T2D Risk in Women with Polycystic Ovary Syndrome

Subjects: Medicine, General & Internal

Contributor: Sarantis Livadas , Rodis Paparodis , Panagiotis Anagnostis , Alessandra Gambineri , Jelica Bjekić-Macut , Tijana Petrović , Bulent O. Yildiz , Dragan Micić , George Mastorakos , Djuro Macut

Women with polycystic ovary syndrome (PCOS) are at increased risk for dysglycemia and type 2 diabetes compared to healthy BMI-matched women of reproductive age.

PCOS diabetes mellitus insulin resistance androgens age

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 6–15% of women of reproductive age depending on ethnic variability as well as the criteria used for diagnosis [1]. PCOS presents with a very wide spectrum of clinical features due to its unusually complex pathophysiology. It is a disorder characterized by the intricate interplay between a multitude of factors, incorporating genetic, epigenetic, and environmental stimuli. All these parameters lead to two major etiopathological factors which are believed to lie at the heart of the disorder, namely, androgen excess and insulin resistance (IR) [2].

PCOS is associated with a large number of reproductive and metabolic sequelae, with impaired glucose homeostasis constituting one of the cardinal metabolic features. Indeed, the two prerequisites for type 2 diabetes mellitus (T2DM) development, IR and β-cell dysfunction, are commonly observed in women suffering from PCOS. IR is in fact a fundamental player in PCOS pathophysiology and is further amplified by the presence of obesity [3], while a higher prevalence of pancreatic β-cell dysfunction, associated with increasing age, is observed in women with PCOS compared to their normal peers [4].

Dysglycemia, on the other hand, is thought to occur mainly in older women with PCOS, while there are several as yet largely unclarified issues in younger women suffering from the syndrome [5]. Of note, the incidence of impaired glucose homeostasis as well as the ideal methods for evaluation and management of the disorder in this specific population have also not to date been fully elucidated. It must be mentioned that in this particular age group, androgens are considerably higher than those in women with PCOS older than 35 years of age: as a consequence, amplification of IR is anticipated, which may moreover lead to T2DM development [6].

2. Pathophysiology of T2DM Development in PCOS

Ovarian androgens are found in higher concentrations in the majority of women with PCOS compared to the general population, a small but significant proportion of these being derived from the adrenal glands [7]. Based on current research, although the exact etiological origins of hyperandrogenemia are not entirely clear, prenatal (in utero) exposure to higher androgen concentrations have been tentatively linked to the syndrome [8]. In addition, higher amplitude of the pulsatile secretion of the gonadotrophin-releasing hormone (GnRH) is seen during puberty in girls affected by PCOS, leading to a more potent excitation of the androgen-producing ovarian cells. This leads to hyperandrogenic symptoms, such as hirsutism, acne, male type hair loss, and ovulatory dysfunction (chronic oligo-anovulation), which produces menstrual irregularity (most commonly oligomenorrhea, i.e., <8 menstrual cycles per year) as well as polycystic ovarian morphology on ultrasound examination, which could lead to infertility in some cases [9].

Even though hyperandrogenemia is the main clinical finding of PCOS in the reproductive years, the metabolic features of the syndrome are equally important. A significant number of teenagers affected by PCOS present with IR, which is in part mediated by genetic predisposition [10]. The disorder is frequently accompanied by pancreatic β-cell dysfunction, hepatic and visceral fat accumulation, increased food intake, and increased waist circumference (central obesity). This, in turn, leads to hyperinsulinemia, which arises due to the inability of the pancreatic islets to enable insulin to exert its actions adequately. The latter is mediated in part by pronounced adipose tissue dysfunction and lipotoxicity frequently found in women with PCOS [11]. Due to this, laboratory findings of this condition could include impaired fasting glucose (IFG), postprandial hyperglycemic excursions (impaired glucose tolerance, IGT), elevations in LDL-cholesterol and triglycerides, lowering of HDL cholesterol, and increased adiponectin and serum markers of inflammation. The sum total of these metabolic derangements can result in the development of T2DM when pancreatic stress reaches a threshold at which insulin production becomes unable to match insulin needs.

IR is an almost universal feature of PCOS, it being found with great frequency, ranging between 44 and 70%, in affected patients [12]. While this finding is more common in obese women with PCOS, it is also often present in their lean counterparts [13]. In adolescents with PCOS, peripheral insulin sensitivity was 50% lower than that found in controls, independent of their body mass index, when measured via hyperinsulinemic euglycemic clamp techniques [14]. IR and β-cell dysfunction are the two prerequisites for development of T2DM both in women with PCOS and in those without the syndrome. The most important trigger of the latter metabolic alteration, however, is obesity.

Nevertheless, there is an enduring argument whether PCOS itself constitutes a risk factor for T2DM or whether T2DM predominantly ensues due to obesity in PCOS [15][16]. A well-designed meta-analysis of genetic studies proposed that PCOS does not possess an inherent risk for T2DM and that, instead, T2DM develops due to elevated androgen levels or as a result of adiposity [17].

Dysglycemia, which is an imbalance in the body's ability to maintain blood sugar levels, is one of the most characteristic metabolic abnormalities in PCOS and should be considered as a continuum, progressing from normoglycemia to impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) and overt T2DM. However, it should be noted that IFG is mostly detected in subjects with mostly hepatic IR and normal muscle insulin sensitivity. On the contrary, severe muscle IR accompanied with normal liver insulin sensitivity is found in those subjects with isolated IGT [18]. This observation is of major importance given that IR in women with PCOS is amplified by androgens and vice versa. Indeed, progression of T2DM is significantly higher in hyperandrogenic women with PCOS [19].

3. Prevalence and Methods of Assessment of Dysglycemia in Women with PCOS

In general, the prevalence of dysglycemia, including T2D, IGT, and IFG, is higher in women with PCOS compared to healthy BMI-matched women of reproductive age: namely, in PCOS it ranges from 1.5 to 12.4%, while in normal women of reproductive age, it is 1–3% [20]. With regard to young women with PCOS, the prevalence of these conditions ranges from 2–14.5% for IFG, from 5.9 to 34% for IGT, and from 1.5–10% for IFG, as illustrated in **Table 1**. However, the above numbers are extrapolated from the literature data, since the vast majority of available studies provide no strict classification according to age. In addition, there is significant variability among the available data due to the different definitions applied for IFG status (the American Diabetes Association (ADA) or the World Health Organization (WHO) criteria) and the PCOS criteria used. The reality is that a higher degree of dysglycemia is expected in women diagnosed with the more strict NIH criteria compared to the mild phenotype D of the Rotterdam criteria (namely, the coexistence of ovulatory dysfunction and polycystic ovaries on ultrasound) due to the lower grade of IR demonstrated in this subgroup [21]. However, this hypothesis was not corroborated in a large study analyzing data of 2000 women wherein a similar T2DM prevalence was documented among different PCOS phenotypes [22]. The considerable heterogeneity observed could, furthermore, be partly due to the wide range of different countries and races discussed in the studies

Table 1. Prevalence of dysglycemia in young women with PCOS.

Group	Year	*n*	Country	PCOS Criteria	T2DM Criteria	Age (Years)	BMI (kg/m^2)	IFG (%)	IGT (%)	T2DM (%)
Rajkhowa et al. [23]	1996	90	UK	N	W	26	31	?	9	2
Legro et al. [24]	1999	254	USA	N	W	14–44	32 ± 3	?	31	7.5
Ehrmann et al. [25]	1999	122	USA	N	A	25 ± 0.7	30–43	9	35	10
Gambineri et al. [26]	2004	121	Italy	R	W	14–37	20–38	?	15.7	2.5
Chen et al. [27]	2006	102	China	R	W	24.2 ± 6	21.7 ± 4	?	20.5	1.9
Mohlig et al. [28]	2006	264	Germany	N	W	28 ± 0.4	30 ± 0.4	?	14.3	1.5
Vrbikova et al. [29]	2007	244	Czech	R	A	27 ± 7.5	27 ± 6.9	12.3	9.4	1.6
Espinos-Gomez al. [30]	2008	102	Spain	N	W	26 ± 6	30.2 ± 8	?	10.7	7.7
Bhattacharya et al. [31]	2009	264	India	R	W	24 ± 4	27 ± 4.5	?	14.4	
Zhao et al. [32]	2010	818	China	R	A	25 ± 5	?	8.5	35.4	4

Group	Year	*n*	Country	PCOS Criteria	T2DM Criteria	Age (Years)	BMI (kg/m^2)	IFG (%)	IGT (%)	T2DM (%)
Stovall et al. [33]	2011	78	USA	N	A	26 ± 6.4	29 ± 6	2	14	?
Celik et al. [34]	2013	252	Turkey	R	A	24 ± 5	26 ± 5.7	?	14.3	2
Lerchbaum et al. [35]	2014	714	Austria	R	A	27 (23–32)	24.2	12.8		1.5
Ganie et al. [36]	2015	2014	India	R	A	23 ± 5.4	25 ± 4.4	14.5	5.9	6.3
Li et al. [37]	2016	2436	China	R	A	27	21.56	13.5	19.8	3.9
Pelanis et al. [38]	2017	876	Sweden	R	A	29 (25–34)	28 (23–33)	11	12	3
Zhang et al. [22]	2018	378	China	R	IDF	27 ± 4.4	30 ± 4.3	31.5		8.7
Ortiz-Flores et al. [39]	2019	400	Spain	R	W	26 (14–49)	28.6	14	14.5	2.5
Choi et al. [40]	2021	262	Korea	R	A	23 ± 5.7	22.7 ± 4.2	19.5%		1.6%

N: NIH, R: Rotterdam, W: WHO, A: ADA. "?" means lack of data.

On the other hand, despite being more complicated, costly, and time consuming than other available methods, OGTT is considered the gold standard for T2DM diagnosis because it is standardized and can detect IGT, which is important for women with PCOS. Early detection of IGT in this at-risk population can lead to lifestyle modifications and/or pharmacological intervention that may prevent or delay the development of T2DM [49].

Nationally, both the ADA and the WHO are in agreement as regards the glucose level cut-off for the diagnosis of IGT [42][43]. There is a significant amount of evidence that an isolated FPG could categorize a noteworthy number of subjects with either IGT or T2DM as having normal glucose homeostasis. This misclassification rate ranges from 20–40%, which is not negligible given the increased risk for T2DM in women with PCOS from their early reproductive years [28][44][45].

4. Baseline Screening in Young Women with PCOS

The question of whether glycemic status should be evaluated in every woman with PCOS or only in certain subgroups remains thus far unanswered. Two points of view exist regarding who should be screened via the OGTT (**Table 2**). One view, supported by the Endocrine Society, the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS), and Australian guidelines, suggests "universal screening for all women with PCOS" [46][47][48]. The other view favored by the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine recommends screening for women with a minimum of one risk factor, such as age over 40 years, a family history of type 2 diabetes or gestational diabetes mellitus, or obesity [49][50][51].

Table 2. Guidelines regarding OGTT upon diagnosis in all women with PCOS.

Body	Suggestion
Joint AACE/ACE and AE-PCOS society	Yes
Australian NHMRC	No (Recommended if: BMI > 25 kg/m^2—iAsians > 23 kg/m^2, history IFG, IGT, GDM, family history of T2DM, hypertension or high-risk ethnicity)
Endocrine Society	Yes
Royal College of Obstetricians & Gynecology	No (Recommended if one or more: BMI ≥ 25 kg/m^2, age ≥ 40 years, previous gestational diabetes or family history of T2DM)
AE-PCOS Society	No
ESHRE and ASRM	No (Recommended if BMI ≥ 27 kg/m^2)

References

1. Conway, G.; Dewailly, D.; Diamanti-Kandarakis, E.; Escobar-Morreale, H.F.; Franks, S.; Gambineri, A.; Kelestimur, F.; Macut, D.; Micic, D.; Pasquali, R.; et al. The Polycystic Ovary Syndrome: A Position Statement from the European Society of Endocrinology. Eur. J. Endocrinol. 2014, 171, P1–P29.
2. Azziz, R.; Carmina, E.; Chen, Z.; Dunaif, A.; Laven, J.S.E.; Legro, R.S.; Lizneva, D.; Natterson-Horowitz, B.; Teede, H.J.; Yildiz, B.O. Polycystic Ovary Syndrome. Nat. Rev. Dis. Primers 2016, 2, 16057.
3. Barber, T.M.; Franks, S. Obesity and Polycystic Ovary Syndrome. Clin. Endocrinol. 2021, 95, 531–541.
4. Dunaif, A.; Segal, K.R.; Futterweit, W.; Dobrjansky, A. Profound Peripheral Insulin Resistance, Independent of Obesity, in Polycystic Ovary Syndrome. Diabetes 1989, 38, 1165–1174.
5. Dunaif, A.; Segal, K.R.; Shelley, D.R.; Green, G.; Dobrjansky, A.; Licholai, T. Evidence for Distinctive and Intrinsic Defects in Insulin Action in Polycystic Ovary Syndrome. Diabetes 1992, 41, 1257–1266.
6. Dunaif, A.; Graf, M.; Mandeli, J.; Laumas, V.; Dobrjansky, A. Characterization of Groups of Hyperandrogenic Women with Acanthosis Nigricans, Impaired Glucose Intolerance, and Hyperinsulinemia. J. Clin. Endocrinol. Metab. 1987, 65, 499–507.
7. Dunaif, A.; Finegood, D.T. Beta-Cell Dysfunction Independent of Obesity and Glucose Intolerance in the Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 1996, 81, 942–947.
8. Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on Women's Health Aspects of Polycystic Ovary Syndrome (PCOS). Hum. Reprod. 2012, 27, 14–24.
9. Gleicher, N.; Darmon, S.; Patrizio, P.; Barad, D.H. Reconsidering the Polycystic Ovary Syndrome (PCOS). Biomedicines 2022, 10, 1505.
10. Rosenfield, R.L.; Ehrmann, D.A. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr. Rev. 2016, 37, 467–520.
11. Abbott, D.H.; Kraynak, M.; Dumesic, D.A.; Levine, J.E. In Utero Androgen Excess: A Developmental Commonality Preceding Polycystic Ovary Syndrome? Front. Horm. Res. 2019, 53, 1–17.
12. [illegible]. J. Clin.
13. [illegible] with [illegible] Score
14. [illegible] olycystic
15. [illegible] ed: An
16. [illegible] aemic Clamp Studies. Hum. Reprod. 2016, 31, 2619–2631.
17. Lewy, V.D.; Danadian, K.; Witchel, S.F.; Arslanian, S. Early Metabolic Abnormalities in Adolescent Girls with Polycystic Ovarian Syndrome. J. Pediatr. 2001, 138, 38–44.

5. Evolution to T2DM and Frequency of Glycemic Status Assessment

The progress from normal glucose levels to IGT or from IGT to T2DM in women with PCOS has been calculated to be lower than that in the general population. In fact, in individuals with IGT among the general population, the conversion rate to T2DM is estimated at 7% annually [52], which is significantly higher than the analogous annual progression rate from 2.5 to 3.6% observed in PCOS [53][54][55]. Therefore, the Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke Diabetes 2021, 70, 627–637 are different from those found in the general population. Note, non-linear progression to T2DM is common in PCOS, related to BMI [19]. Obese women exhibit a four-fold greater risk of developing IGT, while lean women with PCOS have the same probability to develop T2DM as controls.

Hence, the frequency of glycemic status assessment in PCOS women is a topic of debate among experts, with recommendations ranging from yearly to every 5 years, depending on additional factors (Table 3).

Table 3. Guidelines regarding follow-up OGTT.

Body	Suggestion
Joint AACE/ACE and AE-PCOS society	Yearly in women with IGT Every 1–2 years, based on BMI (not specified) and family history of T2DM
Australian NHMRC	Every 1–3 years, based on presence of other diabetes risk factors
Endocrine Society	Every 3–5 years. Sooner if additional risk factors for T2D
Royal College of Obstetricians & Gynecology	Annually in women with IGT or IFG
AE-PCOS Society	Every 2 years in women with risk factors Sooner if additional risk factors for T2D develop
ESHRE and ASRM	Not specified

6. Strategies to Minimize Diabetes Risk in Young Women with PCOS

There are different clinical possibilities for the general reduction of metabolic risk, while diabetes risk may be minimized using diagnostic tools as well. Whereas in overt T2DM, fasting glucose could represent an initial risk marker for IGT and T2DM, this notion is questioned in the case of women with PCOS. Recent analyses of a large European cohort of PCOS women reported that one-third of those with IGT or T2DM had normal basal glucose [56].

In current clinical practice, women with PCOS are often informed as to the possibility of their developing diabetes during the course of their life, while patients with PCOS, especially those of older age, are aware of and concerned about future metabolic derangements and, specifically, T2DM development [57].

Alpha-lipoic acid (ALA) is a natural compound of therapeutic use for the amelioration of IR. ALA has been shown to be more effective in the prevention of glucose metabolism alterations rather than in their treatment.

Vitamin D (VD) deficiency has been shown to be associated with many signs present in PCOS, including adiposity, inflammation, insulin resistance, and diabetes [58]. Therapeutically, VD supplementation as an add-on therapy can lead to an improvement in IR and lipid metabolism, a reduction in circulating androgens, as well as a better response to ovulation induction in PCOS women [58].

The potential for the use of genetic data in personalized medicine in PCOS patients has recently been suggested. In addition, overweight and obese PCOS women with hyperandrogenemia may benefit considerably from a diabetes prevention program. On the other hand, normal-weight PCOS women with normal androgen concentrations do not need to be stressed by being classified as a risk group for diabetes since no association has been found between genetically predicted PCOS and risk of diabetes. Therefore, normal-weight PCOS women should be counseled to avoid weight gain which could convey this risk [17].

In conclusion, given that PCOS is associated with an increased risk of dysglycemia and T2DM, screening for these conditions is recommended in young women with the syndrome. However, there is still uncertainty regarding the optimal screening strategy as well as the exact mechanisms underlying progression of dysglycemia in PCOS. Diagnosis and follow-up should be based on the OGTT, while weight management, regular exercise, and a well-balanced diet should be emphasized among all patients. Further research is needed to better understand these issues and to develop evidence-based guidelines for the management of glycemic abnormalities in young women with PCOS.

15. Spritzer, P.M.; Lecke, S.B.; Satler, F.; Morsch, D.M. Adipose Tissue Dysfunction, Adipokines, and Low-Grade Chronic Inflammation in Polycystic Ovary Syndrome. Reproduction 2015, 149, R219–R227.
16. Gambineri, A.; Patton, L.; Altieri, P.; Pagotto, U.; Pizzi, C.; Manzoli, L.; Pasquali, R. Polycystic Ovary Syndrome Is a Risk Factor for Type 2 Diabetes. Diabetes 2012, 61, 2369–2374.
17. Zhu, T.; Cui, S.; Goodarzi, M.O. Polycystic Ovary Syndrome and Risk of Type 2 Diabetes, Coronary Heart Disease, and Stroke. Diabetes 2021, 70, 627–637.
18. Abdul-Ghani, M.A.; Tripathy, D.; DeFronzo, R.A. Contributions of β-Cell Dysfunction and Insulin Resistance to the Pathogenesis of Impaired Glucose Tolerance and Impaired Fasting Glucose. Diabetes Care 2006, 29, 1130–1139.
19. Persson, S.; Elenis, E.; Turkmen, S.; Yesildaglar, N.; Sahlin, L.; Stener-Victorin, E. Fasting Glucose and Insulin Concentrations during Oral Glucose Tolerance Test as Predictive Markers for Risk of Type 2 Diabetes in Women with Hyperandrogenic Polycystic Ovary Syndrome. Fertil. Steril. 2021, 116, 862–871.
20. Lazaridou, S.; Dinas, K.; Tziomalos, K. Prevalence, Pathogenesis and Management of Prediabetes and [illegible] 30.
21. [illegible], R. [illegible]us [illegible]20.e2.
22. [illegible]n [illegible]18,
23. [illegible]e in [illegible]
24. Legro, R.S.; Kunselman, A.R.; Dodson, W.C.; Dunaif, A. Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome: A Prospective, Controlled Study in 254 Affected Women. J. Clin. Endocrinol. Metab. 1999, 84, 165–169.
25. Ehrmann, D.A.; Barnes, R.B.; Rosenfield, R.L.; Cavaghan, M.K.; Imperial, J. Prevalence of Impaired Glucose Tolerance and Diabetes in Women with Polycystic Ovary Syndrome. Diabetes Care 1999, 22, 141–146.
26. Gambineri, A.; Pelusi, C.; Manicardi, E.; Vicennati, V.; Cacciari, M.; Morselli-Labate, A.M.; Pagotto, U.; Pasquali, R. Glucose Intolerance in a Large Cohort of Mediterranean Women with Polycystic Ovary Syndrome: Phenotype and Associated Factors. Diabetes 2004, 53, 2353–2358.
27. Chen, X.; Yang, D.; Li, L.; Feng, S.; Wang, L. Abnormal Glucose Tolerance in Chinese Women with Polycystic Ovary Syndrome. Hum. Reprod. 2006, 21, 2027–2032.
28. Möhlig, M.; Flöter, A.; Spranger, J.; Weickert, M.O.; Schill, T.; Schlösser, H.W.; Brabant, G.; Pfeiffer, A.F.H.; Selbig, J.; Schöfl, C. Predicting Impaired Glucose Metabolism in Women with Polycystic Ovary Syndrome by Decision Tree Modelling. Diabetologia 2006, 49, 2572–2579.
29. Vrbikova, J.; Dvorakova, K.; Grimmichova, T.; Hill, M.; Stanicka, S.; Cibula, D.; Bendlova, B.; Starka, L.; Vondra, K. Prevalence of Insulin Resistance and Prediction of Glucose Intolerance and Type 2 Diabetes Mellitus in Women with Polycystic Ovary Syndrome. Clin. Chem. Lab. Med. 2007, 45, 639–644.
30. Espinós-Gómez, J.J.; Corcoy, R.; Calaf, J. Prevalence and Predictors of Abnormal Glucose Metabolism in Mediterranean Women with Polycystic Ovary Syndrome. Gynecol. Endocrinol. 2009, 25, 199–204.
31. Bhattacharya, S.M. Polycystic Ovary Syndrome and Abnormalities in Glucose Tolerance. Int. J. Gynaecol. Obstet. 2009, 105, 29–31.
32. Zhao, X.; Zhong, J.; Mo, Y.; Chen, X.; Yang, D. Association of Biochemical Hyperandrogenism with Type 2 Diabetes and Obesity in Chinese Women with Polycystic Ovary Syndrome. Int. J. Gynaecol. Obstet. 2010, 108, 148–151.
33. Stovall, D.W.; Bailey, A.P.; Pastore, L.M. Assessment of Insulin Resistance and Impaired Glucose Tolerance in Lean Women with Polycystic Ovary Syndrome. J. Women's Health 2011, 20, 37–43.
34. Celik, C.; Abali, R.; Bastu, E.; Tasdemir, N.; Tasdemir, U.; Gul, A. Assessment of Impaired Glucose Tolerance Prevalence with Hemoglobin A1c and Oral Glucose Tolerance Test in 252 Turkish Women with Polycystic Ovary Syndrome: A Prospective, Controlled Study. Hum. Reprod. 2013, 28, 1062–1068.

35. Lerchbaum, E.; Schwetz, V.; Giuliani, A.; Obermayer-Pietsch, B. Influence of a Positive Family History of Both Type 2 Diabetes and PCOS on Metabolic and Endocrine Parameters in a Large Cohort of PCOS Women. Eur. J. Endocrinol. 2014, 170, 727–739.
36. Ganie, M.A.; Dhingra, A.; Nisar, S.; Sreenivas, V.; Shah, Z.A.; Rashid, A.; Masoodi, S.; Gupta, N. Oral Glucose Tolerance Test Significantly Impacts the Prevalence of Abnormal Glucose Tolerance among Indian Women with Polycystic Ovary Syndrome: Lessons from a Large Database of Two Tertiary Care Centers on the Indian Subcontinent. Fertil. Steril. 2016, 105, 194–201.e3.
37. Li, H.; Li, L.; Gu, J.; Li, Y.; Chen, X.; Yang, D. Should All Women with Polycystic Ovary Syndrome Be Screened for Metabolic Parameters?: A Hospital-Based Observational Study. PLoS ONE 2016, 11, e0167036.
38. Pelanis, R.; Mellembakken, J.R.; Sundström-Poromaa, I.; Ravn, P.; Morin-Papunen, L.; Tapanainen, J.S.; Piltonen, T.; Puurunen, J.; Hirschberg, A.L.; Fedorcsak, P.; et al. The Prevalence of Type 2 Diabetes Is Not Increased in Normal-Weight Women with PCOS. Hum. Reprod. 2017, 32, 2279–2286.
39. Ortiz-Flores, A.E.; Luque-Ramírez, M.; Fernández-Durán, E.; Alvarez-Blasco, F.; Escobar-Morreale, H.F. Diagnosis of Disorders of Glucose Tolerance in Women with Polycystic Ovary Syndrome (PCOS) at a Tertiary Care Center: Fasting Plasma Glucose or Oral Glucose Tolerance Test? Metabolism 2019, 93, 86–92.
40. Choi, Y.M.; Hwang, K.R.; Oh, S.H.; Lee, D.; Chae, S.J.; Yoon, S.H.; Kim, J.J. Progression to Prediabetes or Diabetes in Young Korean Women with Polycystic Ovary Syndrome: A Longitudinal Observational Study. Clin. Endocrinol. 2021, 94, 837–844.
41. Gillies, C.L.; Abrams, K.R.; Lambert, P.C.; Cooper, N.J.; Sutton, A.J.; Hsu, R.T.; Khunti, K. Pharmacological and Lifestyle Interventions to Prevent or Delay Type 2 Diabetes in People with Impaired Glucose Tolerance: Systematic Review and Meta-Analysis. BMJ 2007, 334, 299.
42. World Health Organization. International Diabetes Federation Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation; World Health Organization: Geneva, Switzerland, 2006; ISBN 978-92-4-159493-6.
43. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021, 44, S15–S33.
44. Vrbikova, J.; Hill, M.; Fanta, M. The Utility of Fasting Plasma Glucose to Identify Impaired Glucose Metabolism in Women with Polycystic Ovary Syndrome. Gynecol. Endocrinol. 2014, 30, 664–666.
45. Veltman-Verhulst, S.M.; Goverde, A.J.; van Haeften, T.W.; Fauser, B.C.J.M. Fasting Glucose Measurement as a Potential First Step Screening for Glucose Metabolism Abnormalities in Women with Anovulatory Polycystic Ovary Syndrome. Hum. Reprod. 2013, 28, 2228–2234.
46. Legro, R.S.; Arslanian, S.A.; Ehrmann, D.A.; Hoeger, K.M.; Murad, M.H.; Pasquali, R.; Welt, C.K. Endocrine Society Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. 2013, 98, 4565–4592.
47. Goodman, N.F.; Cobin, R.H.; Futterweit, W.; Glueck, J.S.; Legro, R.S.; Carmina, E. American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); Androgen Excess and PCOS Society American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and Pcos Society Disease State Clinical Review: Guide to the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome-Part 2. Endocr. Pr. 2015, 21, 1415–1426.
48. Jean Hailes for Women's Health on Behalf of the Pcos Australian Alliance. Evidence-Based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome. 2015. Available online: https://www.google.com/search?sxsrf=ALeKk01a4SY_kUkIOBsnatsG8BkTUXyu6Q%3A1613210561098&ei=waMnYKy9BYqW8gK0gpWAAg&q=jean+hailes+for+women based+guidelines+for+the+assessment+and+management+of+polycystic+ovary+syndrome.+2015%3B+64%E2%80%9365.&oq=&gs_lc wiz (accessed on 13 February 2021).
49. Wild, R.A.; Carmina, E.; Diamanti-Kandarakis, E.; Dokras, A.; Escobar-Morreale, H.F.; Futterweit, W.; Lobo, R.; Norman, R.J.; Talbott, E.; Dumesic, D.A. Assessment of Cardiovascular Risk and Prevention of Cardiovascular Disease in Women with the Polycystic Ovary Syndrome: A Consensus Statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J. Clin. Endocrinol. Metab. 2010, 95, 2038–2049.

50. Polycystic Ovary Syndrome, Long-Term Consequences (Green-Top Guideline No. 33). Available online: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg33/ (accessed on 13 February 2021).
51. 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.
52. Tuomilehto, J.; Lindström, J.; Eriksson, J.G.; Valle, T.T.; Hämäläinen, H.; Ilanne-Parikka, P.; Keinänen-Kiukaanniemi, S.; Laakso, M.; Louheranta, A.; Rastas, M.; et al. Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance. N. Engl. J. Med. 2001, 344, 1343–1350.
53. Norman, R.J.; Masters, L.; Milner, C.R.; Wang, J.X.; Davies, M.J. Relative Risk of Conversion from Normoglycaemia to Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus in Polycystic Ovarian Syndrome. Hum. Reprod. 2001, 16, 1995–1998.
54. Pesant, M.-H.; Baillargeon, J.-P. Clinically Useful Predictors of Conversion to Abnormal Glucose Tolerance in Women with Polycystic Ovary Syndrome. Fertil. Steril. 2011, 95, 210–215.
55. Boudreaux, M.Y.; Talbott, E.O.; Kip, K.E.; Brooks, M.M.; Witchel, S.F. Risk of T2DM and Impaired Fasting Glucose among PCOS Subjects: Results of an 8-Year Follow-Up. Curr. Diab. Rep. 2006, 6, 77–83.
56. Livadas, S.; Bothou, C.; Kuliczkowska-Płaksej, J.; Robeva, R.; Vryonidou, A.; Macut, J.B.; Androulakis, I.; Opalic, M.; Mouslech, Z.; Milewicz, A.; et al. Can Dysglycemia in OGTT Be Predicted by Baseline Parameters in Patients with PCOS? Endocr. Connect. 2022, 11, e210358.
57. Gibson-Helm, M.; Teede, H.; Dunaif, A.; Dokras, A. Delayed Diagnosis and a Lack of Information Associated with Dissatisfaction in Women With Polycystic Ovary Syndrome. J. Clin. Endocrinol. Metab. 2017, 102, 604–612.
58. Yildizhan, R.; Kurdoglu, M.; Adali, E.; Kolusari, A.; Yildizhan, B.; Sahin, H.G.; Kamaci, M. Serum 25-Hydroxyvitamin D Concentrations in Obese and Non-Obese Women with Polycystic Ovary Syndrome. Arch. Gynecol. Obstet. 2009, 280, 559–563.
59. Morgante, G.; Darino, I.; Spanò, A.; Luisi, S.; Luddi, A.; Piomboni, P.; Governini, L.; De Leo, V. PCOS Physiopathology and Vitamin D Deficiency: Biological Insights and Perspectives for Treatment. J. Clin. Med. 2022, 11, 4509.