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Polycystic ovary syndrome and diabetes mellitus type 1 in adult and adolescent females

Zespół policystycznych jajników a cukrzyca typu 1 u dorosłych i nastoletnich kobiet

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Abstract

Introduction. The growing prevalence of type 1 diabetes mellitus (T1DM) and polycystic ovary syndrome (PCOS; the most frequent cause of anovulatory infertility) results in their growing comorbidity. **Objective.** To review the available data on comorbidity of type 1 diabetes mellitus and the polycystic ovary syndrome and their relations, especially in the adolescent group. **Materials and Methods.** The available medical databases have been searched to identify relevant bibliography; then analysis and synthesis of the available data have been conducted. **Results.** At present, the prevalence of comorbid T1DM and PCOS in girls has not been established. **Conclusion.** The available data on T1DM and PCOS comorbidity in adult women suggest the need for early diagnostic investigations to detect their comorbidity and for early therapeutic interventions. Further research to investigate their coprevalence is necessary. In female adolescents, either with or without T1DM, PCOS should be diagnosed not earlier that two years after menarche or when at age of 16 menarche is still absent, with all of the three Rotterdam criteria met. In time between menarche and the end of second year of menstruation high/medium risk of PCOS can be identified. After the fourth year of menstruating, the patient should be treated as an adult. Such approach will eliminate differences in diagnosis resulting from different law definition of adulthood in various countries. In girls with T1DM treatment should be started for any individual component of PCOS to reduce the risk of progression of the syndrome.

Key words

diabetes mellitus type 1, polycystic ovary syndrome, adolescent, female

Streszczenie

Wstęp. Wzrost występowania cukrzycy typu 1 (DM1) i zespołu policystycznych jajników (PCOS), zwykle przyczyny bezowulacyjnej niepłodności, prowadzi do coraz częstszego ich współwystępowania. Celem pracy jest usystematyzowanie wiedzy na temat współwystępowania cukrzycy typu 1 oraz zespołu policystycznych jajników i ich wzajemnego na siebie wpływu, szczególnie w grupie nastolatek. **Materiał i metody.** Przy użyciu dostępnych baz danych medycznych zidentyfikowano piśmiennictwo, przeprowadzając następnie jego analizę i syntezę. **Wnioski.** Obecnie nie jest znana częstość współwystępowania DM1 i PCOS u dziewcząt. Aktualny stan wiedzy na temat współwystępowania DM1 i PCOS u dorosłych kobiet wskazuje na konieczność wczesnej diagnostyki w kierunku ich współistnienia oraz szybkiej interwencji terapeutycznej, konieczne są jednak dalsze badania. Zarówno u dziewcząt z DM1, jak i bez, można rozpoznawać PCOS po upłynięciu 2 lat od menarche lub gdy menarche nie wystąpi do końca 16 roku życia. W obu grupach powinny zostać spełnione wszystkie trzy kryteria rotterdamskie. W okresie od menarche do końca drugiego roku miesiączkowania możliwe jest rozpoznanie średniego/wysokiego ryzyka rozwoju PCOS. Po 4 roku od menarche pacjentkę należy traktować jak dorosłą. Takie podejście zapobiegnie różnicom w diagnozie wynikającym z prawnych definicji dorosłości w różnych krajach. U dziewcząt z DM1 zalecane jest rozpoczęcie leczenia już pojedynczych składowych PCOS celem zmniejszenia ryzyka jego rozwoju.

Słowa kluczowe

cukrzyca typu 1, zespół policystycznych jajników, nastolatka, kobieta

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Introduction

In the age of growing prevalence of diabetes mellitus type 1 (DM1), question about its concomitance with other afflictions of high occurrence rises – especially in context of drugs interactions and disease consequences. The polycystic ovary syndrome (PCOS) is one of the most frequent reasons of anovulation infertility. PCOS affects approximately 10% of adult women [1], and in the population of women with DM1 its frequency is estimated between 18,8% and 40,5% [2]. Diabetes type 1 is the most frequent disease associated with insulin secretion; its rate rises by 3.5% annually, and in the pre-school children even faster [3–5]. A growing prevalence and earlier onset means higher probability of DM1 and PCOS comorbidity, and faster consequences commencement. This article is an attempt to systemize contemporary knowledge about DM1 and PCOS concomitance.

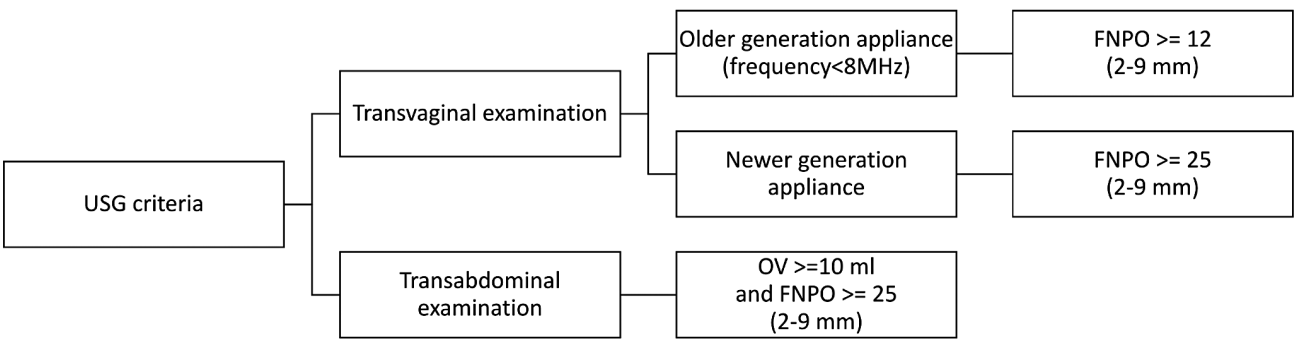
Polycystic ovary syndrome

Polycystic ovary syndrome is a disorder where hyperandrogenism, changes in sex hormones secretion and ovaries leads to specific consequences, like anovulation and insulin resistance.

Diagnostics

Although some controversies have arisen [6], Rotterdam criteria, by which PCOS is diagnosed when occurrence of 2 from 3 traits are found, are still used [6] – oligo/anovulation, clinical or biochemical signs of hyperandrogenemia, morphologically polycystic ovaries, with exclusion of other hyperandrogenemic disorders. Earlier criteria, proposed by NIH (*National Health Institute*), used hyperandrogenism/hyperandrogenemia, oligoovulation and exclusion of other diseases, like Cushing syndrome. Oligoovulation is defined as rare ovulations, predominantly seen as oligomenorrhea, menses occurring 4 to 9 times a year [7, 8]. Clinical signs of hyperandrogenism are strong acne or hirsutism, which is evaluated by modified Ferriman-Gallway scale [9], where 8 or more points means hirsutism in Caucasian population. Biochemical expressions of hyperandrogenism are whole testosterone concentration over 55-58 ng/dl (T) or free testosterone (fT) over 15 ng/dl or sulphate dehydroepiandrosterone (DHEAS) over 248μg/dl, while 17-OH progesterone is under 200ng/dl and FAI (free androgen index) over 4,97% [10]. Polycystic ovaries or the so-called polycystic ovary morphology (PCOM) are diagnosed in ultrasound scan. According to Rotterdam Criteria, ovaries are polycystic when in every ovary at least 11–12 follicles of 2–9 mm diameter are found or when ovaries' volume is bigger than 10 ml [11]. Due to technology advancement and higher ultrasound scan resolution, different sets of criteria depending on the USG head and the way of examination are suggested. In 2013, the experts' panel examined available studies [12]; their conclusions are presented here by a Scheme 1 and in the form of subpoints. The principles of diagnosing the PCOM in ultrasound scan are:

1. When using an appliance of an older generation, with USG head with frequency under 8 MHz, FNPO (follicle number per ovary) parameter is recommended for specifying PCOM. The cut-off value for diagnosing PCOM is 12 or more follicles with 2–9 mm diameter in each ovary.
2. When using an appliance of a newer generation, with USG head even or over 8 MHz, the cut-off value of FNPO meaning PCOM is 25 follicles.
3. When possible, the transvaginal way of proceeding the ultrasound examination is recommended.
4. When using transabdominal way of examination, the OV (ovarian volume) parameter is recommended. The ovary is enlarged if its volume is equal or greater than 10 ml.
5. When using transabdominal way of examination, FNPO is used as additional parameter to confirm the diagnosis.
6. It is recommended to proceed the 2D examination in real time according to a standardized examination protocol, i.e. visualizing an ovary in two dimensions, establishing its size first, and counting follicles with the diameter between



Scheme 1. Diagnostic criteria of the polycystic ovaries morphology (PCOM) depending on examination technique
Abbreviations in scheme 1: FNPO – follicle number per ovary; OV – ovary volume
Schemat 1. *Kryteria diagnostyczne zespołu policystycznych jajników zależne od techniki badania: FNPO ilość pęcherzyków w jajniku, OV objętość jajnika*

2 and 9 millimetres in longitudinal cross-section. The preferred parameter is FNPO, not AFC – all follicle count – sum of FNPO from both ovaries.
7. The 3D techniques are considered to need further assessment.

The risk factors of PCOS development

- Isolated premature (before the 8th year of life) pubarche – almost 50% of those patients have PCOS diagnosed later in life [13].
- Family history of hyperandrogenism or menstrual disorders.
- Family history of PCOS – probably autosomal dominant inheritance [13], although multigene influence (including genes for insulin resistance or obesity) should also be taken into consideration.
- Body mass at birth too small for gestational age – PCOS statistically more frequent [13].
- Fetal exposure to androgens – leading to hyperinsulinism, menstrual disorders, infertility and many more [14].
- Hyperandrogenism – leading to monocytes' activation, rise in their inflammatory response and migration to ovaries and adipose tissue, which may lead to increased androgens synthesis [15].
- Obesity, especially abdominal – increased insulin resistance and risk of hyperinsulinism.
- Hyperinsulinism – body mass growth, leading to rise in insulin resistance.
- Lifestyle.

Natural course of PCOS

The visible PCOS traits depends on patients' age. In adolescents, after menarche, menstrual disorders, body mass growth and hirsutism are most noticeable. In young women the most severe, and therefore most often reported symptom, are problems with conception related to anovulation [16]. In perimenopausal women symptoms connected with menstrual disorders and hyperandrogenism starts to diminish, while the risk of cardiovascular diseases, which was high from the start, rises [11, 13]. During that time also risk of endometrial cancer grows.

PCOS consequences

- As the PCOS is a syndrome, not a disease, its consequences are hard to define and results also from single components found in an individual:
- Hyperandrogenism leads to **insulin resistance,** leading to transitional hyperinsulinemia, causing further ovary dysfunction and excessive gain of **body mass** [17].
- Ovary function disorders lead to **anovulation.**
- **Obesity** increases the risk of **reproductive misfortune** – miscarriages, stillbirths, premature births – similar situation can be observed in women suffering from PCOS and obesity as well as in the general female population with obesity [18]. In sum, with ovulation disorders, which are Syndrome's component, obesity gives higher number of reproductive misfortune than in general population. The exact percentage is still hard to evaluate, as data can be obtained only from patients who used assisted reproduction methods and were under constant gynecological supervision [19].
- Elevated risk of cardiovascular disease.
- Elevated risk of metabolic syndrome.
- Elevated risk of type 2 diabetes [1, 11].
- Elevated risk of endometrial hyperplasia and endometrial cancer [1].
- Elevated risk of metabolic and hormonal profile disorders in both male and female children born from mother with PCOS [20, 21].
- Disordered eating behaviours [22].

Proven connections with other diseases

The frequency of autoimmune thyroiditis in patients with PCOS is 3 times higher than in age matched control groups [23, 24]. By *The Endocrine Society* position, thyroid function disorders should be excluded before diagnosing PCOS. Although not treated disorders or lack of euthyreosis can lead to menstrual disorders [23, 24], thyroid diseases treated properly do not affect fertility. However, it seems prudent to delay making a diagnosis of PCOS till the time when TSH and free thyroxin levels are proper, formerly diagnosed thyroid disease cannot exclude PCOS diagnosis in the future.

PCOS in adolescents

Early diagnosis of PCOS in adolescent girls is problematic, because some symptoms, such as acne or irregular menses, are also typical for puberty. What distinguish the beginning of PCOS from normal adolescence are the time of duration and severity of those symptoms. As an example, the first symptom of PCOS might be very persistent acne, starting during pubarche or just after, and not diminishing through time as well as poorly responding to topical treatment or lack of cycles' normalization 2 years after menarche [25, 26]. The presumption of PCOS is raised by the obesity and overweight beginning during puberty – especially abdominal obesity. In comparison to adult population with PCOS, adolescent girls with that Syndrome are visibly more frequently obese [27–30]. Not only signs of PCOS are suggested to be different, also diagnostic criteria are postulated to be modified, as the clinical features in adolescences are less pronounced. *Carmina et al.* stand that for making a diagnosis of PCOS in adolescents all three Rotterdam criteria: hyperandrogenism, anovulation and PCOM, must be met; this demand is supported by The Endocrine Society [11]. As the term adolescent is subjective and the law defines the term "children" differently depending on the country, it seems proper to condition the diagnosis on the time after menarche. In patients menstruating from two to four years and showing all 3 components of Rotterdam Criteria diagnosis can be made. In those menstruating less than 2 years with all 3 traits, diagnosis of high/medium risk of PCOS can be made. Those menstruating longer than 4 years would be treated as adults, independently from law definition of adulthood. Also in

Witchel et all.' s report – *The Diagnosis of Polycystic Ovarian Syndrome during Adolescence* [26] an emphasis was put on meaning of length of time after menarche and family history of PCOS. At the same time, the investigators respected the concern about overdiagnosing PCOS by suggesting the re-evaluation of diagnosis in later years.

The therapy of PCOS

The target of therapy depends on patient's age, life plans and the most disturbing symptoms of the syndrome. The constant part of therapy are lifestyle modifications, enhancement of physical activity and psychological consultations [8]. At every stage, fight with insulin resistance and obesity is crucial, as the adipose tissue is a place of androgens conversion to active forms [7]. The primary goal of the treatment at childbearing age is preserving fertility and facilitate–conception. In some cases, body mass reduction is the only factor needed to reintroduce regular menses and ovulation. Nonetheless, weight reduction might be more problematic in patients in PCOS than in women without it. When body mass reduction is impossible, clomiphene stimulation of ovulation is employed; there are reports of beneficial influence of metformin for inducing ovulation, both with or without clomiphene [31]. Studies on metformin use during pregnancy, complicated by PCOS or gestational diabetes [32], shows benefits both for children and mothers. That may lead to creating a new group in PCOS treatment schemes – gravid women with PCOS. In women not planning pregnancy, the therapy is concentrated on the reduction or preservation of body mass, diminishing metabolic disturbance and hirsutism, and regulating menstrual cycles. When the main discomfort are menstrual disorders, combined oral contraceptive pills (COCP) are used – those with antiandrogenic progestogens in combination with ethynyloestradiol are the most recommended. Antiandrogenic drugs used in hirsutism treatment must be prescribed with effective contraceptive methods. The therapy of adolescents should be started with non-pharmacological methods – diet, exercises and psychological counselling. The second line of therapy are drugs; as in adult group, drugs are selected depending on most visible traits of the Syndrome. COCP are being used, especially those with drospirenone – spironolactone derivative, to reduce hirsutism. Although used "off-label", metformin is also widely used to increasing insulin sensitivity and ease body mass reduction, and, by that, diminish hirsutism [8].

Type 1 diabetes mellitus

The essence of type 1 diabetes mellitus is the insulin deficiency in the course of autoimmune destruction of pancreatic islet beta cells. If not treated, arising metabolic disorders lead to patients' death shortly after clinical manifestation of the disease.

Type 1 diabetes mellitus diagnosis

Suspicion of DM1 is typically raised when characteristic symptoms are acknowledged – polydipsia, polyuria and nycturia, and the diagnosis is made by fulfilling WHO criteria, modified locally by national diabetes associations. Criteria of diabetes diagnosis [33] by Polish Diabetes Association are:

1. Hyperglycemia's symptoms and random blood glucose level ≥ 200 mg/dl (≥ 11,1 mmol/l);
2. Fasting glucose level ≥ 126 mg/dl (≥ 7,0 mmol/l)
3. Two hours blood glucose level ≥ 200 mg/dl (≥ 11,1 mmol/l) during oral glucose tolerance test.

The risk factors of DM1 development

- **Genetic**: HLA type II, especially *DR3*/*DR4* and *DQ2*/*DQ8* [34,35] Genes are responsible for susceptibility for starting an autoimmune reaction leading to the DM1 development, but it does not mean that every person with such a haplotype will develop the disease. Almost 90% of children with DM1 have haplotype from risk group, but

Table I. Differences in clinical and biochemical symptoms between the polycystic ovary syndrom alone and in comorbidity with diabetes mellitus type 1
Tabela 1. *Różnice w objawach klinicznych i biochemicznych pomiędzy samodzielnie występującym zespołem policystycznych jajników a współistniejącym z cukrzycą typu 1*

	PCOS	PCOS + DM1
Decrease in SHBG production	+	–
Hirsutism symptoms – visibility	↑	↓
DHEAS concentration	↓	↑
Androstendione concentration	↓	↑
Clinical androgenism	frequent	rare
Free testosterone concentration	↑	↓

SHBG – sex hormones binding globulin, DHEAS – dehydroepiandrosterone

from the general population only 5% of people with such a haplotype, will develop diabetes type 1 [34].
- **Family history of**: diabetes type 1, celiac disease, autoimmune thyroiditis and other autoimmune diseases.
- **Degree of kinship** with a person with diagnosed DM1 [35],
- **Sex of parent with DM1**: children from diabetic fathers have higher risk of developing DM1 themselves – 7% risk from father's to 2-3% from mother's side.
- **Viral infections**: enteroviruses, Coxsackie type B viruses, rubella virus, Cytomegalovirus (CMV), Parvoviruses, Rotaviruses [35, 36].

***Therapy of Diabetes mellitus type 1* [33]**

The main aim of the therapy is the artificial reintroduction of the physiological rdythm of insulin secretion and maintaining blood glucose in physiological ranges that is between 80 and 140 mg/dl in venous blood. The intensive insulinotherapy method is recommended, with multiple daily injections (MDI) with pen or continuous subcutaneous insulin infusion (SII) with personal insulin pump, synchronized with the continuous glucose monitoring system if possible. The selection of insulin administration method depends on patients' and their parents' preferences and skills. The proper dose of insulin can be appointed if the mechanisms of glycemia regulations are understood. It is acquired by educating both patients and their parents. Studies are being conducted on new insulins' contrivance, long-acting and short-acting alike.

New methods of therapy, intentioned to prevent or slow down the development of DM1, like transplant of isolated beta cells from Langerhans islets [37] and T regulatory cell-base therapy [38] are also tested.

Diabetes Mellitus type 1 in adolescents

The main difference between adult and pediatric patients with type 1 diabetes is a changing insulin demand, emerging from growing in height and body mass. Adolescence is the phase needing deliberate attention, as physiological insulin resistance influences a daily rhythm of insulin boluses [39], adding to overall hormonal, physiological and psychological changes of that time.

Impact of polycystic ovary syndrome on diabetes mellitus type 1 and differences between isolated PCOS and its comorbidity with DM1

Primary difference between PCOS itself, and PCOS and DM1 combined, is the necessity of administrating exogenous insulin in the second case. Insulin resistance connected with PCOS [17] leads to temporary hyperinsulinemias in patients without DM1, which initiate decreasing SHBG (sex hormone binding globulin) concentration, and, consequently, to increasing of free testosterone [7, 13]. In diabetes, temporary hyperinsulinemias, connected with boluses, also occur, but because of subcutaneous way of dispensing, some insulin omits liver and there is no such decrease in SHBG production. As a result, signs of hirsutism and testosterone-dependent acne are less visible in patients with DM1 and PCOS than in patients with PCOS only, as the pool of free testosterone, dependent on SHBG, might not be changed. It seems that the best way to evaluate hyperandrogenism in patients with DM1 is the measurement of bioactive testosterone (BAT), calculated from testosterone and SHBG [40]. In case of PCOS and DM1 coexistence, insulin resistance leads to increasing insulin requirement [19]. Through its way of action on ovarian insulin receptors, insulin influences steroidogenesis and leads to the changing of LH to FSH ratio [2] and the elevation of androgens production, DHEAS included. DHEAS serum concentration is higher in patients with DM1 and PCOS, than in patients with PCOS only. In Table I theoretical model of differences between PCOS and PCOS coexisting with DM1 is presented. Patients with diabetes type 1 diagnosed in prepubertal age should, theoretically, show symptoms of PCOS earlier because of insulin stimulating effect on ovaries. So far, no sufficient evidence has been produced, yet in some studies connection between diagnosing DM1 before menarche and higher PCOS frequency in later life is postulated [41].

Polycystic ovary syndrome and diabetes mellitus type 1 in adolescents

The coexistence of type 1 diabetes and PCOS in adolescents is still a subject that needs further investigations. In one of the few articles about hyperandrogenism and PCOS in DM1 *Zachurzok et al*. discuss the impact of intensive insulinotherapy method on androgens and gonadotropins concentrations in adolescent girls with DM1 in comparison to the control group. The 19.2% frequency of PCOS in girls with DM1 (using The Androgen Excess and PCOS Society criteria) is similar to frequency in adult women, founded by *Codner et all* [2]. The criteria of inclusion to the study were–minimum 1 year after diagnosing type 1 diabetes and minimum one year after menarche. As in adult women with DM1 and PCOS group, the number of patients with hirsutism that obtained 8 or more points in Ferriman-Gallway scale was low – only 3 out of 9 girls with PCOS and DM1 manifested clinical hyperandrogenism [10]. In lately published article by *Codner et al*. [42], the effect of leuprolide acetate stimulation on sex hormones in healthy adolescent girls and adolescent girls with type 1 diabetes was compared. The conclusion of the study is that there is a possible connection between DM1 existing throughout puberty and onset of PCOS later. Taking into consideration a higher ratio of PCOS in adult women with DM1 than in healthy adult women, studies featuring comorbidity of PCOS and DM1 in adolescent population are vital. They will not only allow to broaden the knowledge on subject, but also to alter the therapy of PCOS and prepare a screening algorithm for PCOS in adult and adolescent females with DM1.

PCOS therapy in DM1 – modifications in standard therapy

For the most part, available literature does not recommend modifying the PCOS therapy in case of its coexistence with DM1.

The basics of the PCOS therapy, that is lifestyle modifications and body mass regulation, are also important part of the DM1 therapy. An additional emphasis should be put on proper metabolic control of DM1, so the doses of insulin are lowered to diminish its impact on ovarian steroidogenesis. The metformin therapy for overcoming insulin resistance and reducing insulin demand, although used "off label" in adolescents, should be considered. Another option, after deliberating possible risks and advantages, are combined oral contraceptive pills [43]. Both groups, adults and adolescents alike, need psychological supervising. The fact of diagnosing a long-term disease alone is a risk factor of developing depression, and both PCOS and DM1 elevate the risk of eating disorders [22, 44].

Conclusions

When taking into consideration the rising frequency of DM1 and PCOS (as well as diseases occurring often with both, i.e. Hashimoto disease), it becomes inevitable to consider possible connections and interactions between them. Both significantly influence patients' daily life, and its distant consequences deteriorate the length and quality of life. In case of their coexistence, symptoms and consequences of PCOS might be hidden under DM1 symptoms. Problems with keeping glucose levels under control might be seen improper self-control of diabetic patients, not a result of hormonal disturbances leading to higher insulin resistance. In consequence, patient's self-monitoring motivation and self-esteem are lowered, and metabolic control of diabetes deteriorates. Similarly, overweight and insulin resistance coming from PCOS will negatively affect attempts of body mass reduction. Orientating diagnostics for the fastest possible identification of PCOS symptoms allows to start the treatment quickly and to minimalize distant consequences of both diseases [1]. Although a precise incidence of the comorbidity of PCOS and DM1 in children and adolescents is unknown, looking for and treating signs of PCOS in girls with DM1 seems to be validated. On the other hand, caution in diagnosing is needed as the diagnosis of PCOS stays with patient for her lifetime. The goal of treating female patients with type 1 diabetes is to avoid the evolution of simple symptoms to PCOS. Especially in females with DM1 *The Amsterdam ESHRE/ASRM – Sponsored 3rd PCOS Consensus Workshop Group* rules must be followed – to start therapy in adolescent girls when even one symptom from PCOS criteria is fulfilled.

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