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Hormonal Profile in Women with Diabetes Mellitus Type 1 and Polycystic Ovary Syndrome - Is It Comparable to the Classic Syndrome?

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Abstract

Development of polycystic ovary syndrome (PCOS) like phenotype in women with diabetes mellitus type 1 (DMt1) on intensified insulin treatment is related to the subcutaneous insulin administration and leads to clinical and biochemical hyperandrogenism. The aim of the study was to perform a comparative hormonal analysis of the hypothalamic-pituitary-gonadal (HPG) axis in women with DMt1 and PCOS and women with classic PCOS without diabetes. 83 women were included - 21 with DMt1 and PCOS and 62 with PCOS only. Basal levels of: luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), testosterone (T), sex hormone biding globulin (SHBG), dehydroepiadrostenedion sulfate (DHEA-S), Androstendion (A4), Anti-Müllerian Hormone (AMH), Prolactin (Prl), Thyroid stimulating hormone (TSH), LH/FSH, free androgen index (FAI), calculated free testosterone (cFT) и bioavailable testosterone (BioT) were calculated. Women with DMt1 and PCOS demonstrated significantly higher E2 levels (p=0.039), but lower DHEA-S (p=0.024) and prolactin (p=0.019) concentrations. No statistically significant differences were observed regarding LH (p=0.950), FSH (p=0.084), LH/FSH (p=0.531), SHBG (p=0.170), AMH (0.633), as well as androgen levels: T (p=0.995), FAI (p=0.0420), cFT (p=0.361), BioT (p=0.199) and A4 (p=0.254). Women with DMt1 and PCOS had hormonal profile similar to the classic PCOS in terms of gonadotropin levels, ovarian androgens and AMH.

Keywords: polycystic ovary syndrome; diabetes mellitus type 1; hypersndrogenism; insulin

1. Introduction

Type 1 diabetes mellitus (DMt1) is a chronic autoimmune disease characterized by decreased production of insulin from the pancreas as a result of beta cell destruction, leading to hyperglycemia.

About 1.8 million children worldwide have type 1 diabetes mellitus (<20) (DMt1) and 9.2 million of all age groups have the disease worldwide. 1481 children are diagnosed with DMt1 in Bulgaria [1]. The pathogenesis is complex, yet the outcomes of the disease relate to protein, lipid, carbohydrate metabolism.

Insulin is a key regulator of the homeostasis but participates in the neuroendocrine regulation of the reproduction as well. The hypothalamic decapeptide gonadotropin-releasing hormone (GnRH) acts on pituitary gonadotrophs and stimulates the pulsatile secretion of gonadotropins. Luteinizing (LH) and follicle-stimulating hormone (FSH) are major regulators of the ovarian development and cyclic function in postpubertal women. Ovarian steroids, mainly estradiol (E2) and progesterone (P),

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but also testosterone (T) and some peptides such as inhibins, provide feedback and regulate GnRH and/or gonadotropin secretion, ensuring the normal functioning of the hypothalamic-pituitary gonadal axis (HCG). The pulsatile secretion of GnRH is extremely sensitive to metabolic factors, hormones, and peripheral signals, which are of particular importance for the maintenance of the homeostasis-reproduction relation [2]. Insulin is one of these hormones. Both states of acute or chronic hypo- and hyperinsulinemia affect the hypothalamic-pituitary-gonadal axis (HPG), causing impairment of the GnRH secretion [2].

The role of insulin in human reproduction is emphasized by the expression of the insulin receptor in both the uterus and the ovaries [3]. In granulosa and theca cells of the ovary, insulin receptors mediate the metabolic, steroidogenic and mitogenic effects of the hormone [4]. Insulin also activates IGF-1R, including in theca, granulosa, and stromal cells, acting primarily through the tyrosine kinase signaling pathway [3,5]. Thus, the hormone stimulates the secretion of androgens in theca cells by increasing the activity of certain steroidogenic enzymes: 3-beta-hydroxysteroid dehydrogenase (3HSD) and 17-alpha-hydroxylase (CYP17A1) [3,5]. In granulosa cells, insulin promotes the recruitment and development of pre-ovulatory follicles [6], suppresses apoptosis and atresia of follicles, and stimulates the action of FSH for folliculogenesis [6]. This is important, taking into consideration conditions related to hyperinsulinemia and their action on the reproductive system.

One of the leading endocrine disorders in women of reproductive age and a leading cause of anovulatory infertility is polycystic ovary syndrome (PCOS), with up to 9.2-15% incidence, depending on the criteria applied [7]. The main features of the syndrome are oligo/anovulation, hyperandrogenism, and morphological polycystic ovaries [8] with heterogeneity in phenotypic expression - from asymptomatic to classic manifestations of the syndrome. There are different theories regarding the etiopathogenesis of PCOS, of which the most commonly accepted is a primary defect in insulin action and/or secretion, leading to hyperinsulinemia and insulin resistance [9].

The prevalence of PCOS in women with DMt1 is about 24%, as the smallest prevalence (7%) is reported in Italian adolescents and the largest (41%) is reported in Chilean adolescent and adult women, depending again on the criteria used in the research [10].

Codner et al. [11] demonstrated that up to 75% of women with DMt1 on intensified insulin treatment have PCOS or polycystic ovarian morphology. Physiologically, the pancreas secretes insulin into the portal circulation, and the liver eliminates part of the secreted insulin, being exposed to the greatest insulin concentrations [12]. In insulinopenic patients, the subcutaneous administration of insulin omits the first-pass effect of the liver and exposes the peripheral tissues to increased insulin concentrations [13]. In order to optimize the glycemic control of the patients and prevent long-term complications, supra-physiological insulin doses are applied, leading to peripheral tissues exposure of the increased insulin concentrations. One of the organs exposed to these increased insulin levels is the ovary, which results in increased androgen synthesis [14] and insulin resistance. The frequency of IR in patients with PCOS varies between 50% and 70% [15], which is much higher than in young healthy individuals. Escobar-Morreale et al. [10] revealed PCOS prevalence according to National Institute of Health criteria up to 18.8% among DMt1 women. When applying the Rotterdam criteria, the percentage increased up to 40.5% [10]. Thus, the proportion of diabetic women affected by the syndrome was significantly higher than found in the control group of women without diabetes - 6.5% [10]. A study from Italy reports up to 25% frequency of PCOS according to ESHRE-ASRM criteria [16].

Given the complex interactions between insulin metabolism and reproductive function, as well as the evidence for a higher prevalence of PCOS among women with type 1 diabetes, it remains unclear whether coexisting DMt1 shapes a distinct hormonal and clinical phenotype compared to PCOS alone. Therefore, the present study aimed to compare the reproductive-endocrine parameters in women with DMt1 and PCOS and those with isolated PCOS.

2. Materials and Methods

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2.1. Study Group

We performed a transversal, observational, case-control study. First were recruited 88 women. During the blood testing, it turned out that 3 of the examined women had primary hypothyroidism, one had elevated levels of 17(OH)PG and was referred for ACTH stimulation tests and further diagnostic evaluation and one refused to finish the diagnostic approach; therefore, their results were not included in the study. The results of 21 women with DMt1 and PCOS and 62 women with classic PCOS were analyzed. Patients were hospitalized in the Clinic of Endocrinology and Metabolic Diseases at the "Sveti Georgy" University Hospital, Faculty of Medicine, Medical University 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 - Plovdiv with protocol No. R-2444/36.10.2020.

Inclusion criteria for the study were: informed consent, signed, patients with diagnosed DMt1 (at least 1 year since diagnosis), diagnosed PCOS according to ESHRE/ASRM consensus criteria [17] (presence of two of the following criteria: clinical and/or biochemical hyperandrogenism, chronic anovulation, morphologically polycystic ovaries). Exclusion criteria: type 2 diabetes, 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 the start of the study, treatment of chronic concomitant pathology that could affect hormonal indices.

Medical history was taken for each study participant, and height, weight, waist, hip, body mass index (BMI), and waist-to-hip ratio were measured and calculated. Blood samples for laboratory tests were collected under standard conditions - early in the morning, after a 12-hour fast, in the follicular phase of the menstrual cycle (day 2-5 of a spontaneous menstrual cycle) or up to day 7 after progesterone-induced withdrawal bleeding. An ultrasound examination of the pelvis was performed using General electric 730 pro system. The venous samples were studied in the Central Clinical Laboratory at the “Sveti Georgy” University Hospital - Plovdiv. For all tests performed, systematic intra-laboratory control and assessment of the quality of the results were carried out through participation in national and international programs. The laboratory has the relevant certificates.

2.2. Anthropometric Measurements

Body mass index (BMI) – calculated using the following formula: **BMI = W/m²**, where BMI – body mass index; W – weight in kilograms; m² – height in meters [18]. **Waist circumference** above 80 cm is accepted as a marker of android obesity **in women** [19]. **Waist-to-hip ratio (WHR)** above 0.85 is accepted as a marker of android obesity in women [20].

2.3. Biochemical Analysis

Clinical-chemical parameters: fasting blood glucose (FBG) was analyzed on a clinical chemistry analyzer AU 480, Beckman Coulter (USA), using original programs with the conventional analytical principles of the applied methods. **Glycated hemoglobin (HbA1c)** – Method principle: turbidimetric immunoinhibition method after hemolysis of erythrocytes in whole blood, performed on an automated clinical chemistry analyzer AU 480, Beckman Coulter (USA).

2.4. Hormonal Analysis

Basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), total testosterone (T), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), Androstendion (A4), Anti-Müllerian Hormone (AMH), 17-hydroxyprogesterone (17-OHPG) thyroid-stimulating hormone (TSH), serum prolactin (Prl) were examined. Free testosterone index (FAI) was calculated, the following formula was used for calculation: Testosterone (nmol/l) x 100/ SHBG (nmol/l)[21]. Testosterone concentrations were recalculated from ng/ml to nmol/l using the coefficient F = 3.47 recommended by the test kit manufacturer, i.e. 1 ng/ml x 3.47 = 1 nmol/l. Free testosterone

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(cFT) and bioavailable testosterone (bioT) were calculated using the Vermeulen formula [22]. Serum concentrations of the hormones were examined by immunoenzyme assay with chemiluminescent detection, analyzer: Access 2 Immunoassay System, Beckman Coulter, Inc., US.

2.5. Statistical Analysis

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. 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 statistical significance.

3. Results

The anthropometric results of the two groups of women are shown in Table 1.

Table 1. Anthropometric parameters of women with DMt1+PCOS and women with PCOS without diabetes.

Parameter	DMt1+PCOS (n=21)	PCOS (n=62)	P-value
	Mean±SD	*Mean±SD*	*T- test*
Age (Y)	29.20±6.15	27.42±5.96	0.608
Weight (kg)	63.90±12.16	70.78±15.89	0.074
WHR	0.76±0.09	0.84±0.03	0.001
BMI (kg/m²)	23.43±3.84	25.56±5.95	0.129
HbA1C (%)	7.82±1.66	5.05±0.38	0.039
FBG (mmol/l)	7.43±2.79	4.99±0.46	0.001

Women with PCOS without diabetes had comparable body weight (p=0.074) and BMI (p=0.129), but presented with higher WHR (p=0.001) compared to the diabetic women. HbA1c and fasting blood glucose levels in the DMt1 group, as expected, were significantly higher compared to women with PCOS without diabetes (p=0.039, p=0.001, respectively).

The results of the hormonal evaluation of the two groups of women are given in Table 2. Women with PCOS without diabetes did not differ in terms of LH, FSH, LH/FSH levels (p=0.950, p=0.084, p=0.531, respectively) compared to the diabetic women. Females with PCOS have significantly lower E2 levels compared to the DMt1 women (p=0.039).

Regarding the androgen levels, T, FAI, cFT and BioT were comparable between the two PCOS groups (p=0.995, p=0.410, p=0.361, p=0.199, respectively). No statistically significant differences in terms of SHBG was also observed in the two groups under consideration (p=0.170).

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Table 2. Hormonal parameters of women with DMt1+PCOS and women with PCOS without diabetes.

Parameter	DMt1+PCOS (n=21)	PCOS (n=62)	P-value
	Mean±SD	*Mean±SD*	*T- test*
LH (IU/L)	9.09±4.13	9.17±5.37	0.950
FSH (mIU/ml)	5.62±0.72	6.15±1.32	0.084
LH/FSH	1.62±0.64	1.50±0.79	0.531
E2 (pg/ml)	57.02±11.90	45.34±24.50	0.039
T (ng/ml)	0.94±0.27	0.89±0.21	0.995
SHBG (nmol/l)	37.31±19.59	45.35±24.06	0.170
FAI	7.41±4.27	8.24±3.87	0.410
cFT (ng/ml)	0.11±0.007	0.14±0.005	0.361
BioT (ng/ml)	0.30±0.13	0.35±0.16	0.199
DHEA-S(μg/dl)	275.11±123.37	336.79±100.80	0.024
A4 (ng/ml)	4.79±1.29	4.39±1.41	0.254
17OHPG(ng/ml)	1.24±1.08	1.37±0.89	0.585
Prl (mU/L)	222.96±90.43	287.90±112.16	0.019
TSH (mU/L)	2.61±1.14	2.42±0.95	0.454
AMH (ng/ml)	8.80±5.17	8.14±5.55	0.633

Regarding the aRegWe demonstrated that women with PCOS had statistically significantly higher levels of DHEA-S (p=0.024), but did not differ in terms of A4 levels compared to the diabetic women (p=0.254). It turned out that women with PCOS had also higher levels of the prolactin than the diabetic females (p=0.019). The two groups examined did not differ in terms of 17OHPG (p=0.585) and TSH (p=0.454). The two groups had also comparable levels of AMH (p=0.633).

4. Discussion

In this study, women with PCOS and type 1 diabetes mellitus (DM1+PCOS) were compared to women with PCOS without diabetes. Age, body weight and BMI were broadly similar between groups, although there was a trend toward lower body weight and statistically significantly lower waist-to-hip ratio in the DM1+PCOS group. These anthropometric findings suggest that DMt1 does not substantially alter the overall body composition phenotype of women with PCOS, though subtle differences in fat distribution may be present. The tendency toward a lower WHR in patients with DMt1 and PCOS could reflect a relative protection from central adiposity, consistent with previous observations that type 1 diabetes is often associated with leaner body composition compared with type 2 diabetes or classic obesity-driven PCOS [23].

An increasing amount of evidence in the global literature indicates a higher prevalence of metabolic syndrome (MS) among patients with DMt1 [24,25]. The average reported prevalence of MS in individuals with DMt1 is around 23.7%, varying depending on the applied diagnostic criteria and study design [26]. Not only is CV risk increased in patients with DMt1 and MS, but MS has also been reported to be associated with a higher risk of development and/or progression of micro- and macrovascular complications in diabetic patients [24]. There is a small, but distinguishable group of women with PCOS with normal or even low BMI [27]. In accordance with this data, in our study, both PCOS groups of women presented without indications for obesity. Women with PCOS without diabetes have significantly higher waist/hip ratio (p=0.001). In accordance with this finding is a study, that demonstrates higher BMI and WHR in women with PCOS compared to women with DMt1 and PCOS and healthy controls [28].

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Hyperandrogenism is usually associated with DMt2, but it was back in 1985 when Djursing et al. [29] reported that women with DMt1 had elevated androgen levels despite the absence of amenorrhea, and O'Hare et al. [30] noted that intensified insulin therapy led to increased testosterone levels in women with insulin-dependent diabetes.

The hormonal profile of women with DMt1 and PCOS is different from that of hyperandrogenic nondiabetics [31]. Frequently observed are serum testosterone levels - similarly elevated in both groups, but free androgens are lower in the former, which is explained by the normal SHBG levels [31].

In our study, the comparative analysis of women with PCOS, with and without type 1 diabetes, revealed broadly similar patterns in gonadotropin and androgen markers. LH, FSH, LH/FSH ratio, testosterone, SHBG, free androgen index (FAI), calculated free testosterone, and bioavailable testosterone did not differ significantly between groups. This is in accordance with the data in the literature. In a recent study, women with DMt1 have comparable levels of T, A4, and DHEA-S, but lower FAI and SHBG than the women with PCOS without diabetes [32]. In another study, no significant differences are reported in the mean levels of LH, LH/FSH, T, SHGB, FAI, and DHEA-S [33]. Only A4 levels were statistically significantly higher in the diabetic women compared to women with PCOS only [33]. Other investigators demonstrated comparable levels of T, DHEA-S, and A4, but lower SHBG and increased levels of FAI in PCOS without diabetes [34].

This finding suggests that the ovarian–pituitary axis dysregulation characteristic of PCOS remains relatively consistent, regardless of concomitant DMt1. Such stability aligns with earlier reports that androgen excess in PCOS is primarily driven by intrinsic ovarian dysfunction and is not substantially modified by the presence of autoimmune diabetes, and is primarily intrinsic, rather than secondary to metabolic state [35].

The decreased SHBG levels, a characteristic feature of women with PCOS without diabetes, are not decreased in those with DMt1 and PCOS [36]. The insulin-resistant women without diabetes have increased levels of insulin in the portal vein, which suppresses the secretion of SHBG. When administered subcutaneously into the systemic circulation, insulin does not lead to an increase in its levels in the portal system, even at supra-physiological doses [37]. The normal SHBG levels in DMt1with PCOS explain why free androgen levels are not increased and hirsutism is milder in these women compared to PCOS without diabetes women [28]. Moreover, normal SHBG levels in women with DMt1 are the reason why the most sensitive serum marker of hyperandrogenism in this case is total testosterone, rather than its free fractions or FAI, as in nondiabetic women with PCOS [38].

The observed comparable SHBG levels in both groups in our study point out the role of total testosterone as a more sensitive marker for androgen excess in DMt1, compared to free testosterone or FAI, which are main indicators in women with PCOS without diabetes [39]. On the other hand, normal levels of AMH, inhibin B, estradiol, SHBG, and LH/FSH observed in another study suggest a different pathophysiological mechanism of hyperandrogenism in women with diabetes and PCOS, distinct from that in the classic syndrome [28].

Elevated AMH levels are a typical feature of patients with PCOS. In females with PCOS, follicular growth is interrupted, follicular development is impaired, FSH is suppressed, and the selection of a dominant follicle is impossible [40]. The highest expression of AMH is observed in preantral and small antral follicles (2–8 mm). With the onset of FSH-dependent stages of development (8–10 mm), AMH synthesis ceases, and in large antral and preovulatory follicles, AMH levels are undetectable [40]. The typical morphological feature of polycystic ovaries is the large number of antral follicles smaller than 8 mm. Due to the increased number of preantral and small antral follicles, which are the main producers of AMH, their levels are 2 to 4 times higher in these women compared to the healthy population. Moreover, AMH is not only a marker of follicle count but also a direct participant in the pathogenesis of PCOS [41].

Despite the increased number of follicles measuring 2–9 mm, AMH levels are normal in women with PCOS and DMt1 [28]. The explanation for this finding is that the increased follicle count is mainly due to follicles larger than 5 mm, which produce only a limited amount of AMH [28].

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In their study, Codner et al. [42] found elevated AMH, inhibin B, and DHEA-S levels in prepubertal girls with DMt1. That finding was explained by the exogenous administration of insulin [42]. The latter acts as a local factor supporting the growth of small follicles (primary, secondary, and small pre-antral). The second phase of folliculogenesis, after the onset of puberty, is gonadotropin-dependent. However, girls with DMt1 at Tanner stage 4–5 had lower AMH levels [42]. Insulin, acting as a co-gonadotropin, stimulates the growth of larger follicles, which secrete little or no AMH [42].

Conversely, we did not find any significant differences in 17-OHPG, TSH, or AMH between the two groups. In particular, the similarity in AMH levels suggests that ovarian reserve and follicle pool characteristics remain largely unaffected by the coexistence of type 1 diabetes. This reinforces the idea that ovarian morphology and follicular recruitment are determined primarily by PCOS status itself [43].

Notably, three significant differences emerged between the groups in our study.

First, DHEA-S was lower in women with DMt1 and PCOS, indicating a relative attenuation of adrenal androgen production compared with PCOS-only subjects. This may point to differential regulation of the HPA axis in women with type 1 diabetes, consistent with reports suggesting altered adrenal responsiveness under conditions of chronic autoimmune and metabolic stress.

In 2000, Escobar-Morreale et al. [13] reported a prevalence of hyperandrogenism of about 38.8% among women with DMt1, with 18.8% of them met the criteria for PCOS, but 20% presented with hirsutism despite the normo-ovulatory cycles. In the absence of statistically significant differences in LH, FSH, DHEA-S, SHBG, and 17OHPG levels, women with DMt1 and PCOS had significantly elevated free testosterone and androstenedione compared to healthy controls and normoandrogenic diabetics [13]. The age of the disease onset, glycemic control, mean daily insulin dose, and disease duration did not statistically affect these results [13]. Normal DHEA-S levels point to the ovary as the main source of androgen excess. The aim for strict glycemic control may result in supraphysiological insulin doses, and the resulting exogenous hyperinsulinemia could stimulate LH-mediated androgen production in the ovary [44].

Our study is in concordance with that of Łebkowska et al. [45] who showed significantly higher AMH levels in women with DMt1 and PCOS compared to those without the syndrome. No significant differences in ovarian volume and follicle count were found between women with PCOS, with or without diabetes, but both parameters were significantly higher compared to healthy controls. A positive correlation of AMH with LH, testosterone, and antral follicle count was also reported [45]. The authors concluded that women with DMt1 and PCOS have a hormonal profile similar to the classic syndrome [45].

The second important finding in our research was the higher E2 levels in the DMt1 with PCOS group compared to PCOS-only women. This could reflect differences in follicular dynamics or altered estrogen metabolism in the context of type 1 diabetes. Previous studies have shown that insulin availability and glycemic milieu can influence aromatase activity, potentially contributing to such variations [46].

Our third discovery was the lower prolactin in women with DMt1 and PCOS compared to PCOS-only. While values in both groups remained within physiological limits, this distinction may be clinically relevant given the interplay between prolactin and gonadotropin secretion. Lower prolactin in type 1 diabetes has been attributed to autoimmune pituitary involvement or differences in dopaminergic regulation, though this remains speculative [47].

5. Conclusions

The results in our study suggest that while the ovarian dysfunction of PCOS remains consistent in women with type 1 diabetes, the hormonal and anthropometric milieu differs in subtle but clinically relevant ways. Specifically, higher estradiol, lower adrenal androgens, reduced prolactin, and a tendency toward lower central adiposity define women with DM1 and PCOS phenotype. These distinctions may inform risk stratification and individualized approaches to fertility and long-term metabolic health in this unique subgroup.

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6. Patents

The authors declare that there are no patents resulting from this work.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. Conceptualization, M.I-G. and M.O.; methodology, M.I-G, P.N. D.K-T; software, R.R.; validation, M.I-G, D.K.-T. and P.N.; formal analysis, T.D..; investigation, T.D.; resources, M.I-G., P.N, M.O.; data curation, D.K.-T., P.N; writing—original draft preparation, M.I-G.; writing—review and editing, M.I-G., P.N. and M.O.; visualization, M.I-G., R.R.; supervision, M.O., D.K.-T; Authorship must be limited to those who have contributed substantially to the work reported.Funding: This research received no external funding.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of MEDICAL UNIVERSITY OF PLOVDIV (protocol R-2444/36.10.2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical restrictions and participant confidentiality, the dataset is not publicly available.

Conflicts of Interest: The authors declare no conflict of interest.
The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

DMt1	Type 1 Diabetes Mellitus
HHG axis	Hypothalamic–Pituitary–Gonadal axis
GnRH	Gonadotropin-releasing hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
E2	Estradiol
T	Testosterone
SHBG	Sex hormone-binding globulin
DHEA-S	Dehydroepiandrosterone sulfate
A4	Androstenedione
Prl	Prolactin
cFT	Calculated free testosterone
BioT	Bioavailable testosterone
FAI	Free Androgen Index
TSH	Thyroid-stimulating hormone
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholestero
LDL-C	Low-density lipoprotein cholesterol
PCOS	Polycystic ovary syndrome
HbA1c	Glycated hemoglobin
BMI	Body mass index
WHR	Waist-to-hip ratio

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References

1. International Diabetes Federation. IDF Diabetes Atlas, 11th ed.; International Diabetes Federation: Brussels, Belgium, **2025**.
2. Sliwowska, J.H.; Fergani, C.; Gawałek, M.; Skowronska, B.; Fichna, P.; Lehman, M.N. Insulin: Its role in the central control of reproduction. *Physiol. Behav.* **2014**, *133*, 197–206.
3. Poretsky, L.; Cataldo, N.A.; Rosenwaks, Z.; Giudice, L.C. The insulin-related ovarian regulatory system in health and disease. *Endocr. Rev.* **1999**, *20*, 535–582.
4. Nestler, J.E.; Jakubowicz, D.J.; de Vargas, A.F.; Brik, C.; Quintero, N.; Medina, F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J. Clin. Endocrinol. Metab.* **1998**, *83*, 2001–2005.
5. Poretsky, L.; Kalin, M.F. The gonadotropic function of insulin. *Endocr. Rev.* **1987**, *8*, 132–141.
6. Distiller, L.A.; Sagel, J.; Morley, J.E.; Seftel, H.C. Pituitary responsiveness to luteinizing hormone-releasing hormone in insulin-dependent diabetes mellitus. *Diabetes* **1975**, *24*, 378–380.
7. March, W.A.; Moore, V.M.; Willson, K.J.; Phillips, D.I.; Norman, R.J.; Davies, M.J. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum. Reprod.* **2010**, *25*, 544–551.
8. Azziz, R. PCOS: A diagnostic challenge. *Reprod. Biomed. Online* **2004**, *8*, 644–648.
9. Kolarov, G.; Orbetzova, M. *Polycystic Ovary Syndrome*; Izd. IK "Vyara": Sofia, Bulgaria, **2004**; ISBN 954-9409-01-5; pp. 1–232
10. Escobar-Morreale, H.F.; Roldan-Martín, M.B. Type 1 diabetes and polycystic ovary syndrome: Systematic review and meta-analysis. *Diabetes Care* **2016**, *39*, 639–648.
11. Codner, E.; Soto, N.; Lopez, P.; Trejo, L.; Avila, A.; Eyzaguirre, F.C.; Iniguez, G.; Cassorla, F. Diagnostic criteria for polycystic ovary syndrome and ovarian morphology in women with type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2006**, *91*, 2250–2256.
12. Yki-Järvinen, H.; Koivisto, V.A. Natural course of insulin resistance in type I diabetes. *N. Engl. J. Med.* **1986**, *315*, 224–230.
13. Escobar-Morreale, H.F.; Roldan, B.; Barrio, R.; Alonso, M.; Sancho, J.; de la Calle, H.; et al. High prevalence of the polycystic ovary syndrome and hirsutism in women with type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 4182–4187.
14. Codner, E.; Escobar-Morreale, H.F. Clinical review: Hyperandrogenism and polycystic ovary syndrome in women with type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 1209–1216.
15. Moran, L.; Teede, H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. *Hum. Reprod. Update* **2009**, *15*, 477–488.
16. Bizzarri, C.; Benevento, D.; Ravà, L.; Patera, I.P.; Schiaffini, R.; Ciampalini, P.; Giannone, G.; Cappa, M. Ovarian hyperandrogenism in adolescents and young women with type I diabetes is primarily related to birth weight and body mass index. *Fertil. Steril.* **2011**, *96*, 1497–1502.
17. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil. Steril.* **2004**, *81*, 19–25.
18. World Health Organization. Obesity: Preventing and Managing the Global Epidemic; WHO Technical Report Series 894; WHO: Geneva, Switzerland, **2000**.
19. Ross, R.; Neeland, I.J.; Yamashita, S.; Shai, I.; Seidell, J.; Magni, P.; et al. Waist circumference as a vital sign in clinical practice: A Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat. Rev. Endocrinol.* **2020**, *16*, 177–189.
20. World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation; WHO: Geneva, Switzerland, **2008**.
21. Vermeulen, A.; Verdonck, L.; Kaufman, J.M. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 3666–3672.
22. American Diabetes Association. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clin. Diabetes* **2022**, *40*, 10–38.

 doi:10.20944/preprints202509.0319.v1

23. Conway, G.S.; Dewailly, D.; Diamanti-Kandarakis, E.; et al. The polycystic ovary syndrome: A position statement. *Hum. Reprod.* **2014**, *29*, 2042–2055.
24. Parente, E.B.; Harjutsalo, V.; Forsblom, C.; Groop, P.H. Waist-Height Ratio and the Risk of Severe Diabetic Eye Disease in Type 1 Diabetes: A 15-Year Cohort Study. *J. Clin. Endocrinol. Metab.* **2022**, *107*, 653–662.
25. Thorn, L.M.; Forsblom, C.; Fagerudd, J.; Thomas, M.C.; Pettersson-Fernholm, K.; Saraheimo, M.; et al. Metabolic syndrome in type 1 diabetes: Association with diabetic nephropathy and glycemic control (the FinnDiane study). *Diabetes Care* **2005**, *28*, 2019–2024.
26. R., A.; Ataro, Z.; Abdu, A.; Sheleme, M. Global prevalence of metabolic syndrome among patients with type I diabetes mellitus: A systematic review and meta-analysis. *Diabetol. Metab. Syndr.* **2021**, *13*, 25.
27. Toosy, S.; Sodi, R.; Pappachan, J.M. Lean polycystic ovary syndrome (PCOS): An evidence-based practical approach. *J. Diabetes Metab. Disord.* **2018**, *17*, 277–285.
28. Codner, E.; Iñíguez, G.; Villarroel, C.; Lopez, P.; Soto, N.; Sir-Petermann, T.; Cassorla, F.; Rey, R.A. Hormonal profile in women with polycystic ovarian syndrome with or without type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 4742–4746.
29. 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*, 147–154.
30. O'Hare, J.A.; Eichold, B.H., II; Vignati, L. Hypogonadotropic secondary amenorrhea in diabetes: Effects of central opiate blockade and improved metabolic control. *Am. J. Med.* **1987**, *83*, 1080–1084.
31. Codner, E.; Merino, P.M.; Tena-Sempere, M. Female reproduction and type 1 diabetes: From mechanisms to clinical findings. *Hum. Reprod. Update* **2012**, *18*, 568–585.
32. Thong, E.P.; Milat, F.; Joham, A.E.; Mishra, G.D.; Teede, H. Obesity, menstrual irregularity and polycystic ovary syndrome in young women with type 1 diabetes: A population-based study. *Clin. Endocrinol. (Oxf.)* **2020**, *93*, 564–571.
33. Amato, M.C.; Guarnotta, V.; Ciresi, A.; Modica, R.; Pantò, F.; Giordano, C. No phenotypic differences for polycystic ovary syndrome (PCOS) between women with and without type 1 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 203–211.
34. Paschou, S.A.; Vryonidou, A.; Melissourgou, M.; Kosteria, I.; Goulis, D.; Chrousos, G.P.; et al. Menstrual disorders and androgen-related traits in young women with type 1 diabetes mellitus: A clinical study. *Endocr. Pract.* **2020**, *26*, 1269–1276.
35. Escobar-Morreale, H.F. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. *Nat. Rev. Endocrinol.* **2018**, *14*, 270–284.
36. Codner, E.; Merino, P.M.; Tena-Sempere, M. Female reproduction and type 1 diabetes: From mechanisms to clinical findings. *Hum. Reprod. Update* **2012**, *18*, 568–585.
37. Yki-Järvinen, H.; Mäkimattila, S.; Utriainen, T.; Rutanen, E.M. Portal insulin concentrations rather than insulin sensitivity regulate serum sex hormone-binding globulin and insulin-like growth factor binding protein 1 in vivo. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 3227–3232.
38. Roldán, B.; Escobar-Morreale, H.F.; Barrio, R.; de La Calle, H.; Alonso, M.; García-Robles, R.; et al. Identification of the source of androgen excess in hyperandrogenic type 1 diabetic patients. *Diabetes Care* **2001**, *24*, 1297–1299.
39. Azziz, R.; Carmina, E.; Dewailly, D.; Diamanti-Kandarakis, E.; Escobar-Morreale, H.F.; Futterweit, W.; et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. *Fertil. Steril.* **2009**, *91*, 456–488.
40. Jamil, Z.; Fatima, S.S.; Ahmed, K.; Malik, R. Anti-Mullerian Hormone: Above and beyond conventional ovarian reserve markers. *Dis. Markers* **2016**, *2016*, 5246217.
41. Abbara, A.; Eng, P.C.; Phylactou, M.; Clarke, S.A.; Hunjan, T.; Roberts, R.; et al. Anti-Müllerian hormone (AMH) in the diagnosis of menstrual disturbance due to polycystic ovarian syndrome. *Front. Endocrinol.* **2019**, *10*, 656.
42. Codner, E.; Iñiguez, G.; Hernández, I.M.; Lopez, P.; Rhumie, H.K.; Villarroel, C.; Rey, R.A. Elevated anti-Müllerian hormone (AMH) and inhibin B levels in prepubertal girls with type 1 diabetes mellitus. *Clin. Endocrinol. (Oxf.)* **2011**, *74*, 73–78.

 doi:10.20944/preprints202509.0319.v1

43. Dewailly, D.; Lujan, M.E.; Carmina, E.; et al. Definition and significance of polycystic ovarian morphology: A task force report. *Hum. Reprod. Update* **2014**, *20*, 334–352.
44. South, S.A.; Asplin, C.M.; Carlsen, E.C.; Booth, R.A., Jr.; Weltman, J.Y.; Johnson, M.L.; et al. Alterations in luteinizing hormone secretory activity in women with insulin-dependent diabetes mellitus and secondary amenorrhea. *J. Clin. Endocrinol. Metab.* **1993**, *76*, 1048–1053.
45. Łebkowska, A.; Adamska, A.; Karczewska-Kupczewska, M.; Nikołajuk, A.; Odziomek, E.; Milewski, R.; et al. Serum anti-Müllerian hormone concentration in women with polycystic ovary syndrome and type 1 diabetes mellitus. *Metabolism* **2016**, *65*, 804–811.
46. Tosi, F.; Bonora, E.; Moghetti, P. Insulin resistance, hyperinsulinemia, and reproductive disorders in women. *J. Clin. Endocrinol. Metab.* **2020**, *105*, e1–e11.
47. Lechan, R.M.; Toni, R. Functional anatomy of the hypothalamus and pituitary. In *Endotext* [Internet]; Feingold, K.R., Anawalt, B., Boyce, A., Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, **2016**.