

Insulin resistance indexes in women with premature ovarian insufficiency — a pilot study

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ABSTRACT

Objectives: Premature ovarian insufficiency (POI) is associated with hypoestrogenism and an increased risk of metabolic disorders. In many clinics, a variety of insulin resistance (IR) tests are used during routine clinical assessments. To date, there is no clear opinion about which of these tests should be applied in women with premature ovarian insufficiency (POI). Therefore, our preliminary aim was to compare the most frequently used insulin resistance indexes in the clinical assessment of a group of POI women and a control group.

Material and methods: Our retrospective study included 98 women with karyotypically normal spontaneous POI aged 18–39 years and a control group of 78 healthy women. Each patient was given an oral glucose tolerance test (OGTT) to evaluate their insulin release and insulin resistance. In addition, each woman's insulin resistance (IR) was evaluated using the homeostasis model assessment for insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI), the fasting glucose-to-insulin ratio (F GIR), and Matsuda and McAuley indexes. The two groups' glucose levels were compared at 0, 60 and 120 min of the OGTT.

Results: At 0 and 60 min of the OGTT, the insulin levels of the POI women were significantly higher than those of the control group. The number of women in whom IR was detected using the various kits was comparable between the two groups.

Conclusions: In conclusion, only the OGTT evaluation revealed a significant difference in insulin concentrations between the two study groups. The indexes most commonly used to detect IR did not detect differences in IR between the POI women and the members of the healthy control group. QUICKI detected significantly more women with IR within both study groups than other tests did.

Key words: premature ovarian insufficiency, insulin resistance

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INTRODUCTION

Premature ovarian insufficiency (POI) is currently defined as the coexistence of menstrual disorders and typical hormonal serum levels. According to the 2015 European Society of Human Reproduction and Embryology (ESHRE) guidelines, a POI diagnosis can be established in patients under 40 years old with oligomenorrhoea/amenorrhoea of at least 4–6 months and folliculotropin (FSH) > 25 IU/L [1]. The prevalence of POI is ~1% of women < 40 years-old, ~0.1% of women < 30 years-old, and ~0.01% of women < 20 years-old [2, 3]. POI, previously described in the literature as premature ovarian failure (POF), is associated with hypoestrogenism

and an increased risk of metabolic disorders [4–6]. POI can have different aetiologies and is found in women with both normal and abnormal karyotypes. Additionally, the disease can be associated with different autoimmunological conditions, such as Hashimoto's disease, Addison's disease, and diabetes [7, 8].

Taking into account that POI is a hypoestrogenic state which can lead to metabolic disorders we wondered if there is a difference in any of the commonly used indices that would distinguish between POI and healthy subjects.

In many clinics, a variety of insulin resistance (IR) tests are used as part of a routine clinical assessment. To date,

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there is no clear opinion which of these tests should be applied in women with POI. Therefore, our preliminary aim was to compare the IR indexes commonly used in assessing both POI women and members of a healthy control group.

MATERIAL AND METHODS

Study population

Our retrospective study was conducted in the Department of Gynecological Endocrinology at the Medical University of Warsaw. Medical records from October 2011 to December 2016 were anonymously reviewed. We obtained approval for our study from the Ethics Committee of the Medical University of Warsaw in Poland (AKBE 52/17). Because new diagnostic criteria for POI were set in 2015, we also included in the study population women who had been previously diagnosed with secondary amenorrhoea (i.e., those with FSH > 25 and < 40 U/L). Additionally, we included women who met the new ESHRE criteria, namely: FSH > 25 IU/L, at least 4 months of oligomenorrhoea, and a normal karyotype.

Our exclusion criteria were as follows: women with a history of iatrogenic ovarian damage, chemotherapy, pelvic surgery, radiotherapy, or metabolic diseases; women previously diagnosed with polycystic ovary syndrome (PCOS); and women who were on hormonal replacement therapy or oral contraceptive pills at least 4 weeks prior to entering the study.

Control group

Subjects in the control group were recruited from healthy women admitted to our outpatient clinic for periodic medical examinations.

These subjects included women who had a regular menstrual cycle (25–35 days) and had not had hormonal treatment in the 4 weeks prior to entering the study. All the women had a gynaecological examination, laboratory tests and transvaginal sonography using a 7.5 MHz vaginal probe, Hitachi Aloca UST 9130 sonograph. Their body mass index (BMI) was calculated as weight (kg) / height (m²) [9].

Assay

The laboratory parameters included follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol (E2), prolactin (PRL), thyrotropin (TSH), free thyroxine (fT4), anti-thyroid peroxidase antibodies (anti-TPO), thyroglobulin-antibodies (anti-TG), total testosterone (T), sex hormone binding globulin (SHBG), androstenedione (A), dehydroepiandrosterone sulphate (DHEAS), and 17-hydroxyprogesterone (17-OHP).

Our laboratory normal reference ranges during the follicular phase were as follows: FSH, 3.03–8.08 mIU/mL; LH, 1.8–11.78 mIU/mL; oestradiol, 21–251 pg/mL; prolactin, 5–35 ng/mL; TSH, 0.35–4.94 μ IU/mL; fT4, 9.01–19.05 pmol/L;

T, 0.1–0.56 ng/mL; SHBG, 19.84–155.2 nmol/L; A, 0.3–3.5 ng/mL; DHEAS, 2.68–9.23 μ mol/L; and 17-OHP, 0.3–1.0 ng/mL. Serum anti-TPO levels greater than 34 IU/mL and anti-TG > 4.11 were considered positive.

Serum FSH, LH, E2, PRL, TSH, fT4, T, and SHBG were measured using an enzyme-linked fluorescent assay (ELFA) (VIDAS, BioMerieux). 17-OHP levels were measured using an enzyme-linked immunosorbent assay (ELISA) (Euroimmun AG Analyzer I). The serum concentration of A was tested using the chemiluminescent immunoassay technique (Immulite 2000XP, Siemens Healthineers). Serum insulin and cortisol were measured using a chemiluminescent microparticle immunoassay (CMIA) (Architect i2000SR, Abbott Diagnostics). Serum anti-TPO and anti-TG levels were measured using an electrochemiluminescence immunoassay (ECLIA) (Elecsys and Cobas e analyzers, Roche).

Serum glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were analysed using an enzymatic colorimetric method (Konelab Prime 30i by Thermo Scientific). The free androgen index (FAI) was calculated as T / SHBG \times 100% [10].

Glucose and insulin concentrations were measured at 0, 60, and 120 min after participants were administered 75 g of glucose as part of an OGTT. Impaired fasting glucose (IFG) was defined as glucose between 100 and 125 mg/dL. An impaired glucose tolerance test (IGT) was defined as a 2 h post-challenge blood glucose level of 140–199 mg/dL. Diabetes was detected when the fasting glucose was \geq 126 mg/dL, random plasma glucose was \geq 200 mg/dL with typical symptoms, or glucose was \geq 200 mg/dL after 2 h of a 75 g OGTT [11]. We applied Ten's study to define hyperinsulinaemia (fasting insulin > 15 IU/mL, > 150 IU/mL after 1 h of OFTT, or > 75 IU/mL after 2 h of an OGTT) [12].

The fasting glucose insulin ratio (FGIR) was obtained by dividing the fasting glucose (mg/dL) by the fasting insulin (mIU/mL), and the cut-off point of the FGIR for IR was accepted as 7.2 [13].

The quantitative insulin sensitivity check index (QUICKI) was calculated using the following formula: $1 / [\log \text{fasting insulin (mIU/mL)} + \log \text{fasting glucose (mg/dL)}]$. IR was defined as a QUICKI value < 0.357 [14].

The Matsuda index was calculated using the following formula: $[10.000 / (\text{mean glucose (0–120)} \times \text{mean insulin (0–120)} \times \text{fasting glucose}/\text{fasting insulin})]$. IR was defined as a Matsuda index value < 7.3 [15].

The homeostasis model for insulin resistance (HOMA-IR) was calculated as follows: $[\text{fasting insulin} \times \text{fasting glucose}/22.5]$. Subjects were considered insulin resistant when the HOMA-IR score was > 2.5 [16].

The McAuley (McA) index was calculated using the following formula: $\exp [2.63 - 0.28 \ln (\text{insulin in mIU/L}) - 0.31 \ln$

(triglycerides in mmol/L)]. IR was considered present when the McA value was ≥ 5.7 [17].

In the POI group, blood samples were collected on the day of admission to the gynaecological department (during the amenorrhoea period). In the control group, blood samples were collected during the early follicular phase of the menstrual cycle (days 3–6). The time elapsed between POI diagnosis and OGTT assessment was between 6 and 36 months.

Statistics

The normality of distributions of continuous variables in the examined groups was analysed using the Shapiro-Wilk test. Because most of the data had a non-normal distribution, data was shown as medians, lower and upper quartiles (Q1–Q3), and minimum and maximum values. Because the groups possess variations in age, they were compared using the regression model adjusted by age for the logarithm of the variables (Tab. 1 and 2). Spearman's correlation

coefficient was used to assess the relationship among the various insulin indexes, lipid parameters and androgens.

Additionally, we categorized participants as insulin resistant or not insulin resistant. Categorical variables are presented as percentages and numbers of subjects. The proportions of IR between the control and POI groups and the proportions of IR within groups were compared using a test for two proportions (Tab. 3).

For all analyses, a p-value of < 0.05 for two-sided tests was accepted as statistically significant. All calculations were performed using IBM SPSS Statistics 24.

RESULTS

A total of 176 women (98 POI and 78 controls) completed the study. The anthropometric characteristics of the POI and control groups are summarized in Table 1. There were no statistically significant differences in serum T, A and DHEAS between the POI and control groups. Compared with the control group, the POI group had significantly lower

Table 1. The anthropometric characteristics and hormones in women with POI and in the control group

	POI (N=98)			Control group (N = 78)			p value
	Mean \pm SD	Range	Median (Q1–Q3)	Mean \pm SD	Range	Median (Q1–Q3)	
FSH (mIU/mL)	69.71 \pm 25.43	25.17–165	67.7 (49.1–87)	9.05 \pm 15.32	3.1–10.91	5.2 (4.3–6)	< 0.001
Age	31.48 \pm 6.07	18–39	32 (29–36)	27.78 \pm 5.25	18–40	27 (24–30)	< 0.001
BMI (kg/m ²)	23.78 \pm 3.563	18–39	23 (21.2–25.9)	22.20 \pm 2.94	18–30	22.5 (20.8–24.8)	NS
First menses (age)	13.13 \pm 1.72	11–18	13 (12–14)	12.56 \pm 1.25	10–15	13 (11.7–13)	NS
WHR	86.53 \pm 12.17	67–122	86.5 (77.7–93.2)	80.28 \pm 10.10	65–103	78.5 (73.7–84.5)	NS
LH (mIU/mL)	34.52 \pm 14.79	9.2–69.4	33.1 (23.3–45)	7.07 \pm 8.60	2.0–51.42	4.8 (3.43–6.9)	< 0.001
E2 (pg/mL)	22.34 \pm 31.69	5–252	13.5 (10–21)	51.0 \pm 41.23	10–303	41.5 (30–55.2)	< 0.001
PRL (ng/mL)	30.0 \pm 13.26	6.17–100.6	27.4 (23.1–33.4)	31.51 \pm 13.77	6–89.45	30.3 (24.3–36.2)	NS
T (ng/mL)	0.40 \pm 0.24	0.1–1.8	0.36 (0.2–0.5)	0.37 \pm 0.12	0.16–0.74	0.35 (0.3–0.5)	NS
SHBG (nmol/L)	53.91 \pm 31.85	11.6–148	48.4 (31.4–64.7)	70.39 \pm 33.50	7.85–161	63.3 (41.6–92.3)	0.002
A (ng/mL)	2.30 \pm 1.11	0.3–5.4	2.1 (1.6–2.9)	2.66 \pm 1.02	0.7–4.8	2.7 (1.7–3.5)	NS
DHEAS (μ mol/L)	5.50 \pm 2.77	0.1–13.62	5.3 (3.4–6.4)	6.67 \pm 2.05	1.96–12.4	6.5 (5.3–7.9)	NS
TSH (mIU/L)	1.56 \pm 1.34	0.16–10.3	1.2 (0.9–1.8)	1.58 \pm 0.80	0.4–4.4	1.4 (0.9–2)	NS
fT4 (pmol/L)	12.65 \pm 2.06	6.1–17.1	12.6 (11.2–14.3)	13.32 \pm 1.45	9.7–17.08	13.3 (12.2–14.3)	NS
anti-TPO (IU/mL)	208.11 \pm 557.35	0–2900	5.5 (0.1–32.3)	45.96 \pm 210.47	0–1407	0.3 (0.1–0.8)	NS
anti-TG (IU/mL)	87.98 \pm 240.87	0–1354.2	7.9 (0.8–43.5)	17.70 \pm 51.79	0–344.9	1.4 (0.8–7.3)	0.013
OGTT ^b (mg/dL)	85.29 \pm 7.42	67–111	85 (81–89)	84.81 \pm 6.32	70–102	85 (81–89)	NS
OGTT1h ^c (mg/dL)	140.89 \pm 35.67	56–237	140 (124–159)	136.48 \pm 38.64	59–248	138 (110–162)	NS
OGTT2h ^d (mg/dL)	104.07 \pm 29.41	41–189	104 (83–122)	100.49 \pm 22.57	56–166	97 (83–114)	NS
Ins 0 h ^e (IU/mL)	6.77 \pm 3.67	1.8–18	6.0 (4–8.4)	5.58 \pm 2.56	1.9–12.3	4.8 (3.5–5.7)	0.032
Ins 1 h (IU/mL)	59.56 \pm 51.94	11.4–390	49.2 (31.7–78.7)	41.77 \pm 24.275	3.8–120.3	34.9 (23.3–54)	0.017
Ins 2 h (IU/mL)	35.61 \pm 30.32	10.2–235	27.3 (17.7–44.4)	36.29 \pm 21.48	8.0–118.2	30.8 (19.6–47.9)	NS
Cortisol ^f	12.45 \pm 3.64	6.02–20.18	11.8 (9.9–15.2)	12.17 \pm 3.70	5.83–18.28	12.2 (8.3–15.5)	NS

^aFAI — free androgen index; ^bOGTT — oral glucose tolerance test — fasting serum glucose; ^cOGTT — 1 hour; ^dOGTT — 2 hours; ^einsulin measured before the OGTT; ^fCortisol measured at 8 a.m.; P — value adjusted for age

Table 2. The number (percent) of women with insulin resistance in POI and in the control group

		POI (N = 98)	Control group (N = 78)	p value
QUICKI	Quicki < 0.357	28.57% (28/98)	23.07% (18/78)	NS
Matsuda	Matsuda < 7.3	15.3% (15/98)	14.1% (11/78)	NS
HOMA-IR	Homa > 2.5	16.32% (16/98)	8.97% (7/78)	NS
FGIR	MG < 7.2	6.12% (6/98)	2.56% (2/78)	NS
McA	McA ≥ 5.7	5.1% (5/98)	1.28% (1/78)	NS
FI	FI > 15	4.08% (4/98)	0% (0)	NA

HOMA-IR — homeostatic model assessment of insulin resistance; QUICKI — quantitative insulin check index; Matsuda index; FGIR — fasting glucose/insulin ratio; McA, McAuley index; FI — fasting insulin > 15; NS — non-significant; NA — not applicable; P-value: POI vs. control group

Table 3. Correlation of insulin resistance indexes with some parameters of POI

Variable	BMI		WHR		FAI		SHBG	
	r	P value	r	P value	r	P value	r	p value
HOMA	0.294	0.007	0.475	0.003	0.207	0.088	-0.379	0.001
QUICKI	-0.275	0.013	-0.476	0.003	-0.236	< 0.05	0.357	0.003
FGIR	0.217	< 0.05	-0.396	0.014		NS		NS
Matsuda		NS	-0.461	0.004	-0.288	0.017	0.279	0.020
McA	-0.244	0.027	-0.420	0.003	-0.265	0.010	0.392	< 0.001
Fasting Insulin	0.269	0.014	0.500	0.001		NS	-0.366	0.002

HOMA-IR — homeostatic model assessment of insulin resistance; QUICKI — quantitative insulin check index; Matsuda index; FGIR — fasting glucose/insulin ratio; McA — McAuley index; FI — fasting insulin > 15; NS — non-significant

values of SHBG [p = 0.002] and 17-OHP [p = 0.007] and higher anti-TG levels [p = 0.013]. No significant differences in lipid profile were detected between the groups. The OGTT, basal, 60-min and 120-min glucose levels and 120-min insulin levels were comparable between the groups. However, the basal and 60 min insulin levels were significantly higher in women with POI than in those in the control group (Tab. 1).

There were no significant differences between the POI patients and controls for median values of the QUICKI and the HOMA, Matsuda, McA, and FGIR indexes (Tab. 2). The number of women detected with IR when assessed using the various kits was comparable between the two groups (Fig. 1).

However, QUICKI proved better than other indexes and tests (p < 0.05) at detecting IR in both the POI and control group, with larger numbers detected in in the former than in the latter (28.57% and 23.07%, respectively) (Tab. 2).

Finally, we determined the correlation of the IR indexes we investigated with other hormonal and biochemical parameters (Tab. 3).

DISCUSSION

POI cases are described as primary when the cause is unknown, and as secondary when other conditions are involved (e.g., after chemotherapy or surgery). Most POI cases are primary [18, 19].

As expected, our study recorded lower androgen levels in women with POI than in the members of the control group, and this is in accordance with previously published data [8]. Additionally, higher levels of thyroglobulin antibodies were found in the POI group, which may be due to the association between POI and thyroiditis.

It is established that POI is the disease associated with hypoestrogenism and characterized by an increased risk of cardio-metabolic changes [20–23]. Additionally, hyperinsulinaemia is regarded as a surrogate marker of IR [24]. There is some data indicating the possible connection between IR and the hypo-oestrogenic state [25]. Thus, when considering the above relationships between oestrogen deficiency and hyperinsulinaemia, we wonder if there may be a difference in the indexes of IR between groups. The gold standard methods in assessing IR are the euglycaemic insulin clamp [26], the intravenous glucose tolerance test (IVGTT), and the minimal model approximation of the metabolism of glucose (MMAMG) [27]. Unfortunately, these methods are rarely applied because of time and cost constraints. In clinical practice, there are many easier methods that can predict insulin resistance, and these are used as surrogates for the “gold standard” methods.

In our study, the groups did not differ with respect to OGTT. However, basal insulin levels and insulin levels after 1 h of an OGTT were significantly higher in the POI group

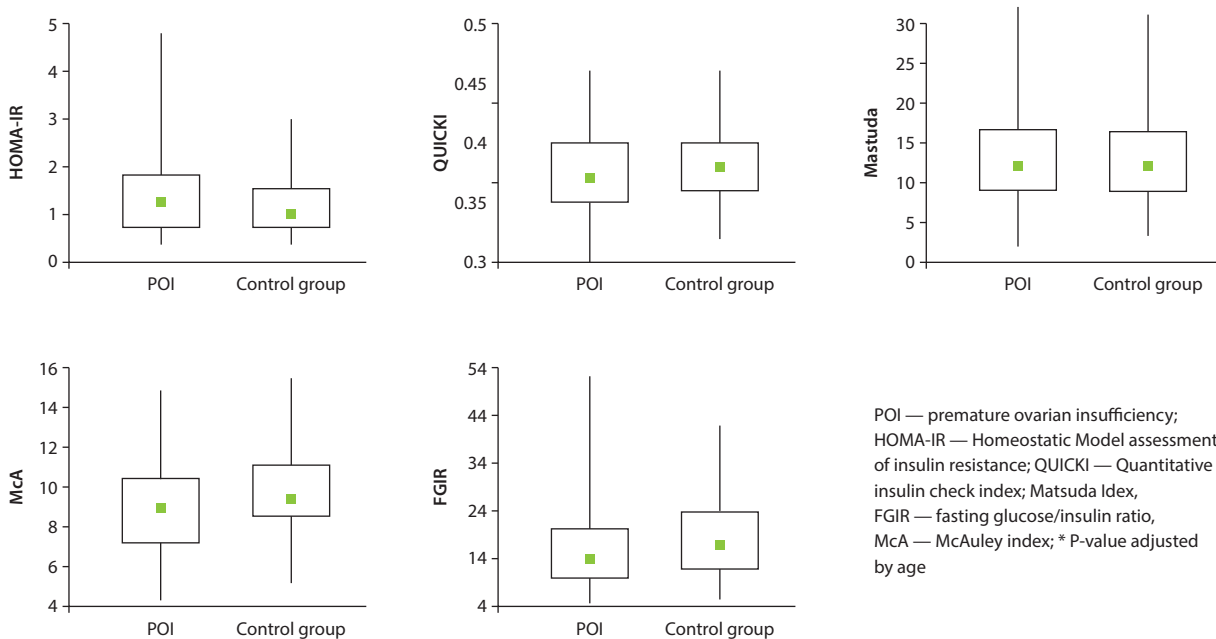


Figure 1. The medians and interquartile 25–75th percentiles of insulin indexes in POI and controls

than in the control group. Our data are partially in agreement with those presented by Ates et al., where IR measured using the HOMA, fasting levels of insulin and glucose appear to be normal in women with POI compared with the data sets of the control group [5]. Daan et al. measured the basal insulin and glucose levels in 83 women with previously diagnosed POI. It was found that both parameters were lower in the women with POI than in the premenopausal controls; however, it is worth noting that the mean age of the women with previously diagnosed POI was 49.3 years at the time of enrolment in the study [4].

In most studies, the insulin resistant indexes of women with polycystic ovary syndrome (PCOS) or diabetes are predominantly presented. It is also worth noting that the literature presents different levels of fasting insulin or insulin post-glucose load as hyperinsulinaemia and IR. Although there is no consensus on a cut-off point for the 2 h insulin level to define IR, Stovall et al. reported that the mean 2 h post-load insulin levels for non-overweight (BMI < 25 kg/m²) and overweight (BMI > 25 kg/m²) patients were 34.2 mIU/mL and 70.0 mIU/mL, respectively [28]. Additionally, Saxena et al. used a value of the 2 h insulin level greater than 41 mIU/mL to determine the presence of IR in Indian women with PCOS [29].

When we compared the number of women diagnosed as IR (considering the QUICKI, HOMA, Matsuda, and FGIR indexes) and their medians we found no statistically significant differences between the POI and control group. However, when we analysed data within the POI group,

hyperinsulinaemia was more often detected when using the QUICKI than when using the other tests.

Based on our results above, the QUICKI index detected many women with hyperinsulinaemia in the POI group; in addition, the insulin levels were significantly higher in the POI women than in the control group at 0 and 60 min of the OGTT.

The data from the literature indicates that the frequency of detection of IR varies with respect to the index applied. For example, according to some data, IR was detected between 30.4% and 53.6% for the HOMA-IR index and between 26.8% and 83.9% for the Matsuda index [30, 31]. We did not find data regarding the POI population; thus, a comparison between POI subjects and healthy controls was not possible.

We also speculate that the lack of differences in commonly use indices between POI women and healthy controls can be the result of a too short time between the onset of POI and OGTT assessment. In some studies, an early postmenopausal status was not associated with decreased insulin sensitivity, as assessed by the hyperinsulinemic-euglycemic clamp [32].

In conclusion, only the OGTT evaluation revealed a significant difference in insulin concentrations between the two study groups. The indexes most commonly used to detect IR did not detect differences in IR between the POI women and the members of the healthy control group. QUICKI detected significantly more women with IR within both study groups than other tests did. We believe that studies with a larger sample size should be performed in the future to elucidate the meaningfulness of these differences.

Conflict of interest

The authors declare that they have no conflicts of interest.

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