eISSN 2255-0569

ORIGINAL

Oligomenorrhoea – is it more frequent in women wtih type 1 diabetes mellitus?

Oligomenorrea: ¿es más frecuente en mujeres con diabetes mellitus tipo 1?

Maria Ilieva-Gerova[1], Daniela Koleva-Tiutiundjieva[1], Maria Orbetzova[1], Presiyana Nyagolova[1], Ralitsa Raycheva[2], Tanya Deneva[3]

1. Department of Endocrinology and metabolic diseases, Medical University - Plovdiv, Bulgaria
2. Department of Social Medicine and Public Health, Faculty of Public Health, Medical University – Plovdiv, Bulgaria
3. Deparmtent of Clinical Laboratory, Faculty of Pharmacy, Medical University – Plovdiv, Bulgaria

Corresponding author
Maria Ilieva-Gerova
E-mail: mimilieva@yahoo.com

Received: 3 - VIII - 2022
Accepted: 8 - VIII - 2022

doi: 10.3306/AJHS.2022.37.06.57

Abstract

Introduction: Recent studies have shown an association of diabetes mellitus type 1 (DMt1) with reproductive disturbancies-delayed puberty and menarche, menstrual cycle abnormalities (oligomenorrhoea/amenorrhea /polymenorrhoea), polycystic ovary syndrome (PCOS) like phenotype, and potentially early menopause.
Objective: To assess menstrual cycle abnormalities in DMt1 women at reproductive age in comparison with age and BMI matched clinically healthy women.
Materials and methods: The study comprised of 37 women with DMt1 and 83 clinically healthy women serving as a control group. A detailed disease history was obtained regarding the duration of DMt1, type of insulin administered, total daily insulin dose (TDD); age at menarche, menstrual cycle (MC) interval, menstruation duration, dysmenorrhea and MC irregilarities, number of pregnancies, births, miscarriages. Oligomenorrhoea was defined as MC longer than 35 days or less than 9 MC throughout at least the past year. Polymenorrhea was defined as menstrual periods occuring at intervals of less than 21 days. Primary dysmenorrhea was interpreted as painfull menstruation unrelated to a secondary pelvic disease. Anthropometric measurements and basal levels of testosterone (T), thyroid-stimulating hormone (TSH) and prolactin (Prl) were studied in all participants. Fasting blood glucose (FG) and glycated hemoglobin (HbA1C) were also evaluated. Body mass index (BMI) and total daily insulin dose per kg body weight (TDD / kg) were calculated. Descriptive statistics, parametric and non-parametric methods were applied. Statistical significance was set at $p<0.05$.
Results: There was no statistically significant difference in terms of age (U=1789, p=0.149) and BMI (U=1686, p=0.392) between patients and controls. Euthyroid function and normoprolactinaemia were reported in all 120 subjects. Women with DMt1 had significantly higher T levels, FG and HbA1C compared to controls (U=2364, t=8.78, t=13.61, p=0.000, resp.). No significant differences were proven in the age at menarche (U=1601, p=0.623) and MC length (U=1574, p=0.564) between the women with DMt1 and the healthy controls. The mean duration of MC interval was significantly longer in DMt1 group as compared to the control group (32;10 days vs. 30;3 days, p=0.018). There was an association between oligomenorrhoea and the groups under consideration (chi-square=27.01, p=0.000). We demonstrated a statistically significant difference between the relative proportion of diabetic women with oligomenorrhoea (40.5%) compared to healthy controls with oligomenorrhoea (3.6%) (z=5.2, p=0.000). There was also an association between dysmenorrhea and the groups under consideration (chi-square=12.16, p=0.000). The relative part of women with dysmenorrhea was higher for DMt1 group compared (51.4%) to the control group (19.8%) (z=3.5, p=0.001). In the group of DMt1 there was a higher number of pregnancies (U=1925, p=0.007) and miscarriages (U=1837p=0.005) compared to healthy controls. In the DMt1 group a significant correlation was found between MC interval and both T levels (rho=0.634, p=0.000) and dysmenorrhea (rho=0.542, p=0.001). Moreover, a positive significant relationship between dysmenorrhea and T concentrations was observed (rho=0.507, p=0.001). When dividing the group of DMt1 into two subgroups – women with MC interval ≥35/<35 days, women with oligomennorhea had signigicantly higher serum T compared to those with normal MC interval (p=0.000). In the oligomennorhea subgroup a positive correlation of MC duration with TDD (rho=0.750, p=0.001) as well as with TDD / kg (rho=0.693, p=0.04) was observed.
Conclusion: Women with DMt1 have higher frequency of menstrual cycle abnormalities compared to age and BMI matched healthy women. Early and precise assessment of DMt1 MC characteristics is essential for the appropriate and complex treatment approach in these women.

Keywords: type 1 diabetes mellitus, oligomennorhea, dysmenorrhea, menstrual cycle, testosterone.

Resumen

Introducción. Estudios recientes han demostrado una asociación de la diabetes mellitus tipo 1 (DMt1) con las alteraciones reproductivas: retraso de la pubertad y la menarquia, anomalías del ciclo menstrual (oligomenorrea/amenorrea/polimenorrea), fenotipo similar al del síndrome de ovario poliquístico (SOP) y, potencialmente, menopausia precoz.
Objetivo: Evaluar las anomalías del ciclo menstrual en mujeres con DMt1 en edad reproductiva en comparación con mujeres clínicamente sanas emparejadas por edad e IMC.
Materiales y métodos: El estudio comprendió 37 mujeres con DMt1 y 83 mujeres clínicamente sanas que sirvieron como grupo de control. Se obtuvo una historia clínica detallada sobre la duración de la DMt1, el tipo de insulina administrada, la dosis diaria total de insulina (TDD); la edad de la menarquia, el intervalo del ciclo menstrual (CM), la duración de la menstruación, la dismenorrea y las irregularidades del CM, el número de embarazos, los partos y los abortos. La oligomenorrea se definió como un ciclo menstrual de más de 35 días o de menos de 9 durante al menos el último año. La polimenorrea se definió como periodos menstruales que ocurren a intervalos de menos de 21 días. La dismenorrea primaria se interpretó como una menstruación dolorosa no relacionada con una enfermedad pélvica secundaria. Se estudiaron las medidas antropométricas y los niveles basales de testosterona (T), hormona estimulante de la tiroides (TSH) y prolactina (Prl) en todas las participantes. También se evaluaron la glucosa en sangre en ayunas (FG) y la hemoglobina glicosilada (HbA1C). Se calcularon el índice de masa corporal (IMC) y la dosis diaria total de insulina por kg de peso corporal (TDD / kg). Se aplicaron métodos estadísticos descriptivos, paramétricos y no paramétricos. La significación estadística se fijó en p<0,05.
Resultados: No hubo diferencias estadísticamente significativas en cuanto a la edad (U=1789, p=0,149) y el IMC (U=1686, p=0,392) entre pacientes y controles. La función eutiroidea y la normoprolactinemia se registraron en los 120 sujetos. Las mujeres con DMt1 tenían niveles de T, FG y HbA1C significativamente más altos en comparación con los controles (U=2364, t=8,78, t=13,61, p=0,000, respectivamente). No se demostraron diferencias significativas en la edad de la menarquia (U=1601, p=0,623) y la duración del MC (U=1574, p=0,564) entre las mujeres con DMt1 y los controles sanos. La duración media del intervalo del CM fue significativamente mayor en el grupo de DMt1 en comparación con el grupo de control (32;10 días frente a 30;3 días, p=0,018). Hubo una asociación entre la oligomenorrea y los grupos considerados (chi-cuadrado=27,01, p=0,000). Se demostró una diferencia estadísticamente significativa entre la proporción relativa de mujeres diabéticas con oligomenorrea (40,5%) en comparación con los controles sanos con oligomenorrea (3,6%) (z=5,2, p=0,000). También hubo una asociación entre la dismenorrea y los grupos considerados (chi-cuadrado=12,16, p=0,000). La parte relativa de mujeres con dismenorrea fue mayor para el grupo de DMt1 en comparación (51,4%) con el grupo de control (19,8%) (z=3,5, p=0,001). En el grupo de DMt1 hubo un mayor número de embarazos (U=1925, p=0,007) y de abortos (U=1837p=0,005) en comparación con los controles sanos. En el grupo DMt1 se encontró una correlación significativa entre el intervalo MC y tanto los niveles de T (rho=0,634, p=0,000) como la dismenorrea (rho=0,542, p=0,001). Además, se observó una relación positiva y significativa entre la dismenorrea y las concentraciones de T (rho=0,507, p=0,001). Al dividir el grupo de DMt1 en dos subgrupos -mujeres con intervalo de MC ≥35/<35 días-, las mujeres con oligomenorrea presentaban una T sérica significativamente mayor en comparación con las que tenían un intervalo de MC normal (p=0,000). En el subgrupo de oligomenorrea se observó una correlación positiva de la duración de la CM con la TDD (rho=0,750, p=0,001) así como con la TDD / kg (rho=0,693, p=0,04).
Conclusiones: Las mujeres con DMt1 tienen una mayor frecuencia de anomalías del ciclo menstrual en comparación con las mujeres sanas emparejadas por edad e IMC. La evaluación precoz y precisa de las características del CM de la DMt1 es esencial para el enfoque terapéutico adecuado y complejo en estas mujeres.

Palabras clave: diabetes mellitus tipo 1, oligomenorrea, dismenorrea, ciclo menstrual, testosterona..

Introduction

The regularity of a menstrual cycle is an indicator of women's reproductive health. An irregular menstrual cycle (MC) is considered to be menstrual bleeding occurring more frequently than a 21-day cycle, less frequently than 35-day cycles, or an irregular bleeding pattern (such as bleeding between periods or abnormally heavy cycles)[1]. Menstrual cycle irregularities in women without diabetes are associated with increased cardiovascular risk, insulin resistance and hyperinsulinemia, as well as a risk of developing type 2 diabetes mellitus[2]. The most frequently observed cause of MC irregularity is functional hypothalamic amenorrhea, being associated with decreased gonadotropin-releasing hormone (GnRH) secretion and hypothalamic–pituitary–adrenal (HPA) axis dysregulation[1]

Insulin plays a key role in regulating female reproductive function through its effects on both GnRH neurons in the central nervous system and the granulosa, thecal, and stromal components in the ovaries[3]. The importance of insulin action on reproductive function in humans is highlighted by insulin receptor expression in most tissues, including the hypothalamus, pituitary, uterus and the ovaries[4].

Type 1 diabetes mellitus (DMt1) is a chronic autoimmune metabolic disease, characterised by a lack of insulin secretion from the pancreas as a result of beta-cell destruction. Insulinopenia causes a number of systemic effects on the every aspect of human health, in terms of its protein, fat and carbohydrate metabolism and not least on

the reproductive system. Is it the hypoinsulinemia or the hyperglycemia, insulin treatment itself or the combination of all affecting and disrupting the hypothalamic-pituitary-ovarian (HPO) axis in women with DMt1 is still a matter of scientific research.

Numerous studies have shown a higher freqency of reproductive disorders in DMt1 women such as late menarche and early menopause, hypothalamic anovulation, MC disorders-oligo-/amenorrhea, polymenorrhea, autoimmune disorders (greater frequency of ovarian antibodies and premature ovarian failure), PCOS-like phenotype (hyperandrogenism and anovulation)5. Women with DMt1 have an increased frequency of MC disorders compared to the healthy population, and this has been shown to increase the risk of coronary artery disease[6]. Given the increasing incidence of diabetes mellitus worldwide and reported gonadal dysfunction, assessment of MC characteristics in women with DMt1 has a wide clinical implication.

The *aim* of the study was to assess menstrual cycle abnormalities in DMt1 women at reproductive age in comparison with age and BMI matched clinically healthy women.

Materials and methods

We performed a transversal, observational, case-control study comprising 37 women with DMt1 and 83 age and BMI matched clinically healthy women. The study was conducted in the Clinic of Endocrinology and Metabolic Diseases at the University Hospital "Sveti Georgy", Faculty of Medicine, Medical University of Plovdiv, Bulgaria. All participants have given their written consent in accordance with the Declaration of Helsinki, as the study was approved by the Scientific Ethics Board of the Research Council at the Medical University of Plovdiv.

Inclusion criteria: women with type 1 diabetes mellitus on insulin treatment;
Exclusion criteria: pregnant and lactating women, presence of heart, respiratory, renal or hepatic failure, proliferative retinopathy, diabetic macroangiopathy, presence of acute decompensation of metabolic disease at the time of the study, contraceptive therapy or less than 3 months prior to study enrollment, treatment of chronic concomitant pathology that could affect hormonal and metabolic parameters.

The participants' data included diabetes mellitus duration, type of insulin administration, total daily insulin dose. A detailed gynecological history was obtained including age at menarche, MC interval, menstruation lenght, MC irregularities, dysmenorrhea, pregnancies, births, miscarriages. Oligomenorrhoea was defined as having a menstrual cycle longer than 35 days or less than 9 periods throughout at least the past year. Polymenorrhea was defined as menstrual periods occuring at intervals of less than 21 days. Primary dysmenorrhea wad defined as painfull menstruation unrelated to a secondary pelvic disease. The following anthropometric measurements were performed: weight, height, and body mass index (BMI) was calculated according to the standard formula[7]. Glycated haemoglobin (HbA1c) and fasting glucose (FG) were assessed. Basal levels of testosterone (T), thyroid-stimulating hormone (TSH), prolactin (Prl), and 17-hydroxyprogesterone - 17(OH)PG were studied in all participants.

Blood samples for laboratory tests were collected under standard conditions - early in the morning, after a 12-hour period of night fasting, during the early follicular phase of MC (3rd-5th day after spontaneous MC). The venous samples were studied in the Central Clinical Laboratory at the University Hospital "Sveti Georgy "- Plovdiv. Serum concentrations of T and PRL were determined by enzyme-linked immunosorbent assay with chemiluminescent detection, analyzer system: Access 2 Immunoassay System, Beckman Coulter, Inc., US. Serum TSH concentration was tested by competitive chemiluminescent immunochemical analysis (CLIA), analyzer system: Access 2 Immunoassay System, Beckman Coulter, Inc., USA. Venous blood sample with EDTA anticoagulant was obtained for HbA1C. Immunoinhiting test of turbodimetric analysis was applied with analyzer system AU 480, Beckman Coulter, Inc., USA. 17(OH)PG was tested by Enzyme-Linked Immunosorbent Assay (ELISA), analyzer system Sirio SEAC – Microplate reader.

Descriptive and inferential statistics were performed. Continuous variables were first tested for normality of statistical distribution by Shapiro–Wilk test. All normal distribution measurement data are expressed as the mean ± standard deviation (SD). Comparisons between two groups were analysed with Student's t-tests for independent samples, with Bonferroni correction for pairwise comparisons. The non-normally distributed data were expressed as median and interquartile range. Comparisons between groups were carried out with use of the nonparametric Mann-Whitney test for two independent groups. Categorical variables were presented as absolute/relative frequencies (counts / %). The Chi-square test was employed to analyse the association between two categorical variables and if proven z-test was applied to test for difference of relative parts between the groups. Significant correlations were presented by Spearman's rho coefficient. Statistical analysis of the data was performed using SPSS v.26 for Windows (IBM Corp. Released 2019. Armonk, NY: IBM Corp). For all tests p-value <0.05 indicated the statistical significance.

Results

Basic demographic, anthropometric, clinical, biochemical and hormonal characteristics of the studied women are summarized in **table I**. The mean age of the subjects in the present study was 30; 9 years with no significant difference between the participants with DMt1 and the control group (31; 8 ys) *versus* (30; 9 ys), (U=1789, p=0.149). In addition, no significant difference in terms of BMI between the DMt1 women and the controls (23.3; 4.9 kg/m^2) *versus* (22.3; 4.9 kg/m^2), (U=1686, p=0.392). Euthyroid function and normoprolactinaemia were reported in all 120 subjects. The participants presented with normal levels of 17(OH)PG, without significant difference between the two groups (U=1187, p=0.551). Thus, non-classic congenital adrenal hyperplasia (CAH) was excluded.

Table I: Basic demographic, anthropometric, clinical, biochemical and hormonal characteristics of the women studied.

	DMt1 (n=37)	Controls (n=83)	p-value
Age (years), *median; IQR*	31;9	30;9	0.149[1]
BMI (kg/m2), *median; IQR*	23.3;4.9	22.3;4.9	0.392[2]
Fasting glucose (mmol/l), *mean±SD*	7.5±2.5	5.0±0.3	**0.000[1]**
HbA1C (%), *mean±SD*	7.8±1.5	4.8±0.3	**0.000[1]**
Testosterone (ng/ml), *median; IQR*	0.6;0.4	0.4;0.2	**0.000[2]**
TSH (mU/l), *median; IQR*	2.2;1.8	1.7;1.2	0.104[2]
Prolactin (mU/l), *median; IQR*	210.6;126	232.6;145.5	0.548[2]
17(OH)PG (ng/ml), *median; IQR*	1;1.6	1.2;2	0.551[2]
Age at menarche (years), *median; IQR*	13;2	13;2	0.623[2]
MC interval (days), *median; IQR*	32;10	30;3	**0.018[2]**
MC duration (days), *median; IQR*	6;2	6;1	0.564[2]
Pregnancies (number), *median; IQR*	1;2	0.0;1	**0.007[2]**
Births (number), *median; IQR*	1;1	0.0;1	0.089[2]
Miscarriages (number), *median; IQR*	0.0;1	0.0;0.0	**0.005[2]**
DMt1 duration (years), *mean±SD*	13.8±8.3	-	-
TDD insulin (units), *mean±SD*	54.3±17.3	-	-
Insulin dose/kg, *mean±SD*	0.9±0.2	-	-

[1] - T-test; [2] - Mann-Withey U test

Women with DMt1 did not differ in terms of age at menarche and MC duration with the control group (U=1601, p=0.623; U=1574, p=0.564, resp.). However, we observed significantly longer MC interval in the diabetic women compared to healthy controls (U=1926, p=0.018). It turned out that in the DMt1 group there was a higher number of pregnancies (U=1925, p=0.007) and miscarriages (U=1837, p=0.005) compared to the healthy group. The two groups did not differ in terms of number of births (U=1758, p=0.089). An association between the number of pregnancies and the examined groups in our study (chi-square=16.43, p=0.002) was observed. The relative proportion of women with no pregnancies was higher in the control women (59.3%) compared to diabetic women (32.4%) (z=2.8, p=0.006). On the contrary, the relative proportion of diabetic women with 3 pregnancies was higher (13.5%) compared to controls (1.2%) (z=2.9, p<0.004).

In our study 40.5% (n=15) with DMt1 and only 3.6% (n=3) in the control group fulfilled the oligomenorrhoea criteria. 51.4% (n=19) with DMt1 and 19.3% (n=16) of the controls reported dysmenorrhea. Only one woman with DMt1 had polymenorrhea. No one reported amenorrhea. There was an association between oligomenorrhoea and the groups under consideration (chi-square=27.01, p=0.000). We demonstrated a statistically significant difference between the relative proportion of diabetic women with oligomenorrhoea (40.5%) compared to healthy controls with oligomenorrhoea (3.6%) (z=5.2, p=0.000). There was also an association between dysmenorrhea and the groups under consideration (chi-square=12.16, p=0.000). The relative part of women with dysmenorrhea was higher for DMt1 group compared (51.4%) to the control group (19.8%) (z=3.5, p=0.001).

As expected, HbA1C and FG were higher in DMt1 women (t=13.61, p=0.000; t=8.78, p=0.000, resp.) compared to healthy individuals. The average duration of the DMt1 was 13.8±8.3 years, the average TDD of insulin was 54.3±17.3 E, and the average calculated insulin dose per kg was 0.9±0.2 E/kg. Women in the DMt1 group had significantly higher serum T levels than healthy controls (U=2364, p=0.000).

In the DMt1 group a significant correlation was found between MC interval and both T levels (rho=0.634, p=0.000) and dysmenorrhea (rho=0.542, p=0.001). Moreover, a positive significant relationship between dysmenorrhea and T concentrations was observed (rho=0.507, p=0.001). As expected, HbA1C demonstrated a strong postive correlation with TDD (rho=0.359, p=0.003) and TDD/kg (rho=0.432, p=0.008).

For more precise assessment of women with DMt1 and oligomenorrhoea, we further divided the DMt1 group into two subgroups – women with MC interval ≥35 and with MC interval <35 days (**Figure 1** and **table II**). The only stastistically significant deference between the subgroups concerned serum T levels. They were significantly higher in the oligomenorrhoea subgroup compared to the subgroup with normal MC interval (U=309, p=0.000). There was also a tendency for prolonged MC duration in women with DMt1 and oligomennorhea compared to those normal MC (U= 224, p=0.070), without reaching statistical significance. No other significant differencies were observed among the examined parameters. In the oligomennorhea subgroup a positive correlation of HbA1C with DM duration was observed (rho=0.603, p=0.020). There was also a positive correlation of MC duration with TDD (rho=0.750, p=0.001) and with TDD/kg (rho=0.693, p=0.040). Diabetic women with MC interval < 35 days were found to have positive correlation of MC duration with FG levels (rho=0.499, p=0.020). The same subgroup presented with negative correleation between dysmenorrhea and number of pregnancies, but without reaching significant level (rho=0.395, p=0.060).

Figure 1: Distrubution of women in DMt1 group and control group by MC interval.

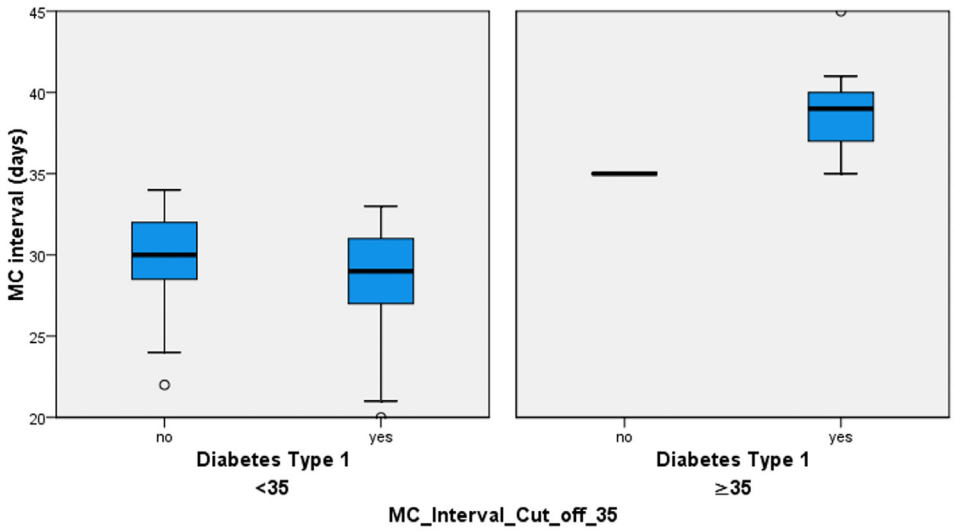

Table II: Anthropometric, anamnestic and hormonal parameters in women with DMt1 according to the MC interval.

DMt1	MC interval≥35 (n=15)	MC interval<35 (n=22)	p-value
Age (years), *mean±SD*	29.3±4.8	31.8±6.5	0.383[1]
BMI (kg/m2), *mean±SD*	23.3±3.7	23.5±3.5	0.680[1]
Fasting glucose (mmol/l), *mean±SD*	7.5±2.9	7.5±2.3	0.725[1]
HbA1C (%), *mean±SD*	7.9±1.6	7.7±1.4	0.531[1]
Testosterone (ng/ml), *median; IQR*	0.9;0.4	0.6;1.2	**0.000[2]**
TSH (mU/l), *mean±SD*	2.5±1.2	2.3±1.2	0.614[1]
Prolactin (mU/l), *median; IQR*	180.6;89.9	224.8;153.3	0.092[2]
17(OH)PG (ng/ml), *median; IQR*	0.6;1.7	1.1;1.6	0.290[2]
Age at menarche (years), *median; IQR*	13;4	13;2	0.614[2]
MC duration (days), *median; IQR*	6;1	5;1	0.070[2]
Pregnancies (number), *median; IQR*	1;2	1;2	0.891[2]
Births (number), *median; IQR*	1;1	1;1	0.636[2]
Abortions (number), *median; IQR*	0.0;1	0.0;1	0.531[2]
DMt1 duration (years), *mean±SD*	11.6±7.0	15.3±8.9	0.680[1]
TDD insulin (units), *mean±SD*	54.4±18.58	54.18±16.76	0.867[1]
Insulin dose/kg, *mean±SD*	0.9±0.3	0.8±0.2	0.703[1]

[1] - T-test; [2] - Mann-Withey U test

Discussion

The DMt1 women in our study presented with oligomenorrhoea and dysmenorrhea more frequently, with higher number of pregnancies and abortions, but with similar age of menarche as compared to healthy controls.

The regularity of the menstrual cycle requires an intact hypothalamus-pituitary-gonadal axis. Back in 1994 Griffin et al. reported that the menstrual cycle disorders in DMt1 might be of hypothalamic origin and represent GnRH pulse generator failure[8]. Central nervous system mediators - dopaminergic, opioidergic activity, catecholamine levels might also have a role in the pathophysiology of hypogonadism in patients with DMt1[9]. Hyperglycemia itself may affect the ovary both directly and through the induction of insulin resistance. Last but not least exogenous insulin administration may cause overstimulation of the IGF-1 receptors in the ovary, increasing steroid secretion stimulating the development of PCOS[10].

A number of studies presented a delay in the age of thelarche, pubarche, and most importantly menarche in girls with DMt1[11,12]. This delay was estimated to be about one year if the onset of disease occurred before puberty[13,14,15]. Even after improvement of insulin therapy and intensification of insulin injections, girls still experienced a delay in the age of menarche compared to the nondiabetic girls of the same age[16]. A research from the year 2010 demonstrated that although there was a decline in age of menarche for the past 4 decades among girls with DMt1, the ones diagnosed prior to menarche still experince a delay compared to those diagnosed after menarche[17]. Codner et al. summarized that the factors associated with the delay in menarcheal age have been poor metabolic control, lower BMI, prepubertal onset of the diasease with a longer duration[18]. In our study we did not find a significant difference in age of menarche in diabetic women compared to healthy population (U=1601, p=0.623), taking into account that the number of participants diagnosed with DMt1 before the age of menarche was only 5. We can conclude that menarcheal age of diabetic women in the study is comparable to the one in healthy individuals if DMt1 occurs after puberty. Further investigation including more women with prepubertal onset of DMt1 is under consideration.

A lot of studies demonstrated the presence of menstrual cycle disorders in women with DMt1[12,14,15]. Strotmeyer et al. reported that type 1 diabetic women have an increased

risk of menstrual disturbancies only at a younger age. Besides, statistical analysis revealed that DMt1 causes an approximate twofold increased risk of menstrual problems before the age of 30 years[19]. The mean age of women with DMt1 in our study was 30; 9 years and still we demonstrated prolonged MC interval compared to healthy individuals (p=0.018). In the DMt1 group there were 15 women (40.5%) with oligomennorhea. Gaete et al. demonstraed oligomenorrhea (58.9% vs. 19.6%) and amenorrhea (10.7% vs. 1.8%) in adolescent girls with type 1 diabetes mellitus compared to controls. When performing regression analysis the authors concluded that for each point of increase in HbA1c, the menstrual cycle duration increased by 5.1 days[20]. The relationship between menstrual cycle disturbances and metabolic control remains not entirely studied. Deltsidou et al. concluded that adolescent girls with DMt1 experience delayded menarche and oligomenorrhoea more frequently. What is more, the relative risk of presenting with oligomenorrhoea is greater when there is an increased value of HbA1c[21].

The mean level of HbA1C in DMt1 group was 7.8±1.45% and FG 7.5±2.5 mmol/l. Only 6 women presented with strict metabolic control (HbA1C <6.5%) and 31 were with HbA1C>6.5%. In addition oligomennorhea and dysmenorrhea did not show any correlation with HbA1C, FG and disease duration. Hypogonadotropic hypogonadism was demonstrated in women with type 1 diabetes mellitus with poorly controled diabetes. Djursing et al. reported that the hypogonadotropic hypogonadism presented in amenorrheic DMt1 women might be similar to the one in anorexia nervosa and heavy exercise with impared LH secretion[22].

But is the metabolic control that only matters in terms of menstrual cycle abnormalities in DMt1? By performing the further subdivision, we tried to look for other markers related with menstrual cycle disorders in DMt1. Still, diabetic women with oligomennorhea did not differ in terms of metabolic control with the normal cycle DMt1 women. Escobar-Morreale proposed that exogenous insulin administered in nonphysiological way results in ovarian huperinsulinemia, PCOS like phenotype and menstrual cycle irregularities[23]. Indeed, only women with oligomennorhea demonstrated positive correletaion of MC duration with TDD and TDD/kg (rho=0.750, p=0.001; rho=0.693, p=0.04 resp.) It was already mentioned that insulin and insulin-like growth factor 1 (IGF-1) receptors are present in the ovary, including theca, granulosa, and stromal cells[3,4]. Since insulin stimulates steroidogenesis and folliculogenesis in theca cells, irregular menstrual cycles may depend on the direct effect of exogenous insulin on the ovaries.

Women with DMt1 are reported to have reduced fertility[24,25]. Wiebe et al. found that women with type 1 diabetes have fewer children than their unaffected siblings but later age of onset of diabetes was associated with a higher number of the offspring[25]. In our study women with DTt1 had a greater number of pregnancies (U=1925, p=0.007) and miscarriages (U=1837, p=0.005) compared to the healthy controls. We also observed an association between the number of pregnancies and the examined groups in our study (chi-square – 16.43, p=0.002). The relative proportion of women with no pregnancies was higher in the control women (59.3%) compared to diabetic women (32.4%) (z=2.8, p=0.006). On the contrary, the relative proportion of diabetic women with 3 pregnancies was higher (13.5%) compared to controls (1.2%) (z=2.9, p<0.004). A study from Finland reported that later age at onset of diabetes was associated with a higher rate of having a second live birth among women (p=0.002)[26].

Developed countries are witnessing a marked change in the pattern of childbearing as increasing numbers of women postpone childbearing until their 30s and 40s[27]. As numerous studies showed that maternal and fetal complications are substantially higher, especially in advanced age in women with type 1 diabetes than in women from the general population, we can assume that this might be the answer to the higher rate of pregnancies in the DMt1 group[28]. Early assessment of reproductive status in women with DMt1 is found to be important for adequate planning of future normal pregnancy, selection of appropriate contraception, improvement of glycemic control and thus reducing the number of miscarriages. Probably this was the main reason for the better reproductive results in the women with DMt1 in our study.

Conclusion

Women with DMt1 have higher frequency of menstrual cycle abnormalities compared to age and BMI matched healthy women. Early and precise examination of menstrual cycle characteristics of women with DMt1 is essential for developing a better approach towards their treatment. Further purposeful studies with higher number of participants are needed to elucidate these observations.

Funding

This research did not receive any financial support

Conflict of Interest

The authors report no conflicts of interest.

References

1. Rostami Dovom M, Ramezani Tehrani F, Djalalinia S, Cheraghi L, Behboudi Gandavani S, Azizi F. Menstrual Cycle Irregularity and Metabolic Disorders: A Population-Based Prospective Study. PLoS One. 2016;11(12):e0168402.

2. Solomon CG, Hu FB, Dunaif A, Rich-Edwards J, Willett WC, Hunter DJ, et al. Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. JAMA. 2001 21;286(19):2421-6.

3. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev. 1987;8(2):132-41.

4. Poretsky L, Cataldo NA, Rosenwaks Z, Giudice LC. The insulin-related ovarian regulatory system in health and disease. Endocr Rev. 1999;20(4):535-82.

5. Codner E, Cassorla F. Puberty and ovarian function in girls with type 1 diabetes mellitus. *Horm Res* 2009; 71(1): 12-21.

6. Snell-Bergeon JK, Dabelea D, Ogden LG, Hokanson JE, Kinney GL, Ehrlich J, et al. Reproductive history and hormonal birth control use are associated with coronary calcium progression in women with type 1 diabetes mellitus. J Clin Endocrinol Metab. 2008;93(6):2142-8.

7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

8. Griffin ML, South SA, Yankov VI, Booth RA Jr, Asplin CM, Veldhuis JD, et al. Insulin-dependent diabetes mellitus and menstrual dysfunction. Ann Med. 1994;26(5):331-40.

9. Arrais RF, Dib SA. The hypothalamus-pituitary-ovary axis and type 1 diabetes mellitus: a mini review. Hum Reprod. 2006;21(2):327-37.

10. Codner E, Cassorla F. Puberty and ovarian function in girls with type 1 diabetes mellitus. Horm Res. 2009;71(1):12-21.

11. Rohrer T, Stierkorb E, Heger S, Karges B, Raile K, Schwab KO, et al; Diabetes-Patienten-Verlaufsdaten (DPV) Initiative. Delayed pubertal onset and development in German children and adolescents with type 1 diabetes: cross-sectional analysis of recent data from the DPV diabetes documentation and quality management system. Eur J Endocrinol. 2007;157(5):647-53.

12. Dorman JS, Steenkiste AR, Foley TP, Strotmeyer ES, Burke JP, Kuller LH, et al; Familial Autoimmune and Diabetes (FAD) Study. Menopause in type 1 diabetic women: is it premature? Diabetes. 2001;50(8):1857-62.

13. Bergqvist N. The gonadal function in female diabetics. Acta Endocrinol Suppl (Copenh). 1954;19:1-20.

14. Kjaer K, Hagen C, Sandø SH, Eshøj O. Epidemiology of menarche and menstrual disturbances in an unselected group of women with insulin-dependent diabetes mellitus compared to controls. J Clin Endocrinol Metab. 1992;75(2):524-9.

15. Yeshaya A, Orvieto R, Dicker D, Karp M, Ben-Rafael Z. Menstrual characteristics of women suffering from insulin-dependent diabetes mellitus. Int J Fertil Menopausal Stud. 1995;40(5):269-73.

16. Picardi A, Cipponeri E, Bizzarri C, Fallucca S, Guglielmi C, Pozzilli P. Menarche in type 1 diabetes is still delayed despite good metabolic control. Fertil Steril. 2008;90(5):1875-7.

17. Schweiger B, Klingensmith GJ, Snell-Bergeon JK. Menarchal timing in type 1 diabetes through the last 4 decades. Diabetes Care. 2010;33(12):2521-3.

18. Codner E, Iñíguez G, Villarroel C, Lopez P, Soto N, Sir-Petermann T, et al. Hormonal profile in women with polycystic ovarian syndrome with or without type 1 diabetes mellitus. J Clin Endocrinol Metab. 2007;92(12):4742-6.

19. Strotmeyer ES, Steenkiste AR, Foley TP Jr, Berga SL, Dorman JS. Menstrual cycle differences between women with type 1 diabetes and women without diabetes. Diabetes Care. 2003;26(4):1016-21.

20. Gaete X, Vivanco M, Eyzaguirre FC, López P, Rhumie HK, Unanue N, Codner E. Menstrual cycle irregularities and their relationship with HbA1c and insulin dose in adolescents with type 1 diabetes mellitus. Fertil Steril. 2010;94(5):1822-6.

21. Deltsidou A. Age at menarche and menstrual irregularities of adolescents with type 1 diabetes. J Pediatr Adolesc Gynecol. 2010;23(3):162-7.

22. Djursing H, Hagen C, Nyboe Andersen A, Svenstrup B, Bennett P, Mølsted Pedersen L. Serum sex hormone concentrations in insulin dependent diabetic women with and without amenorrhoea. Clin Endocrinol (Oxf). 1985;23(2):147-54.

23. Escobar-Morreale HF, Roldán B, Barrio R, Alonso M, Sancho J, de la Calle H, García-Robles R. High prevalence of the polycystic ovary syndrome and hirsutism in women with type 1 diabetes mellitus. J Clin Endocrinol Metab. 2000;85(11):4182-7.

24. Jonasson JM, Brismar K, Sparén P, Lambe M, Nyrén O, Ostenson CG, Ye W. Fertility in women with type 1 diabetes: a population-based cohort study in Sweden. Diabetes Care. 2007;30(9):2271-6.

25. Wiebe JC, Santana A, Medina-Rodríguez N, Hernández M, Nóvoa J, Mauricio D, Wägner AM; Fertility is reduced in women and in men with type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium (T1DGC). Diabetologia. 2014;57(12):2501-4.

26. Sjöberg L, Pitkäniemi J, Haapala L, Kaaja R, Tuomilehto J. Fertility in people with childhood-onset type 1 diabetes. Diabetologia. 2013;56(1):78-81.

27. Trillingsgaard, T., & Sommer, D. (2018). Associations between older maternal age, use of sanctions, and children's socio-emotional development through 7, 11, and 15 years. European Journal of Developmental Psychology, 15(2), 141–155.

28. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. Diabetes Care. 2009;32(11):2005-9.