VANESSA RIBEIRO SANTANA BERINI PICCOLO

ASSOCIAÇÃO DO HORMÔNIO ESTIMULADOR DA TIREOIDE COM RESISTÊNCIA INSULÍNICA E COM PARÂMETROS CLÍNICOS E LABORATORIAIS DA SÍNDROME DOS OVÁRIOS POLICÍSTICOS

THE ASSOCIATION BETWEEN THYROID-STIMULATING HORMONE, INSULIN RESISTANCE AND THE CLINICAL AND LABORATORY PARAMETERS OF POLYCYSTIC OVARY SYNDROME

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Dissertação de Mestrado apresentada ao Programa de Tocoginecologia da Faculdade de Ciências Médicas da Unicamp para obtenção do Título de Mestra em Ciências da Saúde, na área de concentração em Fisiopatologia Ginecológica.

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Dedico este trabalho...

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São Josemaria Escrivá

Sumário

Símbolos, Siglas e Abreviaturas

CA – Circunferência abdominal

CQ – Circunferência de quadril

CAISM – Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - Centro de Atenção Integral à Saúde da Mulher

CEP – Comitê de Ética em Pesquisa

cm – Centímetro(s)

cm^3 – Centímetro(s) cúbico(s)

COLT – Colesterol total

Curva ROC (ROC curve) – *Receiver operating characteristic curve*

DM2 – *Diabetes mellitus* tipo 2

DCV – Doença cardiovascular

DP – Desvio padrão

et al. – e colaboradores

EUA – Estados Unidos da América

FCM – Faculdade de Ciências Médicas

Ferriman – Índice de Ferriman-Galley

GJ – Glicemia de jejum

HDL – HDL colesterol

HOMA-IR – Índice de HOMA (*Homeostatic model assessment of insulin resistance*)

HSC – Hipotireoidismo subclínico

IMC – Índice de massa corpórea

INSUL – Insulina de jejum

Kg – Quilograma(s)

Kg/m² – Quilograma(s) por metro quadrado

LDL – LDL colesterol

m – Metro(s)

mg/dL – Miligrama(s) por decilitro

ml – Mililitro(s)

mmHg – Milímetro(s) de mercúrio

mUI/L – Mili unidades internacionais por litro

mUI/mL – Mili unidades internacionais por mililitro

n – Número(s) de casos

ng/dL – Nanograma(s) por decilitro

ng/mL – Nanograma(s) por mililitro

OMS – Organização Mundial da Saúde

p – Nivel de significância

PAS – Pressão arterial sistólica

PAD – Pressão arterial diastólica

pg/mL – Picogramas por mililitro

PRL – Prolactina *(prolactin)*

RI – Resistência insulínica

SDHEA – Sulfato de dehidroepiandrosterona

SM – Síndrome metabólica

SOP – Síndrome dos ovários policísticos

T4L – Tiroxina

TL – Testosterona livre

TRIG – Triglicérides

TSH – Hormônio estimulador da tireoide

TT – Testosterona total

UNICAMP – Universidade Estadual de Campinas

US – Ultrassonografia

µg/dL – Microgramas por decilitro

µUI/ml – Microunidades internacionais por mililitro

% – Porcentagem

Resumo

Introdução: A síndrome dos ovários policísticos (SOP) associa-se, em 50% a 70% dos casos, ao hiperinsulinismo, obesidade e síndrome metabólica. A relação entre resistência insulínica (RI) e função tireoidiana é ainda pouco estudada, embora se considere haver interação entre disfunção tireoidiana e metabolismo lipídico. **Objetivo:** avaliar a partir de que nível sérico de hormônio estimulador da tireoide (TSH) há maior prevalência de RI e a relação entre TSH e diferentes parâmetros clínicos e metabólicos em mulheres com SOP. **Sujeitos e Métodos:** Foi avaliada a associação do TSH e RI em 168 mulheres com SOP atendidas no ambulatório de ginecologia endócrina do Departamento de Tocoginecologia da Faculdade de Ciências Médicas, UNICAMP não hipotireoideas. Avaliaram-se também as variáveis: índice de Ferriman-Galley, índice de massa corpórea (IMC), pressão arterial sistólica (PAS), pressão arterial diastólica (PAD), circunferência abdominal (CA), circunferência do quadril (CQ), níveis séricos de testosterona total, testosterona livre, glicemia em jejum, insulina em jejum, índice de HOMA (HOMA-IR), colesterol total, HDL colesterol (HDL) e LDL colesterol (LDL), triglicérides (TRIG). Para determinar o ponto de corte que maximize a sensibilidade e a especificidade foi empregada curva ROC para os níveis de TSH, considerando

resistência insulínica quando HOMA-IR ≥ 2,71. As variáveis foram comparadas segundo o ponto de corte do TSH determinado pela curva *ROC* e pela classificação de hipotireoidismo subclínico (HSC) com valores de TSH ≥ 4,5 e <10mIU/L, bem como pela presença de RI. Foi estudada também a correlação das variáveis com TSH e HOMA-IR. **Resultados:** As 168 mulheres com SOP tinham média de idade de 24,2 ± 5,8 anos. A associação entre TSH e RI mostrou um valor de corte de TSH ≥ 2,77mUI/L, com sensibilidade de 47,9% e especificidade de 65,3% para correlação de RI. Os parâmetros clínicos, hormonais e metabólicos foram avaliados e comparados para TSH < 2,77mUI/L e TSH entre 2,77 e 10mUI/L, sem diferença significativa entre as variáveis estudadas. Foram então comparadas mulheres com e sem RI, com valores significativamente maiores para peso, IMC, PAS, PAD, CA e CQ entre as com RI. As mesmas variáveis foram comparadas entre mulheres com função tireoidiana normal ou HSC. Observaram-se valores significativamente maiores de prolactina (PRL) e LDL nas com HSC. Realizadas as correlações entre os parâmetros estudados, observou-se correlação positiva apenas entre TSH e LDL. O HOMA-IR mostrou correlação positiva com peso, IMC, PAS, PAD, CA, CQ e TRIG. **Conclusão:** Há maior associação entre a concentração de TSH ≥ 2,77mUI/L e a presença de RI, porém sem alteração nos parâmetros clínicos e laboratoriais que indique mudança de conduta. Porém, quanto maior a RI, observou-se piora nos parâmetros clínicos relacionados à síndrome metabólica. As mulheres com SOP e HSC apresentaram valores de LDL e PRL significativamente maiores do que nas com níveis de TSH < 4,5 mUI/L.

Summary

Introduction: Polycystic ovary syndrome (PCOS) is associated with hyperinsulinism, obesity and the metabolic syndrome in 50-70% of cases. The association between insulin resistance (IR) and thyroid function has yet to be fully clarified, although an interaction between thyroid dysfunction and lipid metabolism is recognized. ***Objective:*** To evaluate the serum level of thyroid-stimulating hormone (TSH) that results in a greater prevalence of IR and the relationship between TSH and different clinical and metabolic parameters in women with PCOS. ***Subjects and methods:*** The association of TSH and IR was evaluated in 168 women with PCOS without overt hypothyroidism attending a gynecological endocrinology outpatient clinic at the Department of Obstetrics and Gynecology, School of Medical Sciences, University of Campinas (UNICAMP). Other variables evaluated were: the Ferriman-Gallwey Index, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, hip circumference, serum levels of total testosterone, free testosterone, fasting glucose and fasting insulin, the homeostatic model assessment of insulin resistance (HOMA-IR), total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c) and triglycerides (TRIG). To determine the cut-off point that would maximize sensitivity and specificity, a receiver-

operating characteristic (ROC) curve was used for TSH levels, with insulin resistance being defined as HOMA-IR ≥ 2.71. The variables were compared based on the cut-off point for TSH determined by the ROC curve, the classification of subclinical hypothyroidism (SCH) as defined by TSH values ≥ 4.5 and < 10 mIU/L, and the presence of IR. The correlation between the variables, TSH and HOMA-IR, was also assessed. ***Results:*** The mean age of the 168 women with PCOS was 24.2 ± 5.8 years. The association between TSH and IR revealed a cut-off value for TSH ≥ 2.77 mIU/L, with sensitivity of 47.9% and specificity of 65.3% for the correlation with IR. The clinical, hormonal and metabolic parameters were evaluated and compared for TSH levels < 2.77mIU/L and for TSH levels of 2.77 - 10mIU/L, with no statistically significant differences being found between the variables studied. The women with IR were then compared with those without IR, with significantly higher values being found for weight, BMI, SBP, DBP, waist and hip circumference among women with IR. The same variables were compared between the women with normal thyroid function and those with SCH. Significantly higher values of prolactin and LDL-c were found in the women with SCH. Evaluation of the parameters studied showed a positive correlation only between TSH and LDL-c. HOMA-IR correlated positively with weight, BMI, SBP, DBP, waist and hip circumference and TRIG. ***Conclusion:*** There is a stronger association between TSH levels ≥ 2.77mIU/L and the presence of IR; however, no abnormalities were found in the clinical or laboratory parameters that would warrant a change in clinical management. Nevertheless, the higher the IR, the poorer the clinical parameters related to the metabolic syndrome. The women with PCOS and SCH had significantly higher LDL-c and PRL levels compared to women with TSH levels < 4.5 mIU/L.

1. Introdução

A síndrome dos ovários policísticos (SOP) afeta 5% a 10% das mulheres na menacme (1, 2). Apesar da grande incidência e de ter sido descrita há mais de 70 anos por Stein&Leventhal, a SOP continua suscitando discussões quanto à sua caracterização e às suas repercussões em longo prazo.

Caracterizada por espaniomenorreia ou amenorreia, hiperandrogenismo clínico ou hiperandrogenemia e imagem ecográfica de ovários policísticos, é a endocrinopatia mais comum em idade reprodutiva e a desordem metabólica com hiperandrogenismo mais frequente entre as mulheres (3). As mulheres com SOP procuram os serviços médicos geralmente devido à irregularidade menstrual, hirsutismo ou infertilidade e por muito tempo a abordagem médica limitou-se a tais achados. Atualmente, outros aspectos têm merecido atenção (3, 4).

É bem conhecida a associação da SOP com resistência insulínica (RI) e síndrome metabólica (SM) (4). Assim, a visão da SOP como uma doença metabólica, associada a um risco maior de desenvolvimento de *diabetes mellitus* tipo 2 (DM2) e doença cardiovascular (DCV) é relevante, pois em todo o mundo

as DCV são a maior causa isolada de óbito entre as mulheres, respondendo por um terço das mortes. Entretanto, o aumento de mortalidade por DCV em SOP ainda não foi adequadamente demonstrado (5, 6).

As DCV são doenças crônicas cujo desenvolvimento está relacionado a fatores de riscos que se manifestam ao longo da vida. A mortalidade por infarto agudo do miocárdio é baixa em mulheres na idade reprodutiva: 1 a 7 por 100.000, por ano, entre os 35 e 44 anos de idade (3 a 5 vezes menor do que para homens na mesma faixa etária), porém aumenta exponencialmente com a idade, sendo que, após os 65 anos, a incidência de IAM iguala-se entre os sexos (5, 7).

Estima-se que pessoas com SM têm risco duas vezes maior de desenvolver DCV por apresentarem fatores de risco como obesidade abdominal, HDL colesterol (HDL) diminuído, hipertensão arterial e alteração do metabolismo da glicose. Para DM2, o risco é cinco vezes maior do que na população em geral (8).

A prevalência de SM varia no mundo, provavelmente devido a fatores genéticos, estilo de vida e hábitos alimentares (9). Nos Estados Unidos da América (EUA), a prevalência da SM em mulheres com SOP é ao redor de 43% a 46% (5). Na população brasileira, sabe-se que é menor que nos Estados Unidos, como observado em um estudo conduzido na Universidade do Rio Grande do Norte com 102 mulheres com SOP, que mostrou prevalência de 28,4% de SM (10), resultado semelhante ao observado no sul do Brasil, com 27,9% das mulheres SOP apresentando intolerância à glicose (11).

Mulheres com SOP têm maior risco de aumento da RI, semelhante às pacientes com DM2. O mecanismo envolvido relaciona-se ao prejuízo na ação do hormônio na periferia, por exemplo, em células musculares e fígado, levando à consequente hiperinsulinemia. Como consequência do hiperinsulinismo, alguns tecidos têm sua função estimulada – como as células da teca ovariana, que passam a produzir andrógenos em demasia (12).

Segundo Dunaif e colaboradores, 50% a 70% das mulheres com SOP apresentam hiperinsulinismo (4). A RI está relacionada à gênese de distúrbios metabólicos que tendem a agravar-se com os anos, com maior risco de desenvolvimento de obesidade, diabetes e hipertensão arterial. O grau de obesidade nestas mulheres é positivamente associado com o aumento da prevalência e grau da RI (13). A associação entre obesidade e SOP é cada vez mais reconhecida, sendo demonstrado um crescimento da prevalência de obesidade entre as mulheres com SOP em anos recentes (14). A importância da obesidade deve-se à relação com anormalidades metabólicas, com maior associação à hiperinsulinemia, intolerância a glicose, DM2 e hipertrigliceridemia, entre outras (15).

Mulheres com SOP apresentam mais RI do que o esperado para mulheres de mesma idade e índice de massa corpórea (IMC) sem SOP (6). Embora os estudos sugiram influência da hiperandrogenemia, outros fatores também têm sido avaliados (7, 16).

Um desses fatores avaliados é a relação entre RI e função tireoidiana (8, 9). Sabe-se que há uma interação entre a função tireoidiana e possíveis

alterações em parâmetros do metabolismo lipídico, reconhecidamente em pacientes com hipotireoidismo (12). No hipotireoidismo, a captação da glicose pelo músculo e pelo tecido adiposo é resistente à ação da insulina, resultando em hiperinsulinismo (15). Essa condição é acompanhada por um aumento na síntese de colesterol pelo fígado, com aumento na produção, principalmente, de partículas VLDL colesterol precursoras do LDL colesterol (LDL) (17), bem como pela supressão da produção da SHBG (*sex hormone-binding globulin*) pelo fígado, aumentando a biodisponibilidade dos andrógenos, responsáveis pela piora da dislipidemia nos pacientes com RI (18).

Existem ainda interações entre RI e função tireoidiana, que influenciam na elevação do colesterol total (COLT), LDL e triglicérides (TRIG), com redução do HDL (12, 19). Portanto, elevados níveis do hormônio estimulador da tireoide (TSH) parecem afetar esses fatores de risco cardiovascular, especialmente em indivíduos que já estão em risco de desenvolver DCV pela presença de RI (12).

O hipotireoidismo subclínico (HSC) é definido pela elevação dos níveis séricos de TSH acima dos níveis de normalidade com dosagem de hormônios tireoidianos livres normais (20). A etiologia é a mesma do hipotireoidismo clínico, sendo mais frequentes as tireoidites crônicas linfocíticas (tireoidite de Hashimoto e tireoidite atrófica), desordens autoimunes da glândula tireóide, responsáveis pela redução na produção do hormônio da tireoide. Assim como outras doenças autoimunes, manifesta-se com uma prevalência 5 a 10 vezes maior em mulheres, provavelmente pela presença estrogênica, que contribuiria para o desenvolvimento da resposta autoimune à glândula (21, 22). O HSC

pode também resultar de terapias que levam à destruição do tecido glandular, tais como acontece nos tratamentos com iodo radioativo e radioterapia externa. Elevações transitórias ou persistentes dos níveis de TSH também podem ocorrer no pós-parto, após tireoidectomia parcial e utilização de algumas drogas (componentes contendo iodo, carbonato de lítio, interferon etc) (23).

Os parâmetros diagnósticos do HSC não são tão bem estabelecidos, sendo o limite de normalidade do TSH sérico uma questão atualmente discutida. Nas últimas três décadas, o ponto de corte do TSH foi alterado, com o limite superior de 10mUI/L reduzido para níveis convencionalmente aceitos e mais utilizados de 4-5mUI/L (24), porém dois estudos propuseram nível de corte de 2,0-2,5mUI/L (25, 26). Em uma pesquisa para avaliar incidência de hipotireoidismo, com acompanhamento de 1700 indivíduos por 20 anos, observou-se uma alta progressão para a doença naqueles com níveis de TSH acima de 2mUI/L, com risco maior naqueles com anticorpos antitireoidianos positivos (27). Evidências fortes em grandes estudos epidemiológicos indicam que TSH entre 3–4,5 mUI/L apresentam maior risco de progressão para hipotireoidismo, além de maior potencial de morbidade ao longo dos anos (24).

O HSC, sugerido por elevação do TSH, pode ser confirmado com reavaliações da concentração do TSH após 6 ou 12 meses, assegurando que apenas a doença progressiva ou persistente será tratada, reduzindo as chances de erros laboratoriais. Altos níveis de anticorpos antitireoidianos associados com altas concentrações de TSH sérico podem identificar indivíduos com tireoidites autoimunes, com maior risco de desenvolver hipotireoidismo permanente (24).

Estudos realizados nos EUA, entre eles um grande estudo epidemiológico (NHANES III), revelaram prevalência do HSC na população de adultos jovens entre 4% e 10% (28, 29). No estudo de Whickham, o HSC (com níveis de TSH acima de 6 mIU/l) foi identificado em 7,5% das mulheres, principalmente após os 45 anos (30). Outro estudo estima que aproximadamente 10% das mulheres apresentam esta condição em fases mais avançadas da vida (31). Pode-se inferir que o HSC é uma desordem comum e especula-se que a diferença na prevalência da doença deva-se principalmente às diferenças nos níveis de corte do TSH e diferenças em idade, sexo e ingestão de alimentos contendo iodo nas populações estudadas (24).

Em um estudo prospectivo, mulheres com HSC foram seguidas por período médio de 9,2 anos. Ao final do seguimento, 28% progrediram para o hipotireoidismo, 68% mantiveram-se em HSC e 4% regrediram ao eutireoidismo. O valor inicial do TSH constituiu-se o principal fator de risco para predição de progressão ao hipotireoidismo, seguido por anticorpos antimicrossomais positivos (32).

O autoanticorpo antiperoxidase deveria ser solicitado após segunda dosagem de TSH > 4 mIU/l e a sua presença sugere diagnóstico de doença autoimune como causa do hipotireoidismo primário. Nos casos de HSC, a presença desse anticorpo aumenta a taxa de evolução para hipotireoidismo clinico (33).

Assim, em vários estudos observou-se que a taxa de risco de progressão do HSC ao hipotireoidismo aumenta com a idade, sexo feminino, e na presença de anticorpos antitireoidianos positivos. O único fator independente que se

associa à progressão para hipotireoidismo é a concentração sérica inicial do TSH, com maiores taxas quando o TSH inicial for acima de 10 mUI/L (27, 34).

A relação entre o HSC e distúrbios metabólicos é menos compreendida, se comparada à relação com o hipotireoidismo clínico. Em mulheres com SM caracterizada principalmente pela elevação do COLT, LDL, da pressão arterial e dos níveis de TRIG, e redução do HDL, encontrou-se alta prevalência de HSC (cerca de um sexto das pacientes) (35).

O HSC tem sido discutido também como um importante fator de risco para desordens dos sistemas cardiovascular e endócrino (31, 35, 36), porém ainda existem dúvidas quanto às alterações da RI na presença de HSC (12, 31). Alguns autores propõem que níveis maiores de TSH, porém dentro dos limites considerados como parâmetros de normalidade, estão associados a níveis maiores de RI (31).

O hormônio tireoidiano age no sistema cardiovascular. As alterações presentes no hipotireoidismo dependem da gravidade da deficiência hormonal, sendo que as mudanças mais comuns são a elevação da resistência vascular sistêmica, levando à hipertensão, disfunções diastólicas, redução da função sistólica cardíaca, distúrbios endoteliais e alterações de coagulação, fatores que aumentam potencialmente o risco de aterosclerose e doença coronariana no hipotireoidismo e possivelmente no HSC (37, 38, 39).

A relação entre HSC e dislipidemia permanece controversa. Há estudos demonstrando associação do HSC com aumento do COLT e LDL (40, 41), mais

evidente em pacientes com RI (12). Outros estudos não evidenciam piora do padrão lipídico, entre eles o estudo Rotterdam, que revela redução no COLT em mulheres com HSC (42, 43). Recentemente, um estudo mostrou que o HSC pode levar ao aumento dos lipides séricos, mas sem associação com RI em mulheres com SOP (41).

Esses resultados conflitantes devem-se provavelmente às diferenças entre as populações estudadas, mostrando a necessidade de estudos e comparações em populações definidas. Além disso, o hábito de fumar e a RI podem influenciar os efeitos do hipotireoidismo no perfil lipídico (12).

Chubb e colaboradores demonstraram que, em pacientes com RI, o risco de DCV naqueles com TSH de 1mUI/L era quase a metade daqueles com TSH de 7mUI/L, revelando que quanto menor a sensibilidade insulínica, pequenas diferenças nos níveis de TSH sérico estão associadas à mudanças importantes no padrão lipídico, com conseqüente aumento do risco de DCV (19).

Por todas essas observações, a pesquisa de disfunções tireoidianas têm se tornado comum, e o diagnóstico de HSC mais frequente, principalmente em jovens. Porém, a pesquisa rotineira e o tratamento dessa condição são contraditórios, pois os riscos reais do HSC e os benefícios do tratamento são controversos (24).

A decisão de tratar o HSC é baseada frequentemente nos sintomas clínicos e sinais da doença, porém estes achados são inespecíficos, dificultando a avaliação do tratamento precoce (44). No estudo de Kong e colaboradores em mulheres com HSC, os sintomas mais comuns foram cansaço, ganho de peso e

elevado nível de ansiedade (45). É difícil distinguir pacientes eutireoideanos daqueles com HSC avaliando apenas os sintomas clínicos, pois são sintomas não específicos e relacionados com a gravidade, duração da doença e sensibilidade do organismo à deficiência hormonal. Os sintomas devem servir de triagem para identificar pacientes que necessitam de testes para avaliar a função tireoidiana e selecionar aqueles que poderiam beneficiar-se do tratamento de reposição hormonal (24).

Existem poucos estudos controlados que avaliam o benefício da terapia com hormônio tireoidiano nas disfunções do sistema vascular e perfil lipídico. Alguns defendem a hipótese de que a reposição com T4 pode normalizar as alterações hemodinâmicas, melhorar o sistema vascular através da redução da resistência vascular sistêmica, da função endotelial e assim prevenir a aterosclerose e a doença coronariana, bem como ter um efeito benéfico no perfil lipídico, principalmente pela redução do LDL (19, 46, 47, 48, 49). Porém, mais estudos controlados são necessários para a confirmação dos benefícios da terapia hormonal nos pacientes com HSC.

Tem sido descrita alta prevalência de níveis elevados do TSH em mulheres com SOP (21, 22, 50, 51, 52). Também já se demonstrou associação entre TSH e os níveis de insulina de jejum (INSUL) e a sensibilidade à insulina (19, 53). Em mulheres com SOP e elevação dos níveis de TSH, tem-se relatado maior risco de dislipidemia e piora nos fatores de risco de DCV (12).

Porém, a associação de RI e níveis de TSH em mulheres com SOP ainda é pouco estudada, tendo sido avaliada apenas recentemente, em 2009, por Mueller e colaboradores, que sugeriram que nível de corte de TSH em 2mUI/L tem melhor sensibilidade e especificidade para identificar SOP com RI. Neste estudo, as mulheres com TSH≥ 2mUI/L apresentavam valores maiores de IMC e índice de HOMA (*homeostatic model assessment of insulin resistance* – HOMA-IR) em idade mais jovem (8), enquanto Ganie e colaboradores, em estudo com mulheres com SOP e HSC e mulheres com SOP eutiroideas, não observaram diferença na RI em ambos os grupos. Porém, o grupo com HSC apresentou aumento significativo nos valores dos TRIG (41).

Assim, considerando a relação entre SOP, RI, SM e seus parâmetros clínicos, bem como a ação do HSC sob os mesmos fatores; e por ser pouco conhecida e controversa a interação entre estes aspectos e a função tireoidiana em mulheres com SOP, o objetivo deste estudo é avaliar a relação entre níveis séricos de TSH e parâmetros clínicos e laboratoriais de mulheres com diagnóstico de SOP, em especial com a RI.

2. Objetivos

2.1. Objetivo geral

Avaliar a relação entre os níveis séricos de TSH e parâmetros clínicos e laboratoriais na SOP.

2.2. Objetivos específicos

- Avaliar o valor de TSH com maior especificidade e sensibilidade, a partir do qual é possível identificar resistência insulínica em mulheres com SOP.
- Comparar os parâmetros clínicos idade, índice de Ferriman & Galley (Ferriman), IMC, pressão arterial sistólica (PAS), pressão arterial diastólica (PAD), circunferência abdominal (CA), circunferência de quadril (CQ) e os parâmetros laboratoriais testosterona total (TT), testosterona livre (TL), glicemia de jejum (GJ), INSUL, HOMA-IR, COLT, HDL, LDL e TRIG em mulheres com SOP abaixo do nível de corte do TSH e com TSH igual ou maior do que o valor de corte determinado.

- Comparar os mesmos parâmetros clínicos e laboratoriais em mulheres com SOP, com e sem RI.

- Comparar os mesmos parâmetros clínicos e laboratoriais em mulheres com SOP eutireoideas e com HSC.

- Avaliar a correlação entre os níveis séricos de TSH e parâmetros clínicos e laboratoriais em mulheres com SOP.

3. Publicações

Artigo 1 – **Thyroid-stimulating hormone and insulin resistance: their association in polycystic ovary syndrome**

Artigo 2 – **Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal and metabolic parameters**

3.1. Artigo 1

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You are logged in as Vanessa Piccolo
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Thyroid-stimulating hormone and insulin resistance: their association in polycystic ovary syndrome

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Short title: TSH and insulin resistance in PCOS

Keywords*:* polycystic ovary syndrome; thyroid-stimulating hormone; insulin resistance; hypothyroidism; dyslipidemia.

Abstract

This study analyzed the effectiveness of thyroid-stimulating hormone (TSH) as a predictor of insulin resistance (IR) and the association of TSH with the clinical and metabolic parameters of polycystic ovary syndrome (PCOS). Women with PCOS and without overt hypothyroidism (n=168) were included. Age, the Ferriman-Gallwey Index, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP), waist and hip circumference, total and free testosterone, fasting glucose, homeostasis model of assessment of insulin resistance (HOMA-IR), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride levels were also evaluated. Receiver operating characteristic (ROC) curves were used to determine the cut-off point for TSH that would maximize sensitivity and specificity for a diagnosis of IR with HOMA-IR ≥2.71. Variables were compared as a function of the TSH cut-off limit and the presence of IR. Correlations were sought between the variables and HOMA-IR. TSH ≥2.77 mIU/L was associated with a diagnosis of IR, with sensitivity of 47.9% and specificity of 65.3%. There were no differences in clinical, hormonal or metabolic parameters between TSH <2.77 and TSH of 2.77-10 mIU/L. Weight, SBP, DBP, waist and hip circumference were significantly higher in women with IR. HOMA-IR correlated positively with weight, BMI, SBP, DBP, waist and hip circumference and triglyceride level. In women with PCOS, TSH ≥2.77 mIU/L is associated with IR; however, no clinical or metabolic alterations were found that would justify a change in clinical management, showing TSH to be a poor predictor of insulin resistance in PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic disorder that affects between 5% and 10% of women of reproductive age (Adams *et al.* 1986, Azziz *et al.* 2004, Azziz *et al.* 2006). It is already known that around 20-40% of women with PCOS have insulin resistance (IR) compared to a prevalence of 5-10% in the general population (Dunaif 1997). In women with PCOS, IR has been associated with an increased risk of the metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease, and has been reported to cause subfertility (Azziz *et al.* 2004, Dunaif 1997, Lois *et al.* 2010).

The higher incidence of IR in PCOS, even when compared with the population of the same age and body mass index (BMI), remains to be fully clarified (Barber *et al.* 2006, Mueller *et al.* 2009). The genetic component in the origin of IR is already well-established (Diamanti-Kandarakis *et al.* 2004); however, a multifactorial pathogenesis has been suggested, with an effect of hyperandrogenemia (Moghetti *et al.* 1996, Möhlig *et al.* 2006) and other factors including thyroid function (Mueller *et al.* 2009).

An association has been reported between plasma levels of thyroid-stimulating hormone (TSH), fasting insulin and insulin sensitivity (Chubb *et al.* 2005, Michalaki *et al.* 2006). In women with PCOS, the association between IR and different TSH levels has yet to be fully established; however, Mueller *et al.* (2009) reported that serum TSH levels $\geq$ 2 m IU/L showed better sensitivity and specificity for the identification of women with PCOS and IR.

These results have been the subject of much debate and were not always reproducible. The objective of the present study was to evaluate whether thyroid function is associated with a greater risk of IR by identifying the TSH level that would result in the highest sensitivity and specificity for the presence of IR in women with PCOS and

without overt hypothyroidism. Differences in the clinical and laboratory parameters of women with PCOS and TSH levels above and below this cut-off level were also evaluated as a function of the presence or absence of IR.

Subjects and Methods

Subjects

A cross-sectional study was conducted in which 168 women with a diagnosis of PCOS in accordance with the Rotterdam criteria (Rotterdam ESHRE/ASRM 2004), who were receiving care as outpatients at the Department of Gynecology and Obstetrics, School of Medical Sciences, University of Campinas (UNICAMP), were evaluated. The women were included in the study at the time of diagnosis, i.e. prior to the initiation of any hormonal or hypoglycemic drugs.

Patients with chronic diseases such as overt hypothyroidism or hyperthyroidism, kidney or liver failure, hyperprolactinemia, late onset adrenal hyperplasia and diabetes were excluded from the study.

The study was approved by the institution's internal review board.

Methods

Anthropometric data (weight, height, waist and hip circumference) were collected, blood pressure was measured and a clinical evaluation of the androgenic manifestations of all the women included in the study was performed. BMI was calculated from the ratio between the woman's weight and her square height, expressed as kg/m^2. Hirsutism was classified in accordance with the Ferriman-Gallwey Index over nine body areas (Ferriman & Gallwey 1961).

Thyroid-stimulating hormone (TSH), free T4, free testosterone, total testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL), fasting glucose, fasting insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured. The blood samples were obtained from peripheral veins between the 3rd and 9th days of the menstrual cycle or 60 days after the last menstrual period, following a fasting period of at least 12 hours.

Glucose levels were measured using an enzymatic colorimetric method (Roche/Hitachi 904/911 Modular ACN 249, Indianapolis, USA). Insulin was measured using a chemiluminescent immunometric method (Immulite/Immulite 1000, Siemens, Los Angeles, USA).

Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were analyzed using an enzymatic colorimetric test (Roche/Hitachi Modular ACN, Indianapolis, USA).

DHEAS was measured using a chemiluminescent immunometric method (Immulite/Immulite 1000 DHEA-S04, Llanberis, UK). TSH, FT4, prolactin and total testosterone levels were measured by electrochemiluminescence (Cobas e411, Mannheim, Germany). Free testosterone was measured by radioimmunoassay (Beckman Coulter DSL 4900, Prague, Czech Republic).

IR was also evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR), which represents an indirect evaluation of IR made by measuring endogenous insulin and glucose after a 12-hour fasting period. HOMA-IR $\geq$ 2.71, the cut-off point established for a diagnosis of IR in the Brazilian population, was defined as the cut-off point for the present study (Geloneze *et al.* 2006, Geloneze & Tambascia 2006, Vasques *et al.* 2008).

Statistical analysis

Sample size was based on the sensitivity of the cut-off point for TSH. Recent studies indicated sensitivity of around 60% (Mueller *et al.* 2009). Considering a prevalence of IR of 50% (Dunaif 1997) in the sample, with sensitivity and specificity of 60%, 10% sampling error and significance of 5% (expected confidence interval for sensitivity/specificity: 50-70%), according to the calculation proposed by Flahault *et al.* (2005), the total sample would have to consist of at least 134 cases.

To determine the cut-off point for TSH that would maximize sensitivity and specificity for a diagnosis of IR, the receiver operating characteristics (ROC) curve methodology was used for TSH levels, considering IR as the gold standard.

Once the cut-off points were established by the ROC curve, Student's t-test and the Mann-Whitney test were used to evaluate the independent variables in accordance with this cut-off classification of TSH and also as a function of whether IR was present or not.

Correlations were sought between the homeostasis model of assessment of insulin resistance (HOMA-IR) values and the independent variables using Spearman's rank correlation coefficient.

Significance level was defined at 5% and the software used throughout the analysis was the SAS statistical software package, version 9.1.

Results

The mean age of the 168 women with PCOS was 24.2 ± 5.8 years. Mean body mass index was 33.45 ± 8.23 kg/m^2. The mean Ferriman-Gallwey score was 12.05 ± 4.37. Mean serum TSH level was 2.71 ± 1.57 mIU/L and mean HOMA-IR was 3.63 ± 2.75.

The association between TSH and IR, evaluated using the ROC curve, showed a cut-off value for TSH of 2.77 mIU/L, with sensitivity of 47.9% and specificity of 65.3% for a diagnosis of IR (Figure 1).

The clinical, hormonal and metabolic parameters were compared in accordance with the cut-off point established by the ROC curve for TSH levels < 2.77 mIU/L and for TSH levels of 2.77 to 10 mIU/L. In 97 women, serum TSH levels were < 2.77 mIU/L, while in 71 women levels were≥ 2.77 m IU/L. No statistically significant difference was found in the clinical, hormonal or metabolic parameters between the women with TSH levels below the established cut-off limit and those with levels above this limit (Table 1).

Women with PCOS and IR were compared with those without IR, with 57.1% of the women being found to have IR. In the women with IR (HOMA-IR ≥ 2.71), mean weight, BMI, systolic and diastolic blood pressure, waist and hip circumference were all significantly higher; however, there were no statistically significant differences with respect to serum androgen levels or to the Ferriman-Gallwey score (Table 2).

Correlations were sought between HOMA-IR values and the principal variables evaluated, with results showing that the values for BMI, systolic and diastolic blood pressure, waist and hip circumference and triglyceride levels increased as the HOMA-IR score increased (Table 3).

Discussion

This study showed that serum TSH level is not a good predictor of IR in young women with PCOS and without overt hypothyroidism. The metabolic parameters evaluated did not differ as a function of the defined cut-off value; however, a difference was found in the metabolic parameters as a function of whether insulin resistance was present or not.

PCOS is increasingly viewed as a metabolic disease, with important alterations in insulin production and action, generating clinical consequences and high morbidity throughout life. Nevertheless, the association between glucose metabolism, insulin and thyroid function in women with PCOS and without overt hypothyroidism remains to be fully clarified.

To assess this association, young, obese, hirsute women with PCOS and normal TSH levels of up to 10mIU/L, and normal free T4 levels were evaluated. Taking HOMA-IR $\geq$ 2.71 as being indicative of IR, as previously defined for the Brazilian population (Geloneze *et al.* 2006, Geloneze & Tambascia 2006), this metabolic alteration was found in 57.1% of the patients in the present sample. This prevalence was higher compared to other studies in which rates ranging from 20% to 40% have been reported (Dunaif 1997, Ehrmann *et al.* 1999, Legro *et al.* 1999), but lower than the rate reported by DeUgarte *et al.* (2005) in which IR was present in 64.4% of women with PCOS.

In the present study, the TSH value of 2.77 mIU/L was found to offer the best specificity and sensitivity for a diagnosis of IR. Other studies have shown an association of IR with TSH values of 2.0 mIU/L (Mueller *et al.* 2009) and 2.5 mIU/L (Dittrich *et al.* 2009), both very close to the value obtained in the present study.

Elevated TSH levels have been reported to represent an important cardiovascular risk factor, particularly when IR is present, with poorer lipid parameters and an increase in total and LDL cholesterol and a reduction in HDL cholesterol (Chubb *et al.* 2005, Bakker *et al.* 2001). This association remains under debate, since some large epidemiological studies failed to find statistically significant differences in lipid parameters (Tunbridge *et al.* 1977, Brenta *et al.* 2007). Furthermore, both PCOS and subclinical hypothyroidism alone exert negative effects on metabolic parameters; however, effects are unclear in women with

both PCOS and subclinical hypothyroidism. When the clinical and laboratory parameters of women with PCOS were compared for TSH levels < or ≥ the cut-off point of 2.77 up to a limit of 10 mIU/L, no differences were found in the clinical or hormonal manifestations or in metabolic parameters.

In agreement with some of the present results, Ganie *et al.* (2011) compared these parameters in relation to several TSH levels and found differences only in total cholesterol and triglyceride levels with TSH levels >3 and >4 mIU/L, respectively. However, those authors found no statistically significant differences in the other anthropometric and clinical parameters or with respect to the great majority of the laboratory parameters in the women with PCOS and normal thyroid function. Dittrich *et al.*, (2009) on the other hand, showed that BMI, IR indexes and total and free testosterone levels were higher in women with PCOS and TSH levels > 2.5 mIU/L compared to those with lower TSH levels (Dittrich *et al.* 2009).

Therefore, the present findings fail to supply any evidence in support of changing diagnostic management or even therapeutic management in women with PCOS as a function of the association of IR and normal TSH levels. The presence of IR should be investigated in all women with PCOS irrespective of thyroid function.

The relevance of conducting screening tests for IR in women with PCOS has been emphasized when three highly sensitive clinical parameters are present: BMI > 25.7kg/m^2, waist circumference > 76 cm and waist-to-hip ratio > 0.77. Likewise, in the present study, BMI, waist circumference and hip circumference were all higher in women with IR, suggesting that these criteria should be taken into account when considering screening for IR (Dunaif 1997, Barber *et al.* 2006, Salley *et al.* 2007, Azziz *et al.* 2009).

Higher levels of systolic and diastolic blood pressure were also found in the women with PCOS and IR. These findings are in agreement with data reported from other studies, although this relationship has been associated with obesity (Dunaif 1997, DeUgarte *et al.* 2005, Soares *et al.* 2008). The positive correlation between HOMA-IR and BMI, systolic and diastolic blood pressure and waist and hip circumference, in addition to a correlation with triglyceride levels, reinforces the significance of IR in some of the characteristics of PCOS.

IR has been reported to be an independent risk factor for the development of dyslipidemia, characterized principally by an increase in triglycerides and a decrease in HDL-C (Howard 1999, Wild *et al.* 1985); however, large studies have shown a completely normal lipid profile in women with PCOS (Talbott *et al.* 1998, Valkenburg *et al.* 2008).

Likewise, no significant difference was found in lipid profiles as a function of the presence of IR in the present study. It is important to note that this population sample was composed of young women and may not reflect the development of metabolic alterations throughout life, confirming the limitation of cross-sectional cohort studies.

In conclusion, a large number of women were evaluated and, although a cut-off value of 2.77 mIU/L was established for TSH, which was expected to indicate a higher prevalence of IR, this diagnostic model was found to have poor sensitivity and failed to provide any evidence that would justify changes in the investigation of women with PCOS.

References

Adams J, Polson DW & Franks S 1986 Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *British Medical Journal (Clinical Research Ed.)* **293** 355-359.

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE *et al.*; Androgen Excess Society 2006 Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *Journal of Clinical Endocrinology & Metabolism* **91** 4237-4245.

Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE *et al.;* Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society 2009. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and Sterility* **91** 456-488.

Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, Taylor K & Boots LR 2004 Androgen excess in women: experience with over 1000 consecutive patients. *Journal of Clinical Endocrinology & Metabolism* **89** 453-462.

Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ & Gans RO 2001 The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. *Journal of Clinical Endocrinology & Metabolism* **86** 1206-1211.

Barber TM, McCarthy MI, Wass JA & Franks S 2006 Obesity and polycystic ovary syndrome. *Clinical Endocrinology* **65** 137–145.

Brenta G, Berg G, Arias P, Zago V, Schnitman M, Muzzio ML, Sinay I & Schreier L 2007 Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L–T4 treatment. *Thyroid* **17** 453-460.

Chubb SA, Davis WA & Davis TM 2005 Interactions among thyroid function, insulin sensitivity, and serum lipid concentration: the Fremantle diabetes study. *Journal of Clinical Endocrinology & Metabolism* **90** 5317-5320.

DeUgarte CM, Bartolucci AA & Azziz R 2005 Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. *Fertility and Sterility* **83** 1454-1460.

Diamanti-Kandarakis E, Alexandraki K, Bergiele A, Kandarakis H, Mastorakos G & Aessopos A 2004 Presence of metabolic risk factors in non-obese PCOS sisters: evidence of heritability of insulin resistance. *Journal of Endocrinological Investigation* **27** 931-936.

Dittrich R, Kajaia N, Cupisti S, Hoffmann I, Beckmann MW & Mueller A 2009 Association of thyroid-stimulating hormone with insulin resistance and androgen parameters in women with PCOS. *Reproductive Biomedicine Online* **19** 319-325.

Dunaif A 1997 Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocrine Reviews* **18** 774-800.

Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK & Imperial J 1999 Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* **22** 141-146.

Ferriman D & Gallwey JD 1961 Clinical assessment of body hair growth in women. *Journal of Clinical Endocrinology & Metabolism* **21** 1440-1447.

Flahault A, Cadilhac M & Thomas G 2005 Sample size calculation should be performed for design accuracy in diagnostic test studies. *Journal of Clinical Epidemiology* **58** 859-862.

Ganie MA, Laway BA, Wani TA, Zargar MA, Nisar S, Ahamed F, Khurana ML & Ahmed S 2011 Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome. *Fertility and Sterility* **95** 2039-2043.

Geloneze B & Tambascia MA 2006 [Laboratorial evaluation and diagnosis of insulin resistance] *Arquivos Brasileiros de Endocrinologia & Metabologia* **50** 208-215.

Geloneze B, Repetto EM, Geloneze SR, Tambascia MA & Ermetice MN 2006 The threshold value for insulin resistance (HOMA-IR) in an admixtured population IR in the Brazilian Metabolic Syndrome Study. *Diabetes Research and Clinical Practice* **72** 219-220.

Howard BV 1999 Insulin resistance and lipid metabolism. *The American Journal of Cardiology* **84** 28J-32J.

Legro RS, Kunselman AR, Dodson WC & Dunaif A 1999 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. *Journal of Clinical Endocrinology & Metabolism* **84** 165-169.

Lois K, Valsamakis G, Mastorakos G & Kumar S 2010 The impact of insulin resistance on woman's health and potential treatment options. *Annals of the New York Academy of Sciences* **1205** 156-165.

Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, Psyrogiannis AI, Kalfarentzos FE & Kyriazopoulou VE 2006 Thyroid function in humans with morbid obesity. *Thyroid* **16** 73-78.

Moghetti P, Tosi F, Castello R, Magnani CM, Negri C, Brun E, Furlani L, Caputo M & Muggeo M 1996 The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. *Journal of Clinical Endocrinology & Metabolism* **81** 952–960.

Möhlig M, Jürgens A, Spranger J, Hoffmann K, Weickert MO, Schlösser HW, Schill T, Brabant G, Schüring A, Pfeiffer AF, *et al.* 2006 The androgen receptor CAG repeat modifies the impact of testosterone on insulin resistance in women with polycystic ovary syndrome. *European Journal of Endocrinology* **155** 127-130.

Mueller A, Schöfl C, Dittrich R, Cupisti S, Oppelt PG, Schild RL, Beckmann MW & Häberle L 2009 Thyroid-stimulating hormone is associated with insulin resistance

independently of body mass index and age in women with polycystic ovary syndrome. *Human Reproduction* **24** 2924–2930.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Human Reproduction* **19** 41-47.

Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW & Nestler JE 2007 Glucose intolerance in polycystic ovary syndrome – a position statement of the Androgen Excess Society. *Journal of Clinical Endocrinology & Metabolism* **92** 4546-4556.

Soares EM, Azevedo GD, Gadelha RG, Lemos TM & Maranhão TM 2008 Prevalence of the metabolic syndrome and its components in Brazilian women with polycystic ovary syndrome. *Fertility and Sterility* **89** 649-655.

Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, Daniels T & Engberg RA 1998 Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *Journal of Clinical Epidemiology* **51** 415-422.

Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T & Smith PA 1977 The spectrum of thyroid disease in a community: the Whickham survey. *Clinical Endocrinology* **7** 481–493.

Valkenburg O, Steegers-Theunissen RP, Smedts HP, Dallinga-Thie GM, Fauser BC, Westerveld EH & Laven JS 2008 A more atherogenic serum lipoprotein profile is

present in women with polycystic ovary syndrome: a case-control study. *Journal of Clinical Endocrinology & Metabolism* **93** 470-476.

Vasques AC, Rosado LE, Cássia G, Alfenas RC & Geloneze B 2008 [Critical analysis on the use of the homeostasis model assessment (HOMA) indexes in the evaluation of the insulin resistance and the pancreatic beta cells functional capacity]. *Arquivos Brasileiros de Endocrinologia & Metabologia* **52** 32-39.

Wild RA, Painter PC, Coulson PB, Carruth KB & Ranney GB 1985 Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology & Metabolism* **61** 946-951.

Table 1: Comparison of the clinical, hormonal and metabolic parameters of women with PCOS according to serum TSH level < 2.77 or ≥ 2.77 mIU/L

Variables	TSH < 2.77 mIU/L (n=97)	TSH ≥ 2.77 mIU/L (n=71)	p-value
Age (years)	24.67 ± 6.01	23.58 ± 5.48	0.2158
BMI (kg/m²)	32.98 ± 7.1	34.04 ± 9.48	0.6193
Ferriman-Gallwey score	12.16 ± 4.47	11.86 ± 4.24	0.7402
SBP (mmHg)	116.06 ± 13.85	116.18 ± 15.07	0.9542
DBP (mmHg)	74.04 ± 9.31	73.24 ± 9.53	0.8270
WC (cm)	99.74 ± 12.99	102.55 ± 18.02	0.5508*
HC (cm)	116.52 ± 11.76	114.72 ± 11.74	0.8226
TT (ng/mL)	0.72 ± 0.38	2.41 ± 12.26	0.8536
FT (pg/mL)	2.52 ± 1.33	2.64 ± 1.45	0.6395
FT4 (ng/dL)	1.17 ± 0.17	1.26 ± 0.21	0.0051*
PRL (ng/mL)	14.56 ± 12.17	14.34 ± 6.56	0.3425
DHEAS (µg/dL)	178.77 ± 92.73	199.16 ± 134.10	0.7251
GLU (mg/dL)	87.49 ± 12.98	87.63 ± 15.54	0.7642
INSUL (µIU/mL)	16.20 ± 11.19	16.49 ± 10.33	0.7064
HOMA-IR	3.64 ± 2.99	3.62 ± 2.42	0.6687
CHOL (mg/dL)	178.96 ± 36.00	187.86 ± 37.81	0.1949*
HDL-C (mg/dL)	46.44 ± 12.56	47.20 ± 15.38	0.7281
LDL-C (mg/dL)	102.89 ± 30.24	114.05 ± 34.85	0.0718
TRIG (mg/dL)	144.02 ± 94.65	143.12 ± 73.71	0.5232

Variables are expressed as means ± standard deviations.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; TT: total testosterone; FT: free testosterone; FT4: free thyroxine; PRL: prolactin; DHEAS: Dehydroepiandrosterone sulfate; GLU: glucose; INSUL: insulin; HOMA-IR: homeostatic model assessment of insulin resistance; CHOL: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TRIG: triglycerides

* Student's t-test. All other variables were evaluated using the Mann-Whitney test.

Table 2: Comparison of the clinical, hormonal and metabolic parameters of women with PCOS with and without insulin resistance according to HOMA-IR

Variables	HOMA-IR < 2.71 (n=72)	HOMA-IR ≥ 2.71 (n= 96)	p-value
Age (years)	23.59 ± 5.52	24.59 ± 5.95	0.3436
BMI (kg/m²)	29.27 ± 6.15	36.43 ± 8.26	< 0.0001
Ferriman-Gallwey score	11.92 ± 4.40	12.15 ± 4.39	0.9018
SBP (mmHg)	110.90 ± 13.45	119.79 ± 13.84	< 0.0001
DBP (mmHg)	70.00 ± 8.17	76.32 ± 9.35	< 0.0001
WC (cm)	93.00 ± 13.99	108.87 ± 12.93	0.0003*
HC (cm)	111.05 ± 13.53	120.10 ± 7.43	0.0140
TT (ng/mL)	2.36 ± 12.71	0.84 ± 0.62	0.0786
FT (pg/mL)	2.34 ± 1.25	2.73 ± 1.45	0.1438
TSH (mIU/L)	2.44 ± 1.25	2.92 ± 1.75	0.1575
FT4 (ng/dL)	1.22 ± 0.19	1.20 ± 0.19	0.4655*
PRL (ng/mL)	15.00 ± 7.77	13.99 ± 11.74	0.0611
DHEAS (µg/dL)	185.08 ± 103.08	189.50 ± 119.87	0.8767
GLU (mg/dL)	82.17 ± 7.44	91.58 ± 16.38	< 0.0001
INSUL (µIU/mL)	6.78 ± 3.25	23.47 ± 8.75	< 0.0001
CHOL (mg/dL)	184.86 ± 40.99	181.43 ± 34.47	0.6256*
HDL-C (mg/dL)	48.78 ± 16.41	45.64 ± 12.09	0.2250
LDL-C (mg/dL)	108.13 ± 32.93	107.24 ± 32.60	0.8288
TRIG (mg/dL)	126.47 ± 73.15	154.05 ± 91.53	0.0816

Variables are expressed as means ± standard deviations.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; TT: total testosterone; FT: free testosterone; FT4: free thyroxine; PRL: prolactin; DHEAS: Dehydroepiandrosterone sulfate; GLU: glucose; INSUL: insulin; HOMA-IR: homeostatic model assessment of insulin resistance; CHOL: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TRIG: triglycerides.

* Student's t-test. All other variables were evaluated using the Mann-Whitney test.

Table 3: Spearman's correlation for HOMA-IR values and some clinical and laboratory parameters of women with PCOS

Variables	HOMA-IR	
	r	p-value of r
Age (years)	0.09308	0.2689
BMI (kg/m²)	0.43582	<.0001
Ferriman-Gallwey score	0.07182	0.4436
SBP (mmHg)	0.28183	0.0003
DBP (mmHg)	0.28691	0.0002
WC (cm)	0.52494	0.0002
HC (cm)	0.34008	0.0342
TSH (mIU/L)	0.03118	0.6882
CHOL (mg/dL)	-0.05079	0.5833
HDL-C (mg/dL)	-0.17127	0.0685
LDL-C (mg/dL)	-0.07254	0.4621
TRIG (mg/dL)	0.3063	0.0007

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; TSH: thyroid stimulating hormone; CHOL: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TRIG: triglycerides.

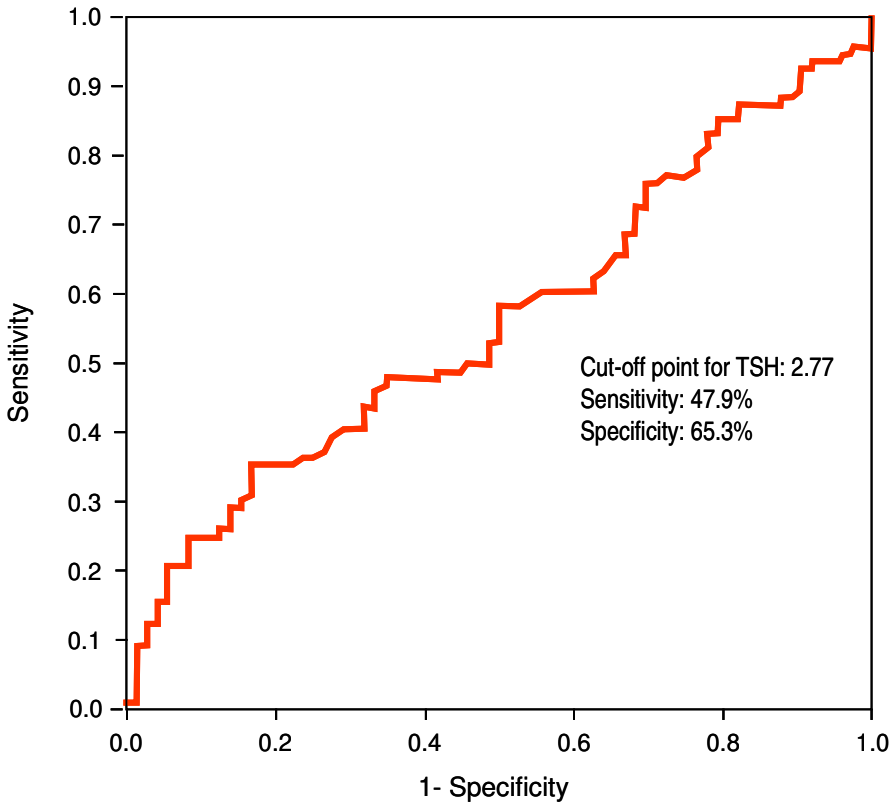

Figure: ROC curve to evaluate the association between TSH and IR, measured according to HOMA-IR, in women with PCOS (n = 168).

3.2. Artigo 2

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Title: Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal and metabolic parameters.
Article Type: Cross-Sectional Study
Keywords: polycystic ovary syndrome; insulin resistance; subclinical hypothyroidism; serum lipids.
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Abstract: Objective: Analysis of the relationship between selected clinical and metabolic parameters in young women with polycystic ovary syndrome (PCOS) and normal thyroid function or subclinical hypothyroidism (SCH). Design: A cross-sectional cohort study. Setting: Tertiary care setting. Patients: Women diagnosed with PCOS according to the Rotterdam criteria (n=168). Interventions: Clinical, hormonal and metabolic parameters were evaluated. SCH was defined as thyroid-stimulating hormone (TSH) levels of 4.5-10 mIU/L. Main outcome measure: Separately, PCOS and SCH exert adverse effects on metabolic parameters; however, in conjunction their effect is unclear. This study evaluated whether SCH in women with PCOS affects clinical, hormonal and metabolic parameters. Results: The mean age of the 168 women was 24±5.8 years. Mean body mass index was 33.4±8.2. Thyroid function was normal in 149 women, while 19 had SCH. Only serum LDL-c and PRL levels were significantly higher in the women with SCH (122.6±25.6 and 17.7±7.7) compared to those with normal thyroid function (105.6±33 and 14±10.3) (p=0.04 and p=0.01 respectively). Conclusion: The present findings show a higher prevalence of subclinical hypothyroidism in young women with polycystic ovary syndrome compared to that reported for the population of young women in general. In young women with PCOS, SCH is associated with higher LDL-c levels, albeit with no changes in other lipid profile parameters, insulin resistance or phenotypic manifestations. This study adds to current evidence supporting an association between PCOS and SCH.
Suggested Reviewers:
Opposed Reviewers:

Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal and metabolic parameters

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Capsule: Young women with polycystic ovary syndrome and subclinical hypothyroidism present higher serum levels of LDL cholesterol with no changes in other lipid profile parameters, insulin resistance or phenotypic manifestations.

Abstract

Objective: Analysis of the relationship between selected clinical and metabolic parameters in young women with polycystic ovary syndrome (PCOS) and normal thyroid function or subclinical hypothyroidism (SCH). ***Design:*** A cross-sectional cohort study. ***Setting:*** Tertiary care setting. ***Patients:*** Women diagnosed with PCOS according to the Rotterdam criteria (n=168). ***Interventions***: Clinical, hormonal and metabolic parameters were evaluated. SCH was defined as thyroid-stimulating hormone (TSH) levels of 4.5-10 mIU/L. ***Main outcome measure:*** Separately, PCOS and SCH exert adverse effects on metabolic parameters; however, in conjunction their effect is unclear. This study evaluated whether SCH in women with PCOS affects clinical, hormonal and metabolic parameters. ***Results:*** The mean age of the 168 women was 24±5.8 years. Mean body mass index was 33.4±8.2. Thyroid function was normal in 149 women, while 19 had SCH. Only serum LDL-c and PRL levels were significantly higher in the women with SCH (122.6±25.6 and 17.7±7.7) compared to those with normal thyroid function (105.6±33 and 14±10.3) (p=0.04 and p=0.01 respectively). ***Conclusion:*** in young women with PCOS, SCH is associated with higher LDL-c levels, albeit with no changes in other lipid profile parameters, insulin resistance or phenotypic manifestations. This study adds to current evidence supporting an association between PCOS and SCH

Key words: polycystic ovary syndrome; insulin resistance; subclinical hypothyroidism; serum lipids.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine metabolic disorder that affects 5-10% of women of reproductive age (1, 2).

Various factors involved in PCOS are also present in women with hypothyroidism. Some authors have affirmed that hypothyroidism is a state of insulin resistance (IR), while IR has also been considered the principal factor in the genesis of PCOS (3). In cases of PCOS alone and in cases of hypothyroidism alone, changes take place in lipid metabolism and there is a risk of arterial hypertension and endothelial dysfunction in addition to ovulatory dysfunction. Consequently, the association between thyroid dysfunction and the clinical and laboratory parameters of PCOS has become the object of recent studies; however, this relationship remains unclear, particularly when the two conditions occur in conjunction (4-9).

More recently, the metabolic alterations present in subclinical hypothyroidism (SCH) have been investigated, as well as their association with IR. Some studies conducted in the general population have shown changes in lipid metabolism with an increase in total cholesterol (CHOL) and in high-density lipoprotein cholesterol (HDL-c) (6, 10) as well as a greater risk of cardiovascular disease in SCH associated with IR (11). Nevertheless, others have reported no negative effect on these parameters (12, 13), reinforcing the need for further studies, particularly in better-defined populations such as women with PCOS. A recent study conducted in 2011 in women with PCOS and normal thyroid function or SCH revealed higher triglyceride (TRIG) levels in SCH; however, there were no differences in any of the other parameters related to lipid metabolism or in clinical parameters such as body mass index (BMI) (6).

Considering the association between PCOS, IR and the metabolic syndrome, as well as the effect of the thyroid on these same factors and the sparse evidence of an interaction between SCH and PCOS, the present study was developed to analyze the relationship between SCH and clinical and metabolic parameters in young women with PCOS.

Subjects and Methods

Subjects

A cross-sectional cohort study was conducted in which 168 women with a diagnosis of PCOS defined in accordance with the Rotterdam criteria (14) were evaluated. The women were all receiving care as outpatients at the Department of Gynecology and Obstetrics, School of Medical Sciences, State University of Campinas (UNICAMP). The women were included at the time of diagnosis and had not yet initiated treatment with hormones or hypoglycemic drugs.

Women with chronic diseases such as overt hypothyroidism and hyperthyroidism, kidney or liver failure, hyperprolactinemia, late-onset adrenal hyperplasia and diabetes were excluded from the study.

The study was approved by the institution's internal review board.

Methods

Anthropometric data (weight, height, waist and hip circumference) were recorded, arterial blood pressure was measured and a clinical evaluation was performed to verify the presence of androgenic manifestations in all the women included in the study. Body mass index (BMI) was calculated from the ratio between the woman's

weight and the square of her height, expressed as kg/m^2. Hirsutism was classified in accordance with the Ferriman-Gallwey Index over nine body areas (15).

Thyroid-stimulating hormone (TSH), free thyroxine (FT4), free testosterone, total testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin (PRL), fasting glucose, fasting insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) levels were measured. The blood samples were obtained from peripheral veins between the 3rd and 9th days of the menstrual cycle or 60 days after the last menstrual period, following a fasting period of at least 12 hours.

Glucose levels were measured using an enzymatic colorimetric method (Roche/Hitachi 904/911 Modular ACN 249, Indianapolis, USA). Insulin was measured using a chemiluminescent immunometric method (Immulite/Immulite 1000, Siemens, Los Angeles, USA).

Total cholesterol, HDL-c, LDL-c and triglycerides were analyzed using an enzymatic colorimetric test (Roche/Hitachi Modular ACN, Indianapolis, USA).

DHEAS was measured using a chemiluminescent immunometric method (Immulite/Immulite 1000 DHEA-S04, Llanberis, UK). TSH, FT4, prolactin and total testosterone levels were measured by electrochemiluminescence (Cobas e411, Mannheim, Germany).

Free testosterone was measured by radioimmunoassay (Beckman Coulter DSL 4900, Prague, Czech Republic).

IR was also evaluated using the homeostatic model assessment of insulin resistance (HOMA-IR), which represents an indirect evaluation of IR made by measuring endogenous insulin and glucose after a 12-hour fasting period. HOMA-IR

values > 2.7, the cut-off point established for a diagnosis of IR in the Brazilian population, were taken into consideration in the present study (16,17).

Subclinical hypothyroidism was defined as serum TSH levels between 4.5 and 10 mIU/L (18).

Statistical analysis

The results were described as means ± standard deviations. Significance level was defined at 5% and the software used for the analysis was the SAS statistical software package, version 9.1.

The independent variables were evaluated in accordance with the classification of TSH < 4.5 mIU/L (normal thyroid function) or TSH = 4.5 – 10 mIU/L (SCH) using Student's t-test and the Mann-Whitney test. The correlation between TSH values and the independent variables was evaluated using Spearman's rank correlation coefficient.

Results

The 168 women with PCOS were young (mean age 24.19 ± 5.78 years), obese (BMI 33.45 ± 8.23 kg/m^2) and hirsute (Ferriman-Gallwey Index 12.05 ± 4.37). Mean fasting glucose, fasting insulin, HOMA-IR and TSH were 87.55 ± 14.07 mg/dl, 16.31 ± 10.8 μIU/mL, 3.63 ± 2.75 and 2.71 ± 1.57 mIU/L, respectively.

A diagnosis of SCH was established in 11.3% of the women with PCOS (n=19), with mean TSH levels of 6.1 ± 1.2 mIU/L. The remaining 149 women had normal thyroid function (TSH = 2.3 ± 1.0 mIU/L). There was no difference between the two groups with respect to age, BMI, hirsutism as evaluated by the Ferriman-Gallwey Index,

systolic blood pressure, diastolic blood pressure, waist circumference or hip circumference (Table 1).

In the evaluation of lipid metabolism, a statistically significant difference was found in LDL-c levels, which were higher in the women with SCH compared to those with normal thyroid function (122.58 ± 25.61 mg/dL and 105.64 ± 32.97 mg/dL, respectively; $p = 0.04$). Prolactin levels were also higher in the group of women with SCH (Table 1). There was no difference between the women with PCOS and normal thyroid function and those with PCOS and SCH with respect to any of the other metabolic parameters or the hormonal parameters evaluated.

A positive correlation was found between TSH and LDL-c: the higher the TSH level, the higher the serum LDL-c level ($R = 0.19$; $p = 0.04$) (Table 2).

Discussion

The present results show that 11.3% of the women with PCOS had SCH, with higher serum LDL-c levels compared to the women with normal thyroid function. A positive correlation was found between serum TSH and LDL-c levels, i.e. within the limits evaluated, the higher the serum TSH level, the higher the level of circulating LDL-c.

SCH is found in 4-10% of the general population; however, in young women of 12-39 years of age, this prevalence falls to 2% (19-21). This study group was composed of young women with a mean age of 24 years, all with PCOS. The prevalence of SCH was higher than that reported for the young population in general, appearing to indicate the existence of a closer relationship between thyroid dysfunction and PCOS. However,

it is unclear whether SCH induces an increase in the prevalence of PCOS or whether SCH is a consequence of PCOS and its etiological factors.

In this respect, studies with metformin in women with PCOS and hypothyroidism have shown a reduction in serum TSH levels (22,23), indicating that treating IR may improve SCH. On the other hand, thyroid hormone replacement (T4) in women with a diagnosis of PCOS also leads to an improvement in the appearance of the ovary and its volume, as well as to a reduction in circulating androgen levels (24). Likewise, studies in rats with induced hypothyroidism have confirmed the increase in the prevalence of PCOS in these animals, indicating that hypothyroidism may induce the appearance of PCOS (25).

Earlier studies have reported a high prevalence of clinical and metabolic signs compatible with PCOS in young women with autoimmune thyroiditis in relation to young women with no thyroid gland abnormalities (5, 26). All these data emphasize the need for further studies to clarify how these disorders are interrelated.

The repercussions of SCH are debatable and routine treatment has been contraindicated (18, 27). Even when metabolic alterations are present, some authors consider that conventional therapies for dyslipidemia and insulin resistance should be the treatment of first choice, a controversial point of view bearing in mind that others have reported that thyroid hormone replacement improves lipid patterns (11). These data suggest that clinical decisions should be based on individual circumstances and on clinical and metabolic manifestations to ensure the optimal management of each individual patient. Nevertheless, increasingly sensitive diagnoses in the most susceptible populations render the indication of generalized therapy difficult in SCH (28).

The association of SCH with cardiovascular disease and with lipid metabolism involves certain controversies (7, 29). SCH has been associated with increases in triglycerides and LDL-c (6, 20, 30-35) and with inconsistent alterations in HDL-c (36-48); however evidence suggests that age, sex, ethnicity and smoking play a role in these findings. Although the current sample is not large, it consists of a group of young women, all of whom have PCOS, with the results showing that LDL-c levels were significantly higher in the women with SCH compared to those with normal thyroid function. These results are in agreement with the data mentioned above; however, no reduction in HDL cholesterol was found in this study when TSH levels were as high as 10 mIU/L. When the clinical and laboratory variables were correlated with thyroid function, a positive, albeit weak, correlation was found between TSH and LDL-c.

A recent study that evaluated women with PCOS and normal thyroid function and women with PCOS and SCH also showed similar levels of total cholesterol, HDL-c and LDL-c in the two groups (49).

With respect to glucose metabolism, mean HOMA-IR values were found to be high in both groups of women with PCOS (those with SCH and those with normal thyroid function), with no statistically significant differences between the two, emphasizing that the relationship between PCOS and IR appears to be unconnected to that of SCH. Furthermore, no difference was found between the two groups with respect to age or BMI, two factors known to affect IR. Ganie et al. also reported no difference between HOMA-IR values between women with PCOS and normal thyroid function and those with PCOS and SCH (6).

Thyroid dysfunction is also associated with female infertility. Therefore, it has been proposed that women with SCH and ovulatory dysfunction, infertility or those

wishing to become pregnant should be treated (22, 24). In the present study, complaints of infertility were reported by around 52% of the women and almost 90% had irregular menstrual cycles; however, there were no statistically significant differences between the groups of women with and without SCH in this respect (data not shown). It should be emphasized, however, that higher prolactin levels were found in the group of women with SCH, a factor that is known to induce infertility and that may be a consequence of increased TRH levels.

No difference was found between the women with PCOS and normal thyroid function and those with PCOS and SCH with respect to BMI, degree of hirsutism, waist circumference or total and free testosterone levels. These findings are in agreement with the results of a study conducted in a similar population (6).

In conclusion, the present findings show a higher prevalence of subclinical hypothyroidism in young women with polycystic ovary syndrome compared to that reported for the population of young women in general; however, further studies with larger sample sizes are required in order to increase understanding on the association between these diseases and provide guidance on which to base therapeutic decisions.

References

1. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006;91:4237-45.
2. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J (Clin Res Ed) 1986;293:355-9.
3. Lamberg BA. Glucose metabolism in thyroid disease. Acta Med Scand 1965;178:351-62.
4. Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol (Oxf) 2007;66:309-21.
5. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004;150:363-9.
6. Ganie MA, Laway BA, Wani TA, Zargar MA, Nisar S, Ahamed F, et al. Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome. Fertil Steril 2011;95:2039-43.
7. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131.
8. Mueller A, Schöfl C, Dittrich R, Cupisti S, Oppelt PG, Schild RL, et al. Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod 2009;24:2924-30.

9. Dittrich R, Kajaia N, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Association of thyroid-stimulating hormone with insulin resistance and androgen parameters in women with PCOS. Reprod Biomed Online 2009;19:319-25.

10. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol 2005;63:670-5.

11. Chubb SA, Davis WA, Davis TM. Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: the Fremantle diabetes study. J Clin Endocrinol Metab 2005;90:5317-20.

12. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. Ann Fam Med 2004;2:351-5.

13. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000;132:270-8.

14. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Hum Reprod 2004;19:41-7.

15. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961;21:1440-7.

16. Vasques AC, Rosado LE, Cássia G, Alfenas RC, Geloneze B. [Critical analysis on the use of the homeostasis model assessment (HOMA) indexes in the evaluation of the insulin resistance and the pancreatic beta cells functional capacity]. Arq Bras Endocrinol Metab 2008;52:32-9.

17. Geloneze B, Tambascia MA. [Laboratorial evaluation and diagnosis of insulin resistance]. Arq Bras Endocrinol Metabol 2006;50:208-15.

18. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.

19. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med 2001;345:260-5.

20. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.

21. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.

22. Rotondi M, Cappelli C, Magri F, Botta R, Dionisio R, Iacobello C, et al. Thyroidal effect of metformin treatment in patients with polycystic ovary syndrome. Clin Endocrinol 2011;75:378-81.

23. Morteza Taghavi S, Rokni H, Fatemi S. Metformin decreases thyrotropin in overweight women with polycystic ovarian syndrome and hypothyroidism. Diab Vasc Dis Res 2011;8:47-8.

24. Muderris II, Boztosun A, Oner G, Bayram F. Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism. Ann Saudi Med 2011;31:145-51.

25. Bagavandoss P, England B, Asirvatham A, Bruot BC. Transient induction of polycystic ovary-like syndrome in immature hypothyroid rats. Proc Soc Exp Biol Med 1998;219:77-84.

26. Ganie MA, Marwaha RK, Aggarwal R, Singh S. High prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: a case-control study. Eur J Endocrinol 2010;162:1117-22.

27. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 2005;90:581-5.

28. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001;86:4585-90.

29. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab 2007;92:1715-23.

30. Lindeman RD, Schade DS, LaRue A, Romero LJ, Liang HC, Baumgartner RN, et al. Subclinical hypothyroidism in a biethnic, urban community. J Am Geriatr Soc 1999;47:703-9.

31. Bauer DC, Ettinger B, Browner WS. Thyroid function and serum lipids in older women: a population-based study. Am J Med 1998;104:546–51.

32. Pirich C, Müllner M, Sinzinger H. Prevalence and relevance of thyroid dysfunction in 1922 cholesterol screening participants. J Clin Epidemiol 2000;53:623-9.

33. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. Clin Endocrinol 1977;7:495-508.

34. Valdemarsson S, Hansson P, Hedner P, Nilsson-Ehle P. Relations between thyroid function, hepatic and lipoprotein lipase activities, and plasma lipoprotein concentrations. Acta Endocrinol 1983;104:50-6.

35. Althaus BU, Staub JJ, Ryff-De Lèche A, Oberhänsli A, Stähelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. Clin Endocrinol (Oxf) 1988;28:157-63.

36. Elder J, McLelland A, O'Reilly DS, Packard CJ, Series JJ, Shepherd J. The relationship between serum cholesterol and serum thyrotropin, thyroxine and tri-iodothyronine concentrations in suspected hypothyroidism. Ann Clin Biochem 1990;27:110-3.

37. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Circulating lipids and minor abnormalities of thyroid function. Clin Endocrinol (Oxf) 1992;37:411-4.

38. Bogner U, Arntz HR, Peters H, Schleusener H. Subclinical hypothyroidism and hyperlipoproteinaemia: indiscriminate L-thyroxine treatment not justified. Acta Endocrinol 1993;128:202-6.

39. Miura S, Iitaka M, Yoshimura H, Kitahama S, Fukasawa N, Kawakami Y, et al. Disturbed lipid metabolism in patients with subclinical hypothyroidism: effect of L-thyroxine therapy. Intern Med 1994;33:413-7.

40. Kung AW, Pang RW, Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism. Clin Endocrinol 1995;43:445-9.

41. Müller B, Zulewski H, Huber P, Ratcliffe JG, Staub JJ. Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. N Engl J Med 1995;333:964-9.

42. Yildirimkaya M, Ozata M, Yilmaz K, Kilinç C, Gündoğan MA, Kutluay T. Lipoprotein(a) concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. Endocr J 1996;43:731-6.

43. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid 2000;10:803-8.

44. Vierhapper H, Nardi A, Grösser P, Raber W, Gessl A. Low-density lipoprotein cholesterol in subclinical hypothyroidism. Thyroid 2000;10:981-4.

45. Müller B, Tsakiris DA, Roth CB, Guglielmetti M, Staub JJ, Marbet GA. Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. Eur J Clin Invest 2001;31:131-7.

46. Efstathiadou Z, Bitsis S, Milionis HJ, Kukuvitis A, Bairaktari ET, Elisaf MS, et al. Lipid profile in subclinical hypothyroidism: is L-thyroxine substitution beneficial? Eur J Endocrinol 2001;145:705-10.

47. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab 2002;87:1533-8.

48. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, et al. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 2003;166:379-86.

49. Celik C, Abali R, Tasdemir N, Guzel S, Yuksel A, Aksu E, et al. Is subclinical hypothyroidism contributing dyslipidemia and insulin resistance in women with polycystic ovary syndrome? Gynecol Endocrinol 2012 Feb 14. [Epub ahead of print], Doi:10.3109/09513590.2011.650765.

Table 1: Comparison of clinical, hormonal and metabolic parameters of women with PCOS and normal thyroid function (TSH < 4.5 mIU/L) and those with subclinical hypothyroidism (TSH 4.5 – 10 mIU/L)

Variables	TSH < 4.5 mIU/L (n=149)			TSH 4.5 - 10 mIU/L (n=19)			p-value
	Mean	SD	Median	Mean	SD	Median	
Age (years)	24.37	5.80	23.89	23.00	5.68	22.97	0.76
BMI (kg/m²)	33.51	7.96	33.03	33.03	10.19	32.00	0.63
Ferriman-Galwey Index	12.23	4.27	12.00	10.50	5.14	9.00	0.15
SBP (mmHg)	116.36	14.42	110.00	114.21	13.87	120.00	0.83
DBP (mmHg)	73.85	9.41	70.00	72.63	9.34	80.00	0.99
WC (cm)	100.76	16.04	103.00	104.75	9.39	103.00	0.62*
HC (cm)	115.20	12.05	118.00	120.00	6.27	119.50	0.42
TT (ng/mL)	1.53	8.50	0.63	0.76	0.34	0.64	0.56
FT (pg/mL)	2.56	1.43	2.30	2.65	0.96	2.79	0.56
FT4 (ng/dL)	1.21	0.19	1.20	1.17	0.17	1.22	0.40*
PRL (ng/mL)	14.04	10.27	12.34	17.74	7.74	16.74	0.01
DHEAS (µg/dL)	178.51	105.73	169.00	243.97	137.93	220.00	0.05
GLU (mg/dL)	87.36	14.61	85.00	89.00	8.94	86.00	0.26
INSUL (µIU/mL)	16.07	11.05	13.70	18.28	8.61	19.60	0.21
HOMA-IR	3.57	2.83	2.84	4.09	2.10	4.00	0.16
CHOL (mg/dL)	181.89	37.95	174.00	188.79	27.87	202.50	0.51*
HDL-C (mg/dL)	47.31	14.20	47.00	42.62	9.76	40.00	0.22
LDL-C (mg/dL)	105.62	32.97	100.00	122.58	25.61	114.50	0.04
TRIG (mg/dL)	143.07	88.08	115.00	147.79	68.63	130.50	0.44

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; TT: total testosterone; FT: free testosterone; FT4: free thyroxine; PRL: prolactin; DHEAS: Dehydroepiandrosterone sulfate; GLU: glucose; INSUL: insulin; HOMA-IR: homeostatic model assessment of insulin resistance; CHOL: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TRIG: triglycerides.

* Student's t-test. All other variables were evaluated using the Mann-Whitney test.

Table 2: Spearman's correlation for TSH values and selected clinical and laboratory parameters of women with PCOS and normal thyroid function (n = 168)

Variables	TSH	
	r	p-value of r
Age (years)	-0.00695	0.93
BMI (kg/m²)	0.06705	0.40
Ferriman-Gallwey Index	-0.00513	0.95
SBP (mmHg)	0.02277	0.77
DBP (mmHg)	0.02619	0.74
WC (cm)	0.15532	0.30
HC (cm)	0.04035	0.80
HOMA-IR	0.03118	0.68
CHOL (mg/dL)	0.08044	0.38
HDL-c (mg/dL)	-0.14305	0.12
LDL-c (mg/dL)	0.19458	0.04
TRIG (mg/dL)	0.14708	0.11

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; HOMA-IR: homeostatic model assessment of insulin resistance; CHOL: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; TRIG: triglycerides.

4. Discussão

A função tireoideana tem importante ação sobre o metabolismo. O hipotireoidismo tem sido alvo de inúmeros estudos, porém mais recentemente tem-se estudado o HSC e suas relações metabólicas, tendo sido considerado importante fator de risco para desordens dos sistemas cardiovascular e endócrino (31, 35, 36). Para populações específicas, como é o caso da SOP, há poucas evidências.

Nesta população tem sido descrita alta prevalência de níveis elevados de TSH e de tireoidite autoimune (21, 22, 51), explicável pela frequência de ciclos anovulatórios, prevalecendo a ação do estrógeno, que estimula o sistema imunológico e predispõe a doenças autoimunes (21).

É mais conhecida a relação entre SOP e RI, considerando-se que a RI desempenha papel importante na gênese da SOP, bem como no aparecimento de alterações metabólicas (4, 13). Quando associadas a níveis de TSH mais elevados, estaria relacionado ao maior risco de dislipidemia e piora nos fatores de risco para DCV (9,12).

Em uma população de mulheres jovens com SOP, objetivou se avaliar se a função tireoidiana poderia precocemente influenciar o aparecimento de RI, antes mesmo de manifestar-se clinicamente como uma disfunção tireoideana. Porém, apesar de ter-se detectado um valor de TSH a partir do qual há um aumento de RI, as mulheres não apresentaram diferença nos parâmetros estudados, de forma a sugerir uma alteração na conduta investigativa ou terapêutica da SOP. Três únicos estudos localizados na literatura mundial também não indicaram evidências suficientes para condutas alternativas, embora tenham obtido níveis de corte de TSH até menores dos que o deste estudo e algumas alterações nos parâmetros da população estudada, como maior IMC e HOMA-IR (8, 9, 41).

Os resultados deste estudo fortaleceram as evidências da importância da RI nas portadoras de SOP, com piora de parâmetros clínicos e metabólicos.

Relacionando especificamente o HSC em jovens com SOP, ficou evidente a maior prevalência desta disfunção da tireoide nesta população do que entre a população geral de jovens. Não foi localizado outro estudo na população brasileira que tenha avaliado tal prevalência.

Quando foram analisados os parâmetros clínicos e metabólicos das mulheres com SOP eutireoidianas e com HSC, observaram-se níveis de LDL mais elevados entre as com HSC. Embora outras alterações metabólicas não tenham sido evidenciadas, deve-se ressaltar que apenas foram estudadas mulheres jovens, provavelmente indicando a necessidade de condutas

preventivas objetivando a redução de complicações que podem ocorrer precocemente ao longo da vida (4, 54, 55).

Estes resultados ressaltam a necessidade de novos estudos com maior número de mulheres com HSC, preferencialmente prospectivos, para avaliar a repercussão destas alterações ao longo dos anos, permitindo a avaliação da interação entre HSC, SOP e RI, fatores que isoladamente ou principalmente em conjunto influenciam negativamente o metabolismo.

5. Conclusões

– O nível sérico de TSH de 2,77mUI/L representa o valor de corte com melhor sensibilidade e especificidade para detectar RI.

– Os parâmetros clínicos e laboratoriais avaliados de mulheres com SOP não diferiram entre as com TSH < 2,77 mUI/L e com TSH entre 2,77 e 10 mUI/L.

– As variáveis: IMC, PAS, PAD, CA, CQ foram significativamente maiores entre as mulheres com SOP com RI do que nas sem RI.

– As mulheres com SOP e HSC apresentaram valores de LDL colesterol e prolactina significativamente maiores do que nas SOP eutireoideas.

– Os níveis séricos de TSH correlacionam-se diretamente aos níveis séricos de LDL colesterol em mulheres com SOP.

6. Referências Bibliográficas

1. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J (Clin Res Ed). 1986;;293(6543):355-9.

2. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab. 2004 ;89(2):453-62.

3. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W et al. Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91(11):4237-45.

4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev. 1997; 18(6):774-800.

5. Women. World Heart Federation. Acesso em 18 de abril de 2012. Disponível em URL: http: // www.worldheart.org/awareness-women.php.

6. Barber TM, McCarthy MI, Wass JA, Franks S. Obesity and polycystic ovary syndrome. Clin Endocrinol (Oxf). 2006;65:137–45.

7. Moghetti P, Tosi F, Castello R, Magnani CM, Negri C, Brun E et al. The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women. J Clin Endocrinol Metab. 1996;81:952–60.

8. Mueller A, Schöfl C, Dittrich R, Cupisti S, Oppelt PG, Schild RL, et al. Thyroid-stimulating hormone is associated with insulin resistance independently of body mass index and age in women with polycystic ovary syndrome. Hum Reprod. 2009;24(11):2924–30.

9. Dittrich R, Kajaia N, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Association of thyroid-stimulating hormone with insulin resistance and androgen parameters in women with PCOS. Reprod Biomed Online. 2009 ;19(3):319-25.

10. Soares EMF, Azevedo GD, Gadelha RGN, Lemos TMAM, Maranhão TMO. Prevalence of metabolic syndrome and its components in Brazilian women with polycystic ovary syndrome. Fertil Steril. 2008;89(3):649-55.

11. Barcellos CRG, Rocha MP, Hayashida SAY, Nery M, Marcondes JAM. Prevalence of abnormalities of glucose metabolism in patients with polycystic ovary syndrome. Arq Bras Endocrinol Metab. 2007;51(4):601-5.

12. Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ, Gans RO. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab. 2001; 86:1206-11.

13. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril. 2005;83(5):1454-60.

14. Carmina E, Lobo RA. Use of fasting blood to assess the prevalence of insulin resistance in women with polycystic ovary syndrome. Fertil Steril. 2004;82:661–5.

15. Dimitriadis G, Mitrou P, Lambadiari V, Boutati E, Maratou E, Panagiotakos DB et al. Insulin action in adipose tissue and muscle in hypothyroidism. J Clin Endocrinol Metab. 2006;91(12):4930-7.

16. Möhlig M, Jürgens A, Spranger J, Hoffmann K, Weickert MO, Schlösser HW et al. The androgen receptor CAG repeat modifies the impact of testosterone on insulin resistance in women with polycystic ovary syndrome. Eur J Endocrinol. 2006;155:127-30.

17. Howard BV. Insulin resistance and lipid metabolism. Am J Cardiol. 1999;84:28J-32J..

18. Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purpose and pitfalls. Obstet Gynecol Surv. 2004;59(2):141-54.

19. Chubb SA, Davis WA, Davis TM. Interactions among thyroid function, insulin sensitivity, and serum lipid concentration: the Fremantle diabetes study. J Clin Endocrinol Metab. 2005;90:5317-20.

20. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab. 2005; 90:581-5.

21. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol. 2004;150(3):363-9.

22. Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol (Oxf). 2007;66(3):309-21.

23. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med. 2001;345:260–5.

24. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008;29(1):76-131.

25. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid. 2003; 13(1):3-126.

26. Völzke H, Lüdemann J, Robinson DM, Spieker KW, Schwahn C, Kramer A et al. The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. Thyroid. 2003; 13(8):803-10.

27. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disease in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol. 1995;43:55–68.

28. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99.

29. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–34.

30. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F et al. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. Clin Endocrinol (Oxf). 1977;7:495–508.

31. Duntas LH, Wartofsky L. Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? Thyroid .2007;17(11):1075-84.

32. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002;87:3221-6.

33. Kabadi UM. Subclinical hypothyroidism: natural course of the syndrome during a prolonged follow-up study. Arch Intern Med.1993;153:957-61.

34. Díez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab. 2004;89(10):4890–7.

35. Uzunlulu M, Yorulmaz E, Oguz A. Prevalence of subclinical hypothyroidism in patients with metabolic syndrome. Endocr J. 2007;54(1):71-6.

36. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228-38.

37. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:501–9.

38. Biondi B, Klein I. Hypothyroidism as a risk factor for cardiovascular disease. Endocrine. 2004;24:1–13.

39. Faber J, Petersen L, Wiinberg N, Schifter S, Mehesen J. Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. Thyroid. 2002;12:319–324.

40. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, et al. Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol. 2005;63:670–5.

41. Ganie MA, Laway BA, Wani TA, Zargar MA, Nisar S, Ahamed F et al. Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome. Fertil Steril. 2011;95(6):2039-43.

42. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. Ann Fam Med. 2004;2:351–5.

43. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000;132:270–8.

44. Bianchi GP, Zaccheroni V, Solaroli E, Vescini F, Cerutti R, Zoli M et al. Health-related quality of life in patients with thyroid disorders. Qual Life Res. 2004; 13:45–54.

45. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M et al. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. Am J Méd. 2002;112:348–54.

46. Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebocontrolled study. J Clin Endocrinol Metab. 2001;86:1110–5.

47. Yazici M, Gorgulu S, Sertbas Y, Erbilen E, Albayrak S, Yildiz O et al. Effects of thyroxin therapy on cardiac function in patients with subclinical hypothyroidism: index of myocardial performance in the evaluation of left ventricular function. Int J Cardiol. 2004;95:135–43.

48. Monzani F, Caraccio N, Kozakowa M, Dardano A, Vittone F, Virdis A et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. J Clin Endocrinol Metab. 2004;89:2099–106.

49. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab. 2007;92:1715–23.

50. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. Hum Reprod Update. 2003;9(2):149-61.

51. Wu X, Zhang Z, Su Y. Functional states of pituitary-ovary, -adrenal and -thyroid axes in women with polycystic ovarian syndrome. Zhonghua Fu Chan Ke Za Zhi.1998;33:153–6.

52. Tudose TI, Zelenetskaia VS, Kozlov GI, Pishchulin AA, Dobracheva AD. Lactotropic and thyrotropic functions of the hypophysis in polycystic ovary syndrome. Problemy Endokrinologii .1986;32:3–7.

53. Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG et al. Thyroid function in humans whith morbid obesity. Thyroid. 2006;16:73-8.

54. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Position statement: glucose intolerance in polycystic ovary syndrome – A position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92(12):4546-56.

55. Carmina E. Cardiovascular risk and events in polycystic ovary syndrome. Climacteric. 2009;12 (S1):22-5.

7. Anexos

7.1. Anexo 1 – Parecer do CEP

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

www.fcm.unicamp.br/pesquisa/etica/index.html

CEP, 25/05/10
(Grupo III)

PARECER CEP: N° 376/2010 (Este n° deve ser citado nas correspondências referente a este projeto).
CAAE: 0288.0.146.000-10

I - IDENTIFICAÇÃO:

PROJETO: **"ASSOCIAÇÃO DO HORMÔNIO ESTIMULADOR DA TIREÓIDE COM RESISTÊNCIA INSULÍNICA E COM PARÂMETROS CLÍNICOS E LABORATORIAIS DA SÍNDROME DOS OVÁRIOS POLICÍSTICOS".**
PESQUISADOR RESPONSÁVEL: Cristina Laguna Benetti Pinto
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 06/05/2010
APRESENTAR RELATÓRIO EM: 25/05/11 (O formulário encontra-se no *site* acima).

II - OBJETIVOS

Avaliar a relação entre os níveis séricos de TSH e parâmetros clínicos e laboratoriais na SOP.

III - SUMÁRIO

Será realizado estudo retrospectivo, com revisão e coleta de dados de prontuários de mulheres com diagnóstico de SOP atendidas no ambulatório de ginecologia endócrina do Departamento de Tocoginecologia, Faculdade de Ciências Médicas da Universidade Estadual de Campinas. Serão excluídas as mulheres que apresentem outras causas de hiperandrogenismo, como tumores produtores de andrógenos, síndrome de Cushing, hiperplasia adrenal congênita, assim como outras desordens endócrinas como hiperprolactinemias, hipo ou hipertireoidismo clínico, ou uso de medicações com ações androgênicas. Serão transferidas para ficha própria do estudo, as dosagens dos hormônios tireoidianos T4Livre e TSH, que serão correlacionados às variáveis dependentes também coletadas do prontuário: Índice de Ferriman-Galley, Índice de massa corpórea, níveis séricos de testosterona total, testosterona livre, glicemia em jejum, insulina em jejum, Homa-IR, colesterol total, HDL e LDL colesterol, triglicérides.

IV - COMENTÁRIOS DOS RELATORES

O projeto apresenta-se bem redigido, com metodologia adequada. Os critérios de inclusão, exclusão dos sujeitos estão bem definidos; cálculo do tamanho amostral e análise estatistica muito bem embasados por cálculos estatísticos. Como trata-se de revisão de prontuários, é pedida dispensa do Termo de Consentimento Livre e Esclarecido. O orçamento é detalhado e será enviado à FAPESP. Considero o projeto adequado a esse tipo de estudo.

V - PARECER DO CEP

O Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP, após acatar os pareceres dos membros-relatores previamente designados para o presente caso e atendendo todos os dispositivos das Resoluções 196/96 e complementares, resolve aprovar sem restrições o Protocolo de Pesquisa, a dispensa do Termo do Consentimento Livre e Esclarecido, bem como todos os anexos incluídos na pesquisa supracitada.

O conteúdo e as conclusões aqui apresentados são de responsabilidade exclusiva do CEP/FCM/UNICAMP e não representam a opinião da Universidade Estadual de Campinas nem a comprometem.

VI - INFORMAÇÕES COMPLEMENTARES

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

Pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.1.z), exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade do regime oferecido a um dos grupos de pesquisa (Item V.3.).

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4.). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projeto do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial (Res. 251/97, Item III.2.e).

Relatórios parciais e final devem ser apresentados ao CEP, de acordo com os prazos estabelecidos na Resolução CNS-MS 196/96.

VII – DATA DA REUNIÃO

Homologado na V Reunião Ordinária do CEP/FCM, em 25 de maio de 2010.

Prof. Dr. Carlos Eduardo Steiner
PRESIDENTE do COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

7.2. Anexo 2 – Ficha de Coleta de Dados

Iniciais: __ __ __ __

Número HC: __ __ __ __ __ __ __ __-__

Número no estudo: __ __ __ __

Data: __ __/__ __/__ __

1-Idade (em anos completos):□□

2-Grau de escolaridade

☐ nenhum ☐ 1 °grau incompleto ☐ 1°grau completo
☐ 2°grau incompleto ☐ 2°grau completo ☐ nível superior

3-Cor

☐ branca ☐ preta ☐ parda ☐ amarela ☐ indígena ☐ outra

4-Número de gestações ☐☐

5-Número de partos ☐☐

6-Número de abortos ☐☐

7-Critérios para diagnóstico da Síndrome dos Ovários Policísticos

☐ espaniomenorreia ou amenorreia
☐ hiperandrogenis
mo clínico
☐ hiperandrogenismo laboratorial
☐ ecografia com ovários multifoliculares

8- Tempo desde o aparecimento dos sintomas: ☐ ☐ ☐ meses

9- Exame físico:

Peso ___ ___ ___ Kg

Altura ___ ___ ___ cm

IMC ___ ____

Índice de Ferriman ___ ___

Acne ☐ ausente ☐ moderada ☐ grave

Circunferência cintura ___ ____ ___ cm

Circunferência Quadril ____ ____ ____ cm

Pressão arterial: sistólica __ __ __ diastólica __ __ __ mmhg

10-Exames laboratoriais

Exame Laboratorial	Resultado	Data
FSH		
LH		
TSH		
T4 LIVRE		
TESTOSTERONA TOTAL		
TESTOSTERONA LIVRE		
SDHEA		
17 OH PROGESTERONA		
PROLACTINA		
GLICEMIA DE JEJUM		
INSULINA BASAL		
TRIGLICÉRIDES		
COLESTEROL TOTAL		
HDL		
LDL		

11-Ecografia pélvica
Volume uterino ___ ___
Vol. ovário direito ___ ___ No de folículos ___ ___ Diâmetro médio __ __ mm
Vol. ovário esquerdo___ ___ No de folículos ___ ___ Diâmetro médio __ __ mm

12- Índice de Homma IR: ___ ___