.6) years were recruited into the study. Assessment of Pubertal development according to Marshall & Tanner (1969) was performed; and age at menarche was evaluated. Auxological assessment (weight, height, and body mass index) were performed. Laboratory investigations were done, including HbA1c levels and Hormone assays (basal and post stimulation levels): Serum follicle- stimulating hormone (FSH), luteinizing hormone (LH), and LH/ FSH ratio was calculated.

Intervention: Girls underwent GnRH- analogue test with triptorelin (0.1 mg) administered subcutaneously.

Results: The mean age at menarche (13.24 ± 1.25 yrs, among the 17 (89.5%) postmenarcheal T1DM girls, showed no significant difference ($P > 0.05$) from the normal population; but still 2 (10.5%) girls did not achieve menarche until after the study period was terminated. Moreover, there was a highly significant delay ($P < 0.01$) in their attainment of adult sexual maturity Tanner stage V (B5, PH5). Only 3 (15.8%) T1DM girls, had achieved optimal metabolic control, at ($< 7.5\%$), while the remaining 16 (84.2%) had a statistically significant insufficient metabolic control (9.93 ± 1.96) ($P < 0.00$). Also it was found that basal and stimulated LH & FSH levels were significantly decreased in T1DM girls ($P < 0.00$).

Conclusion: Type 1 diabetes could affect pubertal development of girls, in the form of delay in their attainment of adult sexual maturity stages, Tanner Breast stage (B5) and Tanner Pubic Hair development (PH5); however, their age at menarche, is within the range of normal Egyptian girls. The disease could alter their growth development, with a decrease in their height than the normal population. LH and FSH were significantly decreased than normal reference ranges.

Keywords: Puberty- Menarche- Insulin- Type 1 diabetes mellitus (T1DM) - Glycemic (metabolic) control.

تطورات البلوغ ووظائف البويضات في البنات المصابات بالنوع الأول من مرض البول السكري

خلفية: مرض السكري النوع الأول يحتمل أن يؤثر على نمو البلوغ، بما في ذلك سن الحيض.

الهدف: دراسة تأثير داء السكري من النوع 1 على تطور البلوغ لدى المراهقات؛ وقياس هرمونات التبويض الخاصة بهم.

المنهجية: أجريت هذه الدراسة بعيادة السكر بمستشفى الأطفال جامعة عين شمس واشتملت على 19 فتاة يعانوا من داء السكري النوع الأول تتراوح أعمارهم من (13، 21، حتى 21، 6 عاماً)، تقييم التطور في البلوغ وفقاً لمارشال وتانر (1969) قد أنجز. وتم تقييم العمر عند بدء الحيض. تم إجراء تقييم القياسات الانثروبومترية (الوزن، الطول، ومؤشر كتلة الجسم). وقد أجريت الفحوص المختبرية، بما في ذلك مستويات نسبة HbA1c وفحوصات هرمون (FSH)، و (LH)، وتحسب نسبة LH/ FSH.

النتائج: خضعت بنات اختبار نره التناظرية مع تريبتوريلين (0.1 مل) تحت الجلد.

النتائج: أظهرت نتائج الدراسة أن متوسط العمر عند بدء الحيض (13.24 ± 1.25)، من بين سبعة عشر (89.5%) Postmenarcheal الفتيات T1DM، لم تظهر أي فروق معنوية ($P > 0.05$)، ولكن لا يزال اثنين (10.5%) الفتيات لم يحقق الحيض حتى بعد إنهاء فترة الدراسة. وكان هناك تأخير ذو دلالة إحصائية ($P > 0.01$) في تحقيقها من البالغين (مرحلة النضج الجنسي) تانر المرحلة الخامسة (B5, PH5). فقط 3 (15.8%) الفتيات T1DM، حققت التمثيل الغذائي الأمثل، في ($< 7.5\%$)، في حين أن النسبة الباقية 16 (84.2%) كان عنصر تحكم التمثيل الغذائي غير كافية (9.93 ± 1.96) مع فارق ذو دلالة إحصائية ($P = 0.00$) أيضاً وجد أن مستوى هرمون LH & FSH كان منخفضاً في الفتيات T1DM ($P = 0.000$) إلى حد كبير.

الخلاصة: داء السكري نوع 1 يمكن أن يؤثر على نمو البلوغ للفتيات، في شكل تأخير في مراحل النضج الجنسي للبالغين (B5, PH5)؛ ومع ذلك فإن سنهم عند بدء الحيض، هو ضمن العمر العادي مقارنة بالفتيات المصريات العادية. ويمكن للمرض أن يؤثر في نموها، مع انخفاض في الطول مقارنة بطول الفتيات المصريات العادية. وكذلك انخفاض في مستويات هرمون (FSH) و (LH)، مقارنة بالمستويات المرجعية العادية.

كلمات مفتاحية: سن البلوغ- الحيض- الأنسولين- مرض السكري من النوع 1 السكري (T1DM)- نسبة السكر في الدم (التمثيل الغذائي).

Introduction:

Type 1 diabetes mellitus (T1DM), is a serious chronic autoimmune disease. Children developing T1DM will depend on lifelong treatment with insulin and have a high rate of complications. The incidence of the disease is increasing worldwide at an annual rate of around 3- 5% (Patterson et.al., 2009). In a childhood T1DM epidemiology study in the Nile Delta region of Egypt, its incidence and prevalence were found to show a progressive increase over a period of 18 years (1994- 2011) among children aged from 0 to 18 years living in the Nile Delta region. Higher disease occurrence was observed in rural areas and female predominance was evident (El- Monem El- Ziny et.al., 2014).

Several lines of evidence have clearly shown that growth is often impaired in children and adolescents with T1DM (Giannini et.al., 2014). Reports on the effect of diabetes on age at menarche, have been inconsistent. Some, mostly retrospective, studies have reported delayed menarche in T1DM, whereas others found no difference compared with the general population (Rohrer et.al., 2007).

Possible causes of the observed delay in menarcheal age in type 1 diabetic girls may lie at the hypothalamic- pituitary level. Clinically, female patients with type 1 diabetes may show oligomenorrhea and amenorrhea (Yeshaya et.al., 1995). There have also been reports of decreased luteinizing hormone (LH) levels, suggesting impairment of the hypothalamic- pituitary axis (Griffin et.al., 1994).

Subjects And Methods:

Phase I: Clinical assessment was performed for collection of the subjects by screening of the T1DM girls, followed at the Pediatric Diabetes Clinic, Children's Hospital, Ain Shams University, Egypt, for a cross- sectional study, according to the inclusion and exclusion criteria; the study was initiated in 2011, and took approximately 2 years; the study sample comprised approximately 38 patients. However, 5 girls were excluded due to the presence of complications (nephropathy) and/ or concomitant diseases; and due to refusal of the remaining 14 girls and their parents to recruit into the study.

Phase II: Nineteen Egyptian girls with an age range of 13.74- 21.60 years (mean age± SD, 16.94± 2.56 yr), fulfilling the inclusion criteria were finally, recruited for the study.

Subjects:

Inclusion criteria: Girls with T1DM aged ≥ 13 years; disease duration not less than 2 years before recruitment in the study.

Exclusion criteria: Type 2 diabetes mellitus and other specific types of diabetes mellitus; age < 13 years; other endocrine disorders such as, hypothyroidism and Addison's disease; presence of other concomitant chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease; as well as other autoimmune disorders; use of sex steroids.

All girls were in the average socioeconomic status. They were receiving intermediate (NPH) and soluble (regular) insulin in three or more daily injections, intensive insulin therapy (Danielson et.al., 2005).

T1DM girls were classified according to the International Society of Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines into 2 groups; the 1st group with an optimal metabolic control (≥ 7.5%), and a second one with an insufficient metabolic control (≥ 7.5%), (Rewers et.al., 2007).

Ethical approval was taken by the Medical Ethical Committee of The Institute of Postgraduate Childhood Studies and The National Research Centre. All parents and caregivers signed informed written consents and girls were given their assent before entering the study.

Methods:

All Patients were subjected to the following:

1. Full medical history: Laying stress on age at menarche (years), and menstrual history; age of diabetes onset and the disease duration (years), insulin dose (U/ kg per day) and number of insulin injections per day; regimen of insulin therapy.
2. Reviewing of the Medical Records: This was done for all patients to collect data regarding general health, hospital admission, hypoglycemic attacks, and regimen of insulin therapy.
3. Clinical Assessment:
 - a. A complete physical examination was performed by the researcher: general; laying stress on skin, mouth, eyes, hands and feet, and systemic; endocrine, renal, neurological, respiratory and cardiovascular system.
 - b. Assessment of Pubertal development according to Tanner (1962) and Marshall& Tanner (1969).
 - c. Auxological assessment: Weight was measured using a conventional Seca scale with a precision of 100g. Height was measured with a Harpenden stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated, BMI= weight (kg)/ height (m²).
4. Laboratory investigations: These were performed for all subjects of the study:
 - a. HbA1c levels were measured using a commercially available automatic system (Gonen& Rubenstein, 1978).
 - b. Hormone Assays:
 - c. Serum FSH (follicle- stimulating hormone) and LH (luteinizing hormone), levels was measured by Chemiluminescence Immunoassay, Immulite system, DPC (Babson, 1991). Calculation of LH/ FSH ratio, was done.
 - d. Girls underwent GnRH- analogue test with triptorelin (0.1 mg) administered subcutaneously (Ibanez et.al., 1997). The test was started at ≈ 9.00 AM, and blood samples were obtained before and 4 and 24 hours post stimulation. FSH and LH were analyzed in the basal and 4- hours samples. In postmenarcheal girls, the test was performed during the follicular phase of menstrual cycle between days 3 and 8.

Limitations of the study:

Presence of complications and/or concomitant diseases among the

T1DM girls; or refusal of the girls and/or their parents to participate into the study.

Statistical Analysis:

Data were collected and entered on a PC computer; all statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS for Windows, version 12.0; SPSS). Qualitative nominal data were represented in the form of number (n) and percentage (%); and quantitative data were represented in the form of Mean± SD, in the proper significant test of usage; the z-scores were calculated. Values of P<0.05 were considered to indicate statistical significance in all analyses.

Anthropometric data were evaluated using the Egyptian Growth data (El Nofely, 2012). Pubertal development data were evaluated using the normal Egyptian female's reference data (Ghaly et.al., 2008). The mean age at menarche of the study sample was evaluated using the normal Egyptian middle class girls in Cairo, reference data (Attallah, 1977). Laboratory data were evaluated according to the normal international reference ranges (Ehrmann et.al., 1992; Neely et.al., 1995; and Virdis et.al., 1997).

Results:

Analysis of the present study data was performed; of the patients' Tanner breast stages (B), 7 (36.8%) were at B4; and 12 (63.2%) were at B5; and of the patients' Tanner Pubic hair development (PH), 8 (42.1%) were at PH4, and 11 (57.9%) were at PH5, Table (1). T1DM girls who were lying at Tanner stage IV (B4& PH4) had shown a significant difference (P= 0.007, 0.001, respectively) revealing their delay to reach Tanner stage V, adult sexual maturity, (B5, PH5), when compared with the normal Egyptian females, Table (9).

The mean age at menarche (13.24± 1.25 yrs), among the seventeen (89.5%) postmenarcheal T1DM girls, showed no significant difference (P= 0.639) when compared with that (13.09± 0.17 yrs) for normal Egyptian middle- class girls in Cairo, Table (10). Also, it was found that two (10.5%) girls did not achieve menarche until after the study period was terminated, Table (3). seventeen postmenarcheal girls experienced their 1st menses after T1DM diagnosis at mean age (13.24± 1.25) yrs Table (4). Moreover, a significant decrease in the height SDS (P<0.05), of the studied T1DM girls, was found, when compared with normal Egyptian data, Table (11).

Only 3 (15.8%) among T1DM girls had achieved optimal metabolic control at (< 7.5%), while the remaining 16 (84.2%) had an insufficient metabolic control (9.93± 1.96) with a highly significant difference (P= 0.00) Table (5& 12). There was no significant difference between T1DM girls with optimal vs. those with insufficient metabolic control, regarding their clinical or anthropometric characteristics (P>0.05), Table (13). The basal and stimulated LH& FSH, levels were significantly decreased in T1DM girls (P= 0.000), when compared with the normal international reference ranges, Table (14). There was no significant difference between the T1DM girls with optimal, vs. those with insufficient metabolic control, regarding the basal and stimulated gonadotropins levels (P>0.05), Table

(15).

Table (1) Pubertal development according to Tanner Breast staging, and pubic hair development, among the study sample.

Tanner Breast stage (B)	Study Sample (n= 19)
B1	0 (0%)
B2	0 (0%)
B3	0 (0%)
B4	7 (36.8%)
B5	12 (63.2%)
Tanner Pubic Hair development (PH)	
PH1	0 (0%)
PH2	0 (0%)
PH3	0 (0%)
PH4	8 (42.1%)
PH5	11 (57.9%)

Table (2) Pubertal development (Mean± SD) among the study sample.

N	B4	B5	PH4	PH5
	(1)	(12)	(8)	(11)
Study Sample	15.26± 1.20	17.92± 2.66	14.80± 0.79	18.50± 2.23

Table (3) Age at menarche (Mean± SD) among the study sample.

	Menarche	No Menarche
N (%)	17 (89.5%)	2 (10.5%)
Study sample (n= 19)	13.24± 1.25	0

Table (4) Clinical and anthropometric characteristics, among the study sample.

	Study Sample (19)
	Mean± SD
Chronological Age (Yrs)	16.94± 2.56
Weight (Kg) SDS	- 0.01± 1.01
Height (Cm) SDS	- 0.32± 1.08
BMI (kg/m2) SDS	0.18± 0.99
Age of T1DM onset (yrs)	8.21± 2.74
T1DM Duration (Yrs)	8.73± 3.61
Age at menarche (yrs)	13.24± 1.25

Table (5) HbA1c% (Mean± S. D) among the study sample and according to the metabolic control

	HbA1c (%)	
	N (%)	Mean± S. D
Study Sample	19	9.44± 2.13
Optimal control (< 7.5%)	3 (15.8%)	6.87± 0.40
Insufficient control (≥ 7.5%)	16 (84.2%)	9.93± 1.96

Table 6: Clinical and anthropometric characteristics, among girls with T1DM according to the metabolic control.

	Optimal Control (n= 3)	Insufficient Control(n= 16)
	Mean± SD	Mean± SD
Chronological Age (Yrs)	17.33± 3.72	16.87± 2.44
Weight (Kg) SDS	0.19± 1.45	- 0.05± 0.96
Height (Cm) SDS	0.44± 0.72	- 0.46± 1.10
BMI (kg/m2) SDS	0.15± 1.71	0.19± 0.89
Age of T1DM onset (yrs)	6.00± 2.00	8.63± 2.71
T1DM Duration (Yrs)	11.33± 5.59	8.24± 3.14
Insulin dose (U/kg/d)	0.97± 0.29	1.03± 0.29

Table (7) Basal and stimulated gonadotropins levels among the study sample.

	Study Sample (n= 19)
	Mean± SD
Serum basal LH (mIU/ml)	0.64± 1.29
Serum stimulated LH (mIU/ml)	1.58± 2.11
Serum basal FSH (mIU/ml)	0.13± 0.91
Serum stimulated FSH (mIU/ml)	3.97± 3.56

Table (8) Basal, and stimulated gonadotropins levels among T1DM girls according to the metabolic control.

	Optimal Control (n= 3)	Insufficient Control (n= 16)
	Mean± SD	Mean± SD
Serum basal LH (mIU/ml)	4.09± 0.73	4.84± 3.57
Serum stimulated LH (mIU/ml)	69.03± 38.30	63.86± 44.11
Serum basal FSH (mIU/ml)	6.50± 1.28	5.53± 2.21
Serum stimulated FSH (mIU/ml)	33.57± 12.82	22.33± 11.08
Serum basal LH/ FSH ratio	0.63± 0.07	0.88± 0.70
Serum stimulated LH/ FSH ratio	1.96± 0.72	2.94± 1.53

Table (9) Pubertal development and attainment of sexual maturity (Mean± SD) among T1DM girls (Compared to Normal population).

	B4 (n= 7)	PH4 (n= 8)
	Study Sample	15.26± 1.20
Normal Egyptian Females	13.45± 1.81	13.32± 1.62
P Value	0.007*	0.001*

Significant *

Table (10) Age at menarche (Mean± SD) among the study sample (compared to normal population).

	Menarche
N (%)	17 (89.5%)
Study sample (n= 19)	13.24± 1.25
Normal Egyptian Females	13.09± 0.17
P Value	0.639

Table (11) Anthropometric characteristics, among the study sample (Compared to Normal population).

	Study Sample (n 19)	
	Mean± SD	P Value
Weight (Kg) SDS	- 0.01± 1.01	>0.05
Height (Cm) SDS	- 0.32± 1.08	<0.05*
BMI (kg/m2) SDS	0.18± 0.99	>0.05

Table (12) HbA1c% (Mean± S.D) among the study sample according to the metabolic control.

	HbA1c (%)		
	N (%)	Mean± S. D	P Value
Optimal control (< 7.5%)	3 (15.8%)	6.87± 0.40	0.00*
Insufficient control (≥ 7.5%)	16 (84.2%)	9.93± 1.96	

Table (13) Clinical and anthropometric characteristics, among T1DM girls with optimal vs. those with insufficient metabolic control.

	Optimal Control (n= 3)	Insufficient Control (n= 16)	P Value
	Mean± SD	Mean± SD	
Chronological Age (Yrs)	17.33± 3.72	16.87± 2.44	0.88
Weight (Kg) SDS	0.19± 1.45	- 0.05± 0.96	0.96
Height (Cm) SDS	0.44± 0.72	- 0.46± 1.10	0.14
BMI (kg/m2) SDS	0.15± 1.71	0.19± 0.89	0.88
Age of T1DM onset (yrs)	6.00± 2.00	8.63± 2.71	0.11
T1DM Duration (Yrs)	11.33± 5.59	8.24± 3.14	0.36
Insulin dose (U/kg/d)	0.97± 0.29	1.03± 0.29	0.63

Table (14) Basal and stimulated gonadotropins levels among the study sample (compared to normal reference ranges).

	Study Sample (n= 19)		
	Mean± SD	z- score (SDS)	P Value
Serum basal LH (mIU/ml)	0.64± 1.29	- 4.06	0.0000*
Serum stimulated LH (mIU/ml)	1.58± 2.11	- 3.23	0.0006*
Serum basal FSH (mIU/ml)	0.13± 0.91	- 6.64	0.0000*
Serum stimulated FSH (mIU/ml)	3.97± 3.56	- 6.46	0.0000*

Table (15) Basal, and stimulated gonadotropins levels among T1DM girls with optimal vs. those with insufficient metabolic control.

	Optimal Control (n= 3)	Insufficient Control (n= 16)	P Value
	Mean± SD	Mean± SD	
Serum basal LH (mIU/ml)	4.09± 0.73	4.84± 3.57	0.96
Serum stimulated LH (mIU/ml)	69.03± 38.30	63.86± 44.11	0.79
Serum basal FSH (mIU/ml)	6.50± 1.28	5.53± 2.21	0.49
Serum stimulated FSH (mIU/ml)	33.57± 12.82	22.33± 11.08	0.14
Serum basal LH/ FSH ratio	0.63± 0.07	0.88± 0.70	0.71
Serum stimulated LH/ FSH ratio	1.96± 0.72	2.94± 1.53	0.25

Discussion:

As a chronic disease also occurring in childhood, T1DM is a factor potentially affecting pubertal development; Age at menarche, a mid-pubertal event, is considered a more reliable event for determining sexual maturity in girls than the appearance of secondary sexual characteristics (Parent et.al., 2003). Several publications have reported the effect of T1DM on the age of menarche. A significant menarche delay was described during the first half of the 20th century. In the 1940s and 1950s, menarche occurred 2 years later in girls with T1DM than in the general population (Schweiger et.al., 2010). With the advent of intensive insulin therapy in the 1990s, only a mild delay in menarche in girls with T1DM, ranging from 2 to 9 months, has been reported in countries in Europe and North and South America (Deltsidou, 2010). The current study found that the mean age at menarche among the postmenarcheal T1DM girls, showed no delay when compared with normal Egyptian girls. Whereas, Rohrer et.al., in 2008, found significant delay in age at menarche of type 1 diabetic girls.

Clinically, female patients with T1DM may exhibit amenorrhea (Kromeyer et.al., 1999). There have also been reports of decreased LH levels in T1DM, suggesting impairment of the hypothalamic- pituitary axis (Griffin et.al., 1994). The current study found that 10.5% of the study sample did not achieve menarche until after the study period was terminated.

The current study found that T1DM girls who were lying at Tanner stage IV (B4& PH4) had shown delay to reach Tanner stage V, adult sexual maturity, (B5, PH5), when compared with the normal Egyptian females. This was inconsistent with Rohrer et.al., in 2008, who found that diabetic girls ultimately reach sexual maturity at a normal age.

High HbA1c serum levels as a marker of poor glycemic control and an indicator that these patients lack insulin. Insulin mainly serves as a signal of satiety in the hypothalamus, but is also involved in the regulation of reproductive function. Increased HbA1c levels due to the lack of tightly regulated insulin levels may affect ovarian maturation and function, and hence pubertal development in T1DM (Poretsky et.al., 1999). Based on this explanation, insulin dose would be expected to have a normalizing effect on age at menarche.

The current study found that the height SDS (P<0.05), of the T1DM girls, was significantly decreased when compared with normal Egyptian data. Several studies have clearly documented impaired prepubertal and

pubertal growth in children and adolescents with T1DM (Singh et.al., 2001). Consistent results have reported a decline in height SDS from diagnosis to the onset of puberty in children with T1DM. Data reported by Brown et.al. demonstrated a change in height SDS between diagnosis and the onset of the pubertal spurt (Brown et.al., 1994). The severity of the impaired prepubertal and pubertal growth is mainly related to glycemic control and to the adopted insulin regimes. Children with T1DM and poor metabolic control have a significantly lower growth velocity (Gunczler et.al., 1996).

The current study found that the basal and stimulated LH& FSH, levels were significantly decreased in T1DM girls ($P < 0.000$), when compared with the normal international reference ranges, These data suggested that under insulin deficiency, higher centers of the central nervous system decrease their GnRH stimuli over the pituitary (Bruning et.al., 2000).

Type 1 diabetes could affect pubertal development of girls, in the form of delay in their attainment of adult sexual maturity stages (B5, PH5); however, no significant difference was found regarding their mean age at menarche, compared to normal Egyptian girls. Moreover, the disease could alter their growth development, a significant decrease in their height SDS ($P < 0.05$), was found. Also, their basal and stimulated gonadotropins were found to be significantly decreased than normal reference ranges.

In Conclusion, the current study suggests that Type 1 diabetes could affect pubertal development of girls, in the form of delay in their attainment of adult sexual maturity stages (B5, PH5); however, their age at menarche, is within the range of normal Egyptian girls. Moreover, the disease could alter their growth development, with a decrease in their height than the normal population. Also, their basal and stimulated gonadotropins could be affected, with a significant decreased levels than normal reference ranges.

Recommendations:

It is of great clinical importance to improve glycemic control, as the most readily modifiable factor, to reduce any derangement in pubertal development and gonadotrophic hormonal profile, among type 1 diabetic adolescent girls. Future treatment modalities could address some of the current problems observed in these T1DM girls, by attempting to deliver insulin in a more physiologic fashion achieving a better balance between insulin deficiency and insulin excess in these patients.

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