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ORIGINAL ARTICLE

Cardiovascular risk markers among obese women using the levonorgestrel-releasing intrauterine system: A randomised controlled trial☆

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Atherosclerosis

Summary According to international guidelines, women with obesity without other comorbidities can safely use any hormonal contraceptive (HC). However, limited information is available about contraceptive safety for women with obesity since obesity is an exclusion criterion of most contraceptive clinical trials. As such little is known about the possible risks of HC exposure for women with obesity without comorbidities. One way to assess possible long-term risks in this population, even prior to the development of any clinical disease, is to measure alterations in subclinical atherosclerosis markers. We evaluated the effects of the levonorgestrel-releasing intrauterine system (LNG-IUS) on subclinical markers of cardiovascular risk in women with obesity. This is a randomised clinical trial in which 106 women with obesity [body mass index (BMI) $\geq$ 30 kg/m^2] were randomised to the LNG-IUS (n = 53) or to non-hormonal methods (n = 53) and followed for 12 months. We evaluated waist circumference (WC), blood pressure, blood glucose, insulin, lipid profile, and endothelial function markers (carotid intima-media thickness, brachial artery flow-mediated dilation, and carotid arterial stiffness). At 12 months, BMI (p = 0.005), WC (p = 0.045), and glucose levels (p = 0.015) were significantly lower in the LNG-IUS group than in the control group. We did not find any clinically relevant changes in

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subclinical markers of cardiovascular risk among with obesity women at 12 months after LNG-IUS placement compared to users of non-hormonal contraceptive methods.

Introduction

The prevalence of obesity has increased in recent years, varying according to ethnicity and geographical location. In Brazil, 25% of women present obesity [1,2]. Many of these women with obesity are of reproductive age, and addressing their contraceptive needs by providing them with safe and effective contraceptive methods is essential [3].

According to the World Health Organization's (WHO) medical eligibility criteria (MEC) for contraceptive use, any hormonal contraceptive can be safely used by women with obesity who have no other comorbidities [4]. However, these women are at increased risk for hypertension and metabolic syndrome, which are Category 3 (a condition for which the risks usually outweigh the advantages of using the method) or 4 (a condition that represents an unacceptable health risk if the contraceptive method is used) for combined hormonal contraceptives (CHCs) use. Progestogen-only contraceptives (POCs), especially long-acting reversible contraceptives (LARCs) [implants and levonorgestrel-releasing intrauterine system (LNG-IUS)], and non-hormonal contraceptives can therefore be a safer option for these women [4].

Obesity itself may increase the risk for venous thrombosis two to three folds, even in the absence of associated comorbidities [5]. According to the Royal College of Obstetricians and Gynecologists (from the United Kingdom), the use of CHCs is category 3 for women with obesity with a body mass index (BMI) $\geq 35\,kg/m^2$ [6] and only POCs and non-hormonal methods are eligible for these women [7].

Accumulating evidence indicates that acute and chronic uncontrolled overproduction of oxidative stress-related factors including reactive oxygen species causes cardiovascular diseases, atherosclerosis, and diabetes [8]. Carotid intima-media thickness (c-IMT), arterial stiffness and vascular calcification are considered important markers of atherosclerosis and have been associated with an increased in cardiovascular events [9,10]. Accurate, reproducible and easy detection of these parameters could increase the prognostic value of traditional cardiovascular risk factors in many subjects at low and intermediate risk [10]. Therefore, these markers are useful for evaluating cardiovascular risk before over clinical disease develops, particularly in adolescents or women of reproductive age [11—13].

Since obesity is an exclusion criterion in most contraceptive clinical studies, no randomised studies have previously evaluated the impact of POCs on cardiovascular risk markers in women with obesity. The objective of this study was to evaluate the effects of a LNG-IUS on subclinical markers of cardiovascular risk in women with obesity over a follow-up period of 12 months.

Patients and methods

Study design

This was an open, randomised clinical trial study. Screening was carried out consecutively between April 2009 and October 2010 through radio announcements and print media available at the Hospital of Ribeirão Preto Medical School, University of São Paulo (HCFMRP-USP), and at primary care units in Ribeirão Preto, Brazil. The study was registered at ClinicalTrials.gov (www.clinicaltrials.gov — NCT01320917).

Participants

Inclusion criteria were 18—40 years-old women with a BMI $\geq 30\,kg/m^2$ and $<40\,kg/m^2$ and who desired reversible contraception. Exclusion criteria were as follows: known clinical diseases or diseases classified as category 3 or 4 by WHO MEC for hormonal contraceptives (combined or progestogen only), LNG-IUS, and copper intrauterine device (IUD-Copper) [14]; tobacco smokers; drug addicts or alcoholics; use of hormonal contraception without

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