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Endothelial function in women using levonorgestrel-releasing intrauterine system (LNG-IUS)☆

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Abstract

Background: Oral levonorgestrel has been linked to increased cardiovascular risk, but currently, no information is available on the effect of the levonorgestrel-releasing intrauterine system (LNG-IUS) on endothelial dysfunction. The objective of this study was to assess endothelial function in LNG-IUS users.
Study Design: Sixty women underwent insertion of either an LNG-IUS (n=30) as study group or Copper-T intrauterine contraceptive device (TCu 380A intrauterine device) as control group (n=30). In the midluteal phase of menstrual cycle, endothelium-dependent flow-mediated dilatation (FMD) and endothelium-independent dilatation of brachial artery were studied before and after 3, 6 and 12 months of device insertion. We also assessed the correlation of FMD and serum concentrations of estradiol (E_2), progesterone (P) and LNG.
Results: With LNG-IUS, there was a nonsignificant decrease in mean FMD of brachial artery ($p>.05$) compared with the control group at different time points of the study. Before LNG-IUS, reactive hyperemia caused an 8.3%±1.3% increase in brachial artery diameter compared with 7.1%±1.1%, 7.4%±0.9% and 7.5%±0.9% after 3, 6 and 12 months of LNG-IUS ($p>.05$). The mean±SD LNG plasma levels at 3, 6 and 12 months of LNG-IUS application were 228±87, 204±94 and 191±79 pg/mL, respectively. E_2 levels were comparable in women of both studied groups. Mean P levels were significantly lower after LNG-IUS insertion compared with before device insertion and with the control group ($p<.05$) at all study visits. No correlation was found between LNG levels and FMD.
Conclusions: A nonsignificant change detected in endothelial function in LNG-IUS indicates that it has no increased cardiovascular risk.

Keywords: Levonorgestrel-releasing intrauterine system; Endothelial dysfunction; Flow-mediated vasodilatation

1. Introduction

Endothelial dysfunction is characterized by a proinflammatory, prothrombotic and vasoconstrictive phenotype [1]. Maintenance of nitric oxide (NO) bioavailability through activation of endothelial NO synthesis is of central importance in maintaining vascular homeostasis [2]. The detection of endothelial dysfunction in the brachial artery is an indicator of systemic endothelial dysfunction [3]. Flow-mediated dilation (FMD) has been widely used as a noninvasive technique to assess endothelial function and is known to parallel endothelial function in the coronary arteries [4–6]. FMD serves as an index of NO-mediated endothelium-dependent vasodilator function, so it is regarded as a marker of cardiovascular disease and can determine cardiovascular risk in women [6–8].

FMD is lowest during menstruation (low-estrogen, low-progesterone phase) [9] and has been shown to vary with the rise and fall of estrogen throughout the menstrual cycle [10,11]. Endothelium-dependent vasodilatation increases when circulating levels of estrogen increase naturally or synthetically in women [12,13]. Androgens and orally administered synthetic gestagens with androgenic properties, such as levonorgestrel (LNG), counteract some of the effects of estrogens [14,15]. This is supported by data showing endothelium-dependent vasodilatation increases in men during androgen suppression and decreases in men using anabolic androgenic steroids [16,17].

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Bagger et al. [18] reported that the main factor responsible for endothelial dysfunction in women using hormonal therapy or hormonal contraception is hypoestrogenism. Young women with hypoestrogenism from surgical menopause or premature ovarian failure are at higher risk for cardiovascular disease and show decreased endothelial function compared to age-matched women with normal estrogen levels [19–21]. Hormonal contraceptives have variable effects on vascular function depending on the progestin type, estrogen dose and route of delivery [12]. Each progestin can have dramatically different effects on the body based on the parent molecule from which it was created, its chemical structure, pharmacokinetics, activity and specificity to given receptors [10–12]. It is the androgenic properties inherent to certain progestins that have been blamed for antagonizing the beneficial cardiovascular effects of estrogen [22–24]. Since a number of women are using hormonal contraception, there is increasing importance to understand how variations in progestin type and formulation can impact vascular health in women.

The levonorgestrel-releasing intrauterine system (LNG-IUS) is well known as a highly effective, safe and long-acting contraceptive method [25,26]. Besides its contraceptive use, the hormone-releasing IUS has some therapeutic benefits including a reduction in dysmenorrhea and menstrual bleeding and as endometrial protection in women using estrogen therapy [27]. The LNG-IUS consists of a T-shaped polyethylene frame body with a cylindrical reservoir containing 52 mg of LNG [28,29].

However, despite the amount of information regarding the contraceptive effect and the health benefits of the use of the LNG-IUS, we have been unable to find any study that evaluated its effect on endothelial function. Therefore, this study aimed to evaluate the effects of the LNG-IUS on endothelial function by detection of FMD in healthy, young, reproductive-aged women before LNG-IUS insertion and then after 3, 6 and 12 months of device insertion. In addition, this group of women was compared with a group of women who had been using a TCu 380A intrauterine device (IUD) for the same length of time and who served as a control group.

2. Participants and methods

This study was conducted at the Jeddah Clinic Hospital, Jeddah, Saudi Arabia, between October 2009 and September 2011. The study was designed as a nonrandomized, prospective, observational, comparative protocol.

Women were eligible to participate if they chose to use an intrauterine contraceptive device as a method of contraception for a duration of more than 1 year. The type of device inserted (LNG-IUS or Copper-T) was chosen by the patient. The Hospital Review Board approved the study, and all participants signed an informed consent. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki [30].

Sixty women underwent insertion of either an LNG-IUS (n=30) (Mirena®, Schering Health, Berlin, Germany), considered as the study group, or Copper-T intrauterine contraceptive device (IUD) (n=30) (TCu 380A IUD, Schering, Vienna, Austria), considered as the control group. The subjects were 18–35-year-old normally active women not taking any cardiovascular medications or prior hormonal treatment before. All patients had regular menstrual cycles (24–35 days of interval), uterine size corresponding to a sound measure of the endometrial cavity of 8–10 cm, a normal cervical smear result within 12 months and normal breast palpation.

All subjects were screened to ensure that they did not have any of the following health conditions: cardiac disease, obesity, hypertension, hypercholesterolemia, metabolic disorders, menstrual disorders, or a personal or family history of blood clots. Absolute contraindications for IUD insertion include pregnancy, active sexually transmitted disease including pelvic inflammatory diseases within the previous 3 months, along with sepsis following childbirth or abortion. Owing to the progestational component, Mirena is contraindicated in patients who have a current deep venous thrombosis, active liver disease, or hormone-responsive tumors of the breasts or ovaries [27].

2.1. Protocol

All gynecologic assessments and procedures were done by the same gynecology researcher (Selim M.F.). Also, all participants were screened for cardiovascular disease and assessed for endothelial function by a cardiologist (Hussein A.F.) who was blind about the type of contraceptive device inserted in the studied woman.

Each woman eligible for the study was examined four times, the first in the midluteal phase 6–9 days before the expected onset of menstruation. LNG-IUS or TCu 380A insertion was performed as an office procedure within 7 days of the start of menstruation [27]. The second, third and fourth examinations took place in midluteal phase 3, 6 and 12 cycles after device insertion or 3, 6 and 12 months after device insertion in cases of LNG-IUS women who reported amenorrhea.

At each examination visit, gynecological reassessment was done followed by cardiologic examination that includes the heart rate, mean arterial blood pressure and endothelial functions. A blood sample was taken from a peripheral vein; after coagulation, the serum was separated and frozen at −20°C until measurement of serum estradiol (E_2), progesterone (P) and LNG concentrations by using standard radioimmunoassay method [31]. A serum value corresponding to <73.4 pmol/L was beyond the detectable limit for E_2, a serum value <0.76 nmol/L was beyond the detectable limit for P, and a serum value <47 pg/mL was beyond the detectable limit for LNG. The intraassay and interassay variations for E_2, P and LNG were less than 15%, 20% and 10%, respectively.