Methods & Protocols

Renin Angiotensin Aldosterone System in women using injectable hormonal contraceptive: protocol of a comparative observational study of cross-sectional

Sistema Renina Angiotensina Aldosterona em mulheres que utilizam contraceptivo hormonal injetável: protocolo de um estudo observacional comparativo de corte transversal

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ABSTRACT | INTRODUCTION: Oral contraceptives are the most widely used form of birth control, reaching 200 million users since its inception in the 1960. Since 2013, our research group has presented results that suggest that women using Combined Oral Contraceptives (COC) and without other risk factors, have a higher value of C-reactive protein, postprandial lipemia, oxidized low-density lipoprotein and decreased insulin sensitivity, when compared to their counterparts without the use of COC. Recently, it was found that the use of COC increases plasma renin values by 600%, which may explain why the use of this drug is a risk factor for the development of systemic arterial hypertension. Although the use of Injectable Hormonal Contraceptives (IHC) is increasing, we have not found clinical studies that addressed the topic, demonstrating a gap in the scientific literature. **OBJECTIVE:** Compare the values of plasma renin, angiotensin-converting enzyme 1 and aldosterone of women using IHC with women who do not use any hormone-based contraceptives. **METHODS:** Protocol of a comparative observational cross-sectional study, composed of women aged between 18 and 30 years, eutrophic, irregularly active by the International Physical Activity Questionnaire, short version, who have been in continuous use of IHC for at least 6 months or that do not use. The sample will be for convenience and the selected participants will sign the informed consent form. Subsequently, they will answer a standard questionnaire, undergo a physical examination, and be sent to collect blood samples.

KEYWORDS: Contraceptive Agents. Renin-Angiotensin System. Hypertension. Women's Health

RESUMO | INTRODUÇÃO: Os contraceptivos orais são a forma mais utilizada para o controle de natalidade, chegando a 200 milhões de usuárias desde sua iniciação na década de 1960. Desde 2013, nosso grupo de pesquisa tem apresentado resultados que sugerem que mulheres em uso de Contraceptivos Orais Combinados (COC), e sem outros fatores de risco, apresentam maior valor de proteína C reativa, lipemia pós-prandial, lipoproteína de baixa densidade oxidada e diminuição da sensibilidade insulínica, quando comparadas a suas congêneres sem uso de COC. Recentemente, foi verificado que o uso de COC eleva os valores de renina plasmática em 600%, podendo explicar por que o uso desse fármaco é um fator de risco para o desenvolvimento de hipertensão arterial sistêmica. Apesar de o uso de Contraceptivo Hormonal Injetável (CHI) estar aumentando, não encontramos estudos clínicos que abordassem o tema, demonstrando uma lacuna na literatura científica. **OBJETIVO:** Comparar os valores de renina plasmática, enzima conversora de angiotensina 1 e aldosterona de mulheres que utilizam CHI com mulheres que não utilizam nenhum contraceptivo à base de hormônio. **MÉTODOS:** Protocolo de um estudo observacional comparativo de corte transversal, composto por mulheres com idade entre 18 e 30 anos, eutróficas, irregularmente ativas pelo Questionário Internacional de Atividade Física, versão curta, que estão em uso continuado de CHI há pelo menos 6 meses ou que não fazem uso. A amostra será por conveniência, as participantes selecionadas assinarão o termo de consentimento livre e esclarecido. Posteriormente, responderão a um questionário padrão, serão submetidas a um exame físico, e serão encaminhadas para coleta das amostras sanguíneas.

PALAVRAS-CHAVE: Anticoncepcionais. Sistema Renina-Angiotensina. Hipertensão. Saúde da Mulher.

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Introduction

The United Nations reported that in 2019 the number of women of reproductive age using contraceptive methods exceeded 920 million.[1] Among the possibilities offered for birth control, oral contraceptives are the most used form of contraception, reaching 200 million users since its initiation into medicine in 1960.[1]

Since 2013, our research group has presented results that strongly suggest that women without other risk factors, using Combined Oral Contraceptives (COC), have a higher value of C-reactive protein[2], postprandial lipemia[3], low-density lipoprotein oxidized[4] in addition to decreased insulin sensitivity[5], when compared to their counterparts without the use of COC. However, the use of Injectable Hormonal Contraceptives (IHC) has increased. In Brazil, an estimate made in 2014 showed that 5% of women living in urban areas, aged 15 to 49 years and non-pregnant and who use any contraceptive, use IHC.[6]

Recently, we observed that the use of COC increases plasma renin values by 600%[7], which may explain why the use of this drug is a risk factor for the development of systemic arterial hypertension, as pointed out by a meta-analysis including 24 studies and more than 250,000 participants.[8] Furthermore, renin is a fundamental part of the Renin-Angiotensin System (RAS), a system that is currently being discussed in global science, since SARS-CoV-2 uses the angiotensin-2 converting enzyme, another element of this system, to penetrate the cells of the human body.[9]

Despite the interaction between the RAS and SARS-CoV-2, we know that this system regulates various physiological variables that directly impact clinical conditions, such as systemic blood pressure[10], myocardial muscle mass, and strength.[11] Thus, the increasing use of IHC and the clinical importance of the RAS encouraged us to investigate the effects of IHC on the RAS. Furthermore, in a search carried out in the Pubmed database, we did not find clinical studies that had studied this topic, identifying a gap that still exists in the scientific literature.

Objective

Compare plasma renin, angiotensin-1 converting enzyme, and aldosterone values of women using IHC with women not using any hormone-based contraceptive.

Methods

Study design

The research is characterized as a cross-sectional comparative observational study protocol.

Context

The sample will be composed of users of the Family Planning Program of the Ministry of Health in the city of Ibicaraí - BA, recruited from the Family Health Units of the city and stratified into two groups: injectable contraceptive Group (ICG), composed of volunteers who use of IHC for at least 6 months, and the Group Without Contraceptives (GWC) formed by volunteers who have not used any IHC for at least 6 months. The period foreseen for recruiting volunteers, data collection, physical examination, and laboratory collection is in the first half of 2021.

Study population

Irregularly active young women who have been in continued use of IHC for at least 6 months and women with the same medical conditions who do not use IHC.

Eligibility criteria

Women aged between 18 and 30 years, eutrophic, irregularly active by the International Physical Activity Questionnaire short version[12], who have been using IHC for at least 6 months, and women with the same clinical conditions who do not use IHC for at least 6 months.

Women with inconsistent clinical data, diabetic, hypertensive or using antihypertensive drugs, with cardiac, renal, or metabolic diseases, smokers or alcoholics evaluated by the Cut-down, Annoyed, Guilty and Eye-opener (CAGE) questionnaire will be excluded. In addition, women with polycystic ovary syndrome will be excluded because this condition causes complications of menstrual cycle dysregulation, endometrial cancer, and metabolic disorders, such as pancreatic beta-cell dysfunction and elevation of inflammatory markers such as Protein C reactive (PCR).[13]

Data collect

The selected volunteers will answer a standard questionnaire and undergo a physical examination to collect general information about the characteristics of the sample. The physical examination will consist of measurements of Heart Rate (HR) and Blood Pressure (BP) at rest, total body mass, height, and later calculation of the Body Mass Index (BMI) and Abdominal Circumference (AC). This data collection will take place in the physical space of the triage rooms of the Family Health Units in the city.

A Choicemmed pulse heart rate monitor will be used to measure HR. As for the measurement of BP, the recommendations of the American Heart Association will be followed, using a sphygmomanometer for adults duly calibrated by the National Institute of Metrology (INMETRO) and a duo-sonic stethoscope, both from the Premyum brand.

Height will be measured with the aid of a professional Sanny stadiometer with 0.1cm precision, performed with the subjects barefoot and with the buttocks and shoulders supported on a vertical backrest. The total body mass will be measured with a Filizola digital scale, maximum capacity of 150kg, measured by INMETRO and with its own certificate specifying a margin of error of ±100g.

The BMI will be calculated with the measurements of mass and height, according to the following formula: BMI = mass (kg) / height2 (cm). The BMI cutoff points adopted will be those recommended by the IV Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of the Atherosclerosis Department of the Brazilian Society of Cardiology[14], being low weight (BMI < 18.5); eutrophy (BMI 18.5-24.9); overweight (BMI 25-29.9) and obesity (BMI ≥ 30).

To measure the AC, a metallic and flexible measuring tape, brand Wiso will be used with a measurement definition of 0.1cm. AC will be measured at the smallest curvature located between the ribs and the iliac crest without compressing the tissues. When it is not possible to identify the smallest curvature, the measurement will be taken two centimeters above the umbilical scar. The cutoff points adopted for AC will be stipulated according to the degree of risk for cardiovascular diseases for women (AC ≥ 88cm) and men (AC ≥ 102cm).[13]

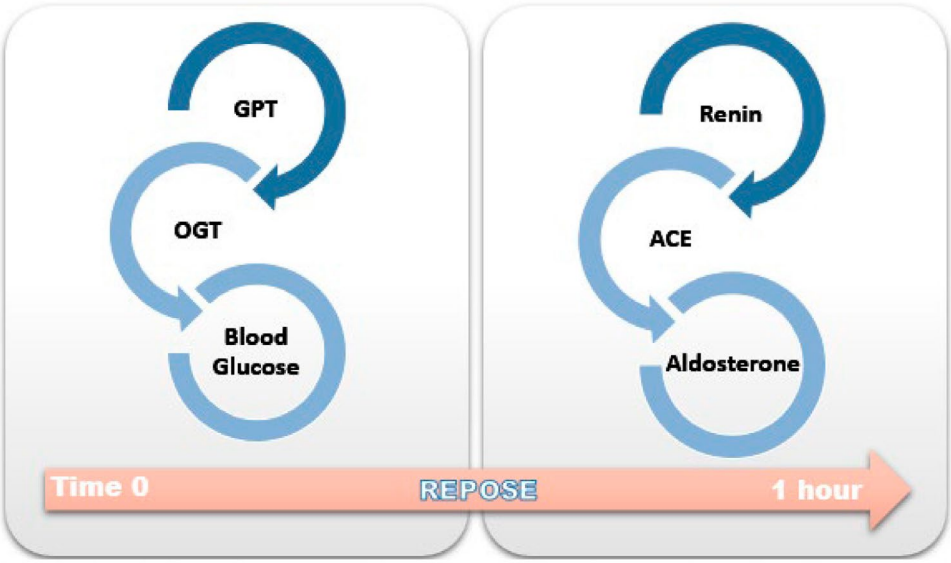
Laboratory collection

All volunteers will be instructed to fast for 12 hours, not change their diet during the test week, not to practice any physical effort other than usual, and not to drink alcoholic beverages 24 hours before the laboratory exam. Furthermore, they will be forwarded to the Laboratory of Clinical Analysis in the municipality of Ibicaraí – BA to collect blood samples.

The collections will be carried out in two moments, at time 0 and after 60 minutes of rest. At time 0, 10mL of blood will be collected to measure Oxaloacetic Glutamic Transaminase (OGT), Glutamic Pyruvic Transaminase (GPT) to assess liver function, and blood glucose to assess sugar levels. The values for OGT and GPT will be obtained by the colorimetric method (Reitman-Frankel), and the values for fasting glucose will be obtained by the enzymatic colorimetric method of Trinder.

Subsequently, the volunteers must remain at rest in the supine position for 60 minutes to measure plasma renin, angiotensin I-converting enzyme, and aldosterone.[15] Renin will be measured by kinetic radioimmunoassay method in plasma with EDTA, values for an angiotensin-converting enzyme will be obtained by the U.V. optimized kinetic method and aldosterone by the radioimmunoassay method. The organization of collections can be seen in figure 1.

Figure 1. Blood collection



ACE: Angiotensin Converting Enzyme; OGT: Oxaloacetic Glutamic Transaminase; GPT: Glutamic Pyruvic Transaminase.

Ethical aspects

The Research Ethics Committee approved this study of the Escola Bahiana de Medicina e Saúde Pública under CAAE nº 35292220.2.0000.5544. The selected volunteers will be previously oriented about the research and sign the free and informed consent form. Two copies will be filled in, one for the volunteer and the other for the researcher. According to Resolution No. 466/2012 of the National Health Council, all ethical and legal precepts for research with human beings will be respected. The Municipal Health Department of the municipality of Ibicaraí – Ba and the Clinical Analysis Laboratory received and signed a letter of consent containing the study information and release for application of the research in the Family Health Units and blood collection.

Variables

Predictor variable - use of IHC
Outcome variables - Plasma renin, angiotensin-1 converting enzyme, and aldosterone.

Primary outcomes

Plasma renin, angiotensin-1 converting enzyme and aldosterone.

Sample size

The sample will be for convenience, targeting 60 participants.

Statistical analysis

Initially, to verify the data distribution, symmetry and kurtosis tests and the Shapiro-Wilk test will be applied. Then, values of variables with normal behavior will be described as mean and standard deviation and values of non-parametric variables as median and interquartile range. Next, categorical variables will be presented as absolute and relative frequency. Finally, for the intergroup comparison of parametric variables, the unpaired bidirectional Student's t-test will be used, and the Mann-Whitney test for non-parametric variables will be used. The significance level adopted for this study will be 5%, and all data will be analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0.

Authors' contributions

Santos PA participated in the conception and writing of the manuscript. Oliveira AM participated in the writing of the manuscript. Petto J participated in the conception, writing of the manuscript, and critical review of the manuscript regarding intellectual content.

Conflicts of interest

No financial, legal, or political conflicts involving third parties (government, companies, and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to grants and funding, advisory board participation, study design, preparation manuscript, statistical analysis, etc.).

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