Sexual Dysfunction and Metabolic/Hormonal Changes in Women Using Long-Term Hormonal and Non-Hormonal Contraceptives

Igor Fernando de Aquino Moreira  
Faculdade de Ciencias Medicas de Minas Gerais

Maria Passos Bianchini  
Faculdade de Ciencias Medicas de Minas Gerais

Gabrielle Rodrigues Campos Moreira  
Faculdade de Ciencias Medicas de Minas Gerais

Alessandra Maciel Almeida  
Faculdade de Ciencias Medicas de Minas Gerais

Bruno Almeida Rezende (✉ bruno.rezende@cienciasmedicasmg.edu.br)  
Faculdade de Ciencias Medicas de Minas Gerais  
https://orcid.org/0000-0002-4460-0572

Research article

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Abstract

Background

Female sexual dysfunction is a common condition that negatively impacts the emotional health and quality of life of the affected individuals. Long-acting reversible contraceptives (LARCs) are becoming increasingly popular due to their effectiveness and convenience. LARCs can be hormonal (etonogestrel releasing implant—ENG and Levonorgestrel intrauterine system—LNG) or non-hormonal (copper intrauterine device—CuIUD and copper-silver intrauterine device—SIUD). There are very few studies that assess the influence on LARCS on sexual function are lacking. This study aimed to assess changes in sexual function as well as metabolic and hormonal parameters in women after implantation with LARCs.

Methods

In this prospective cohort study, we assessed 80 women who visited the Military Police Hospital in Brazil for LARCs placement. The study participants were divided into 4 groups according to the type of LARC received: ENG n = 17; LNG n = 21, CuIUD n = 18 and SIUD n = 23. The four groups were evaluated twice (prior to LARC placement and approximately 3 months later) for sexual function, using the Female Sexual Function Index (FSFI) and Female Sexual Quotient (QS-F) questionnaires. Metabolic and hormonal parameters were also assessed using blood tests. p < 0.05 was considered to indicate statistical significance.

Results

We observed an improvement in sexual function with CuIUD placement according to QS-F (p < 0.017) and SIUD (FSFI: p = 0.06 and QS-F: p < 0.001). However, ENG worsened sexual function according to FSFI and QS-F (p < 0.001 and p = 0.003), across all domains. A decrease in sex hormone-binding globulin (SHBG) was observed for all groups (LNG: p = 0.019; ENG: p = 0.024; CuIUD: p = 0.010; SIUD: p = 0.022) and an increase in total testosterone levels (p = 0.007 and p = 0.003) and prolactin (p = 0.049 and p = 0.001) with CuIUD and SIUD placement. Hemoglobin levels increased with LIS (p < 0.001) and ENG (p = 0.025) and decreased with CuIUD placement (p < 0.001).

Conclusion

The use of non-hormonal LARCS improved sexual function, especially in the desire domain. Etonogestrel implants, had a negative influence on sexual function, probably by blocking ovarian function, and thus reducing the production of androgens and estrogens. SIUD placement was superior as it improved sexual function, interfered less with hormonal levels, and did not decrease hemoglobin levels.

Background

Contraceptive techniques have progressively improved over the past few years since contraceptive pills were approved in the 1960s. The emergence of new hormonal types, dosages, and administration routes increased the effectiveness, safety and convenience of these devices (1). Long-term reversible contraceptives (LARCs) have shown greater effectiveness and continuity compared to short-term contraceptive methods (2). Non-hormonal LARCs include the copper intrauterine device (CuIUD) and silver intrauterine device (SIUD). These devices gradually release copper in the uterus, causing inflammatory reactions that lead to endometrial and mucus changes as well as reduced tubal motility, making the environment hostile to spermatozoids (3). Hormonal LARCs are represented by the levonorgestrel intrauterine system (LNG) and the etonogestrel-releasing implant (ENG). LNG has a stem that releases synthetic progestin in small amounts in the uterus, causing cervical mucus thickening, endometrial atrophy, tubal motility and ciliary movement inhibition. In addition, it gets absorbed into the bloodstream and causes an ovarian function block (3). Moreover, the device generally acts in the same way as the copper IUD—changing the uterus environment to prevent pregnancy. ENG is a subcutaneous device that systematically releases a progesterone-like synthetic substance, thereby preventing ovulation, changing the cervical mucus, and hindering the entrance of spermatozoids. This is considered the most effective contraceptive method available in the world (4).
Regardless of costs, women have preferred the use of LARCs as contraceptive methods due to their ease of use and lower incidence of side effects compared to oral contraceptives combining estrogen and progesterone (5). The use of oral contraceptives may have a negative effect on the woman's sexual function, which may cause the discontinuation of the method (6). In addition, they are often associated with important metabolic changes caused by the estrogenic component of the drug, such as increased insulin resistance (7), changes in the lipid profile (increased LDL and decreased HDL), and increased risk of cardiovascular incidents (8). Combined oral contraceptives increase thrombo-embolic events by two to four times (9, 10), and some studies suggest that these medications increase the risk of breast cancer (11).

In addition to being very effective as a contraceptive, hormonal LARCs are well known for being effective in decreasing pelvic pain and menorrhagia (2). Non-hormonal LARCs, on the other hand, may interfere less with hormonal and metabolic parameters and, for this reason, may be preferred by some women and professionals concerned with the consequences of continuous progesterone release. These devices can reduce the fear of unwanted pregnancy, promoting a more relaxed and pleasurable sexual experience and, thus, improving the user's sexual function (12). This may be possible because a satisfactory sexual response and the perception of sexual pleasure during intercourse is influenced by a complex multifactorial set, involving biological, psychological, and environmental factors (12). The way LARCs affect female sexual experiences have only been studied by researchers in the last few years (13). Thus, further studies are needed to determine the influence of these devices on the female sexual function. Oral contraceptives have garnered more attention since the 1970s as these medications have been associated with decreased libido. This may be related to androgen metabolism, which increases the sex hormone-binding globulin (SHBG) and concomitantly decreases free testosterone and other androgens (14, 15).

Based on the association between sexuality and use of contraception, the aim of this study was to assess sexual function changes in women after the implantation of hormonal and non-hormonal LARCs, in addition to evaluating, changes in metabolic and hormonal parameters.

**Methods**

**Study design**

This is a prospective, cohort study conducted from October 2018 to October 2019, at the General Gynecology Clinic of the Military Police Hospital of Minas Gerais, Brazil.

**Study participants**

We included women between the ages of 20–35 years who expressed the desire to use LARCs. Inclusion criteria included the desire for the use of contraception for a minimum of one-year; an active sex life (more than four relationships in the previous month); and normal oncotic cytology.

Exclusion criteria included the evidence of adrenal, cardiovascular, liver or kidney disease; uncontrolled hypothyroidism; diabetes; hyperprolactinemia; severe arterial hypertension; gynecological abnormalities (fibroids, endometriosis, congenital abnormalities, and active uterine infections); clinical history of thromboembolic disease or thrombophilia; smoking; pregnancy, lactation or abortion in the previous four months; any malignant or pre-malignant disease; history of migraines; and use of antidepressant and anticonvulsant medications.

Detailed information was provided on the duration of the study and the place of implantation. Each patient chose the desired type of LARC available, which depended on the number of samples provided by the laboratories: i) CuIUD (Andalan Classic Cu 380®, DKT do Brasil, São Paulo, Brazil) (42 samples), ii) SIUD (Andalan Silverex®, DKT do Brasil, São Paulo, Brazil) (28 samples), iii) LNG (Mirena®. Bayer SA, Bayer Oy, Turku, Finland) (32 samples), iv) ENG (Implanon®, Schering-Plough, New Jersey, USA) (19 samples). In addition to receiving the devices free of charge, there was no cost to implant the selected method.

The participants were allocated into four groups by individual interest in the available methods, always respecting the WHO eligibility criteria for each case (16): (16): CuIUD group (copper intrauterine device), SIUD group (silver intrauterine device), LNG group (levonorgestrel intrauterine system), and ENG group (etonogestrel-releasing implant).

[place Fig. 1 here]
Sexual function Instruments

Sexual function was assessed using the Female Sexual Quotient (QS-F) and Female Sexual Function Index (FSFI) questionnaires.

The QS-F is a questionnaire developed by the Program on Sexuality Studies of the Institute of Psychiatry of Hospital das Clínicas, School of Medicine of the University of São Paulo (IPq/HCFMUSP) and validated specifically for the Brazilian female population (17). The instrument consists of ten questions with answers scored on a scale from zero to five, with zero indicating “never”, and five, “always”. It assesses the various phases of the sexual response cycle, in addition to the domains desire and sexual interest, foreplay, excitement and harmony, comfort, and orgasm and satisfaction, identifying specific dysfunctions and sexual difficulties (18). The final score obtained is the result of the sum of the points of all questions multiplied by two, which results in a score ranging from 0 to 100. The closer to 100, the greater the sexual performance/satisfaction. Namely: 82–100 points (good to excellent), 62–80 points (fair to good), 42–60 points (unfavorable to fair), 22–40 points (bad to unfavorable), 0–20 points (null to bad). Details on the calculation of the final score can be found in the study by Abdo et al. (19).

The FSFI was developed in the United States in the 2000s, and is one of the main instruments used to assess female sexual function (20, 21). This instrument was translated into and validated for the Portuguese language (21, 22). It consists of 19 multiple-choice questions with increasing scores ranging from 0 to 5 regarding the presence of the questioned function, and six domains (desire, excitement, vaginal lubrication, orgasm, sexual satisfaction, and pain). The total score can vary from 2 to 36 points, with values ≤26 indicating sexual dysfunction (21).

A questionnaire proposed by Higgins et al. (23) on the reasons why patients chose their contraceptive method was administered in the first stage of the study. This questionnaire had seven direct questions on the importance of each of the reasons presented for choosing the contraceptive method. Patients should choose between extremely important, very important, slightly important, and not at all important.

Clinical Procedures

The general medical history of all participants was investigated by the same gynecologist and they underwent gynecological examination as is routinely performed in the gynecology service of the Military Hospital of Minas Gerais. At the first consultation, the material for Pap smear was collected according to the Brazilian Guideline for cervical cancer screening of the José Alencar Gomes da Silva National Cancer Institute (24).

The study participants were assessed for clinical, metabolic, and hormonal parameters and sexual function at two different times during the study (at the initial evaluation and approximately three months after the implantation of the contraceptive device). At the first consultation, blood samples were collected for the following tests: CBC, CRP, blood glucose, glycated hemoglobin, insulinemia, prolactin, TSH, free T4, free and total testosterone, and lipid profile.

Other information relevant to the study, such as sociodemographic data, previous medical history and smoking habit were obtained from the medical records of the Military Police Hospital of Minas Gerais.

LARC implantation followed the recommendations provided by the manufacturers and the care recommended by the Brazilian Federation of Gynecology and Obstetrics (Febraogo).

Statistical analysis

Qualitative variables were represented as frequencies, and quantitative variables as mean ± standard deviation (median). The quantitative variables were analyzed with the Shapiro-Wilk normality test. The Wilcoxon or the Student’s t tests for paired samples were used to compare quantitative variables of quality of life before and after implantation. The association between the reasons for choosing the methods and the devices was assessed by binomial logistic regression. The analyses were performed using the free R software version 3.5.2 and p < 0.05 was considered significant.

Results

A total of 121 women agreed to participate in the study and signed the Informed Consent Form in the first stage of the study. Of these, 41 did not attend the follow-up consultation or attended it outside the proposed period. A total of 80 patients completed the study, with
the following distribution: LNG (n = 21), ENG (n = 17), CuIUD (n = 18), and SIUD (n = 23) (Fig. 1). The mean time between the first and second stage was 96 ± 10 days, the shortest period between stages was 78 days and the longest was 109 days.

The groups were homogeneously aged, with a mean age of 28.2 ± 4.3 years. Most of the patients had a college degree and were in a relationship of more than five years. Half of the patients reported practicing physical activity on a regular basis at least three times a week, with a minimum duration of one hour per activity. Most women had not given birth (58.4%) (Table 1).

Table 1
Socio-demographic characteristics of the study cohort

|                     | LNG (n = 22) | ENG (n = 17) | CuIUD (n = 18) | SIUD (n = 23) | Total (n = 80) |
|---------------------|-------------|-------------|---------------|--------------|----------------|
| Age (years)         | 28.3 ± 4    | 28.2 ± 4.2  | 27.8 ± 4.6    | 28.6 ± 4.3   | 28.2 ± 4.3     |
| "Relationship length" (years)* |             |             |               |              |                |
| less than 1         | 7 (31.8%)   | 2 (12.5%)   | 1 (5.6%)      | 5 (23.8%)    | 15 (19.5%)     |
| 1 to 5              | 6 (27.3%)   | 4 (25%)     | 4 (22.2%)     | 6 (28.6%)    | 20 (26.0%)     |
| 5 to 10             | 5 (22.7%)   | 5 (31.2%)   | 9 (50%)       | 8 (38.1%)    | 27 (35.1%)     |
| More than 10        | 4 (18.2%)   | 5 (31.2%)   | 4 (22.2%)     | 2 (9.5%)     | 15 (19.5%)     |
| Education           |             |             |               |              |                |
| High School         | 2 (9.1%)    | 3 (17.6%)   | 8 (44.4%)     | 5 (21.7%)    | 18 (22.5%)     |
| College / University| 15 (68.2%)  | 11 (64.7%)  | 5 (27.8%)     | 15 (65.2%)   | 46 (57.5%)     |
| Post-graduation     | 5 (22.7%)   | 3 (17.6%)   | 5 (27.8%)     | 3 (13%)      | 16 (20%)       |
| Physical activity (3 h / week) |             |             |               |              |                |
| Parturition         | 11 (50%)    | 6 (35.3%)   | 6 (33.3%)     | 17 (73.9%)   | 40 (50%)       |
| 0                   | 15 (71.4%)  | 9 (52.9%)   | 7 (41.2%)     | 14 (63.6%)   | 45 (58.4%)     |
| 1                   | 3 (14.3%)   | 7 (41.2%)   | 9 (52.9%)     | 7 (31.8%)    | 26 (33.8%)     |
| 2                   | 3 (14.3%)   | 1 (5.9%)    | 1 (5.9%)      | -            | 5 (6.5%)       |
| 3 or more           | -           | -           | -             | 1 (4.5%)     | 1 (1.3%)       |

* Variables have missings. (LNG) levonorgestrel intrauterine system; (ENG) etonogestrel-releasing implant; (CuIUD) copper intrauterine device; (SIUD) silver intrauterine device.

Table 2 shows the criteria used by the patients to choose the contraceptive method. Most of them reported that it is very to extremely important that the contraceptive method is effective. In addition, they reported that it was very or extremely important not to reduce libido and not to interrupt sex (93.6% and 83.8% of the total patients in the study, respectively). The only point presenting statistically significant differences between the groups was the choice of the method without hormones - non-hormonal LARCs (CuIUD and SIUD) compared to the hormonal method ENG (P < 0.001).
As for the hormonal and metabolic parameters evaluated in both stages of the study (Table 3), all LARC groups showed decreased levels of SHBG following implantation: LNG (p = 0.019), ENG (p = 0.024), CuIUD (p = 0.010), and SIUD (p = 0.022). Following implantation, increased total testosterone levels were observed in the non-hormonal LARC groups (CuIUD (p = 0.007) and SIUD (p = 0.003)), increased free T4 levels were seen in ENG (p = 0.034), and decreased prolactin in CuIUD (p = 0.049) and SIUD (p = 0.001) groups. Lipid levels showed no significant changes between the two stages of the study for the groups studied. Decreased insulinemia was observed in the LNG (p = 0.002) group. A slight increase in hemoglobin levels was observed in the hormonal LNG (p < 0.001) and ENG (p = 0.025) groups, while a decrease was observed in the CuIUD (P < 0.001) group. SIUD showed no significant hemoglobin levels (P = 0.055). When comparing sexual function between the two stages of the study, using both the FSFI (Table 4) and QS-F (Table 5) instruments, LNG users presented no significant changes in the domains evaluated. In contrast, ENG users presented worse results in all domains assessed by both instruments between the two stages of the study (p-values for total FSFI (p < 0.001) and QS-F scores (p = 0.003), Tables 4 and 5). For non-hormonal LARCs, however, the data show an improvement in sexual function, since the total score in both instruments showed statistically significant differences for SIUD [FSFI (p = 0.06) and QS-F (p < 0.001)], and CuIUD [QS-F (p = 0.017)] (Fig. 2). The domain desire was highlighted for presenting significant improvement in both instruments for both non-hormonal methods, CuIUD (p = 0.012) and SIUD (p < 0.001) in FSFI, and CuIUD (p = 0.004) and SIUD (p = 0.009) in QS-F.

**Table 2**

| Reason for choosing the control method | Total (n = 80) | LNG (n = 22) | ENG (n = 17) | CuIUD (n = 18) | SIUD (n = 23) | P-value |
|---------------------------------------|---------------|-------------|-------------|--------------|-------------|---------|
| It's the most effective method (quite/extremely important) | 78 (97.5%) | 21 (95.5%) | 17 (100%) | 17 (94.4%) | 23 (100%) | 0.567 |
| It doesn't reduce my libido (quite/extremely important) | 75 (93.6%) | 19 (86.4%) | 17 (100%) | 17 (94.4%) | 22 (95.7%) | 0.353 |
| It doesn't interrupt sex (quite/extremely important) | 67 (83.8%) | 16 (72.7%) | 14 (82.4%) | 16 (88.9%) | 21 (91.3%) | 0.075 |
| It is acceptable to my partner (quite/extremely important) | 41 (51.2%) | 16 (72.7%) | 12 (70.6%) | 12 (66.7%) | 12 (51.2%) | 0.489 |
| It doesn't contain hormones (quite/extremely important) | 57 (71.3%) | 11 (50%) | 7‡ (41.2%) | 17‡ (94.4%) | 23* (100%) | <0.001 |
| It's recommended by my friends (quite/extremely important) | 39 (48.8%) | 13 (59.1%) | 7 (41.2%) | 9 (50%) | 10 (45.5%) | 0.711 |
| It's in line with my religious beliefs (quite/extremely important) | 22 (30.4%) | 9 (40.9%) | 4 (23.5%) | 2 (11.1%) | 7 (30.4%) | 0.145 |

LNG: levonorgestrel intrauterine system; ENG: etonogestrel-releasing implant; CuIUD: copper intrauterine device; SIUD: silver intrauterine device. The p-values refer to the binary logistic model, and the symbols ‡ and * indicate the pairs in which they differ.)
Table 3
Hormonal and metabolic parameters at the different stages of the study for the 4 types of LARCs evaluated.

| Parameter                  | LNG stage 1 | LNG stage 2 | ENG stage 1 | ENG stage 2 | CuIUD stage 1 | CuIUD stage 2 | SIUD stage 1 | SIUD stage 2 |
|----------------------------|-------------|-------------|-------------|-------------|---------------|---------------|-------------|-------------|
| SHBG (nmol/L)              | 97.5±79(68.8) | 51.7±17.1(52.6) | 112.5±73.7(84.4) | 61.8±18(63.5) | 71.4±51.2(54.9) | 46.1±13.4(47.3) | 100.4±79.2(77) | 38.2±16.1(32.7) |
| P-value                    | 0.019^W     | 0.024^T     | 0.010^W     | 0.022^W     |               |               |             |             |
| Total testosterone (mg/dL) | 31.3±21.2(24.4) | 33.5±8.7(32) | 26±15.8(21.2) | 26.3±7(27.3) | 27.4±17.1(22.1) | 32.3±8.8(31.6) | 25.3±9.6(24) | 32.7±8.8(34.8) |
| P-value                    | 0.157^W     | 0.679^W     | 0.007^W     | 0.003^T     |               |               |             |             |
| Free testosterone (mg/dL)  | 0.4±0.5(0.2) | 0.3±0.3(0.3) | 0.3±0.3(0.2) | 0.3±0.1(0.3) | 1±2.5(0.3)    | 1.8±5.8(0.3)  | 1.1±3.9(0.2) | 0.4±0.2(0.3)  |
| P-value                    | 0.985^W     | 0.451^W     | 0.208^W     | 0.296^W     |               |               |             |             |
| TSH (mU/L)                 | 2.1±1(1.8) | 2.1±0.7(2.2) | 2±1(1.6) | 2.2±0.8(2.1) | 2.1±1.7(1.5) | 1.9±1(1.6)    | 2.5±1.9(2.1) | 1.7±0.7(1.7) |
| P-value                    | 0.686^T     | 0.278^W     | 1.000^W     | 0.268^W     |               |               |             |             |
| Free T4 (ng/dL)            | 0.9±0.2(0.9) | 0.9±0.2(0.9) | 0.9±0.3(0.9) | 1.1±0.2(1.1) | 1±0.3(1)      | 1.1±0.2(1.1)  | 1±0.2(1) | 1±0.2(1) |
| P-value                    | 0.813^W     | 0.034^T     | 0.411^T     | 0.106^T     |               |               |             |             |
| Prolactin (ng/mL)          | 19.3±18.8(12.1) | 10.8±5.1(9.3) | 20.5±15.1(13.9) | 12.5±5.6(11.2) | 17.9±13.6(12.6) | 11.6±5.8(9.3) | 14.9±9.6(10.9) | 10.1±3.2(9.4) |
| P-value                    | 0.130^W     | 0.131^W     | 0.049^W     | 0.001^W     |               |               |             |             |
| Insulin (mU/L)             | 7.4±3.1(6.6) | 6.3±1.7(6.4) | 6.5±4.9(5.4) | 6.6±2.2(5.7) | 6.7±3.8(6)    | 6.9±3.1(6.2)  | 6.6±5.1(5.3) | 6.2±3(5.3) |
| P-value                    | 0.002^T     | 0.350^W     | 0.379^W     | 0.850^W     |               |               |             |             |
| HDL (mg/dL)                | 59±16.6(54) | 60.8±11.7(57) | 55±12.4(55) | 53.1±10.8(52) | 58.1±15.9(55) | 60.5±11(55)  | 62.1±16.2(59) | 60.8±11.3(55) |
| P-value                    | 0.542^W     | 0.647^T     | 0.332^W     | 0.829^T     |               |               |             |             |
| Triglycerides (mg/dL)      | 84.5±40.7(71.5) | 83.5±23.5(78) | 98.5±47.8(100) | 86.1±27.5(85) | 72.5±36.6(66.5) | 75.8±24.8(73.5) | 85.9±38.2(70) | 78.8±26.6(71) |
| P-value                    | 0.781^W     | 0.207^T     | 0.233^W     | 0.478^W     |               |               |             |             |
| LDL (mg/dL)                | 97.7±22.5(100.5) | 103.6±21.5(103) | 93.6±30.4(88) | 93.1±22.5(88) | 105.3±26.7(100.5) | 107.5±24(101) | 101.1±21.7(100) | 103.1±16.2(105) |
| P-value                    | 0.051^T     | 0.928^W     | 0.615^W     | 0.509^T     |               |               |             |             |
| Fasting glycemia (mg/dL)   | 82±6.7(82.5) | 80.4±4.1(81) | 80.6±6.3(83) | 78.9±9.6(82) | 79.3±9(79.5)  | 80.1±5.2(81)  | 80.8±7.5(81.5) | 80.1±4.4(81) |
| P-value                    | 0.122^T     | 0.345^W     | 0.690^W     | 0.631^T     |               |               |             |             |
| Glycatedhemoglobin (%)     | 5.3±0.4(5.3) | 5.2±0.4(5.2) | 5.1±0.3(5.1) | 5.2±0.2(5.3) | 5.4±0.4(5.5)  | 5.2±0.3(5.2)  | 5.3±0.3(5.2) | 5.3±0.3(5.2) |
| P-value                    | 0.061^T     | 0.059^W     | 0.054^W     | 0.944^W     |               |               |             |             |

LNG: levonorgestrel intrauterine system; ENG: etonogestrel-releasing implant; CuIUD: copper intrauterine device; SIUD: silver intrauterine device. SGBH: sex hormone binding globulin; paired samples Wilcoxon test, ^P^ Paired Student's t-test. Data presented as mean ± SD (median).
| Parameter                | LNG       | ENG       | CuIUD     | SIUD      |
|--------------------------|-----------|-----------|-----------|-----------|
|                          | stage 1   | stage 2   | stage 1   | stage 2   |
| Hemoglobin (g/dL)        | 13.4 ± 0.8(13.6) | 13.8 ± 0.6(13.4) | 13.4 ± 1.3(13.2) | 13.7 ± 0.8(13.5) |
|                          | 13.7 ± 0.8(13.5) | 13.2 ± 0.6(13.2) | 13.4 ± 0.8(13.5) | 15 ± 7(13.2)    |
| P-value                  | < 0.001W  | 0.025W    | < 0.001T  | 0.055W    |
| LNG: levonorgestrel intrauterine system; ENG: etonogestrel-releasing implant; CuIUD: copper intrauterine device; SIUD: silver intrauterine device. SGBH: sex hormone binding globulinW paired samples Wilcoxon test, T Paired Student's t-test. Data presented as mean ± SD (median). |

Table 4
Comparison of domain scores for Female Sexual Function Index (FSFI) questionnaire in the different stages of the study for the 4 types of LARCs evaluated.

| Domain       | LNG       | ENG       | CuIUD     | SIUD      |
|--------------|-----------|-----------|-----------|-----------|
|              | Stage 1   | Stage 2   | Stage 1   | Stage 2   |
| Desire       | 4 ± 0.9(3.9) | 4.3 ± 0.9(4.2) | 3.5 ± 1.1(3.6) | 2.6 ± 0.9(2.4) |
| P-value      | 0.057W    | < 0.001T  | 0.012T    | < 0.001W  |
| Arousal      | 4.8 ± 0.9(4.8) | 4.8 ± 0.9(4.8) | 4.4 ± 0.9(4.8) | 3.4 ± 1.3(3.6) |
| P-value      | 0.702T    | 0.002W    | 0.305T    | 0.005W    |
| Lubrication  | 5 ± 0.9(4.8) | 5.2 ± 0.8(5.4) | 4.7 ± 1.2(4.8) | 3.5 ± 1.4(3.9) |
| P-value      | 0.068W    | 0.001T    | 0.958W    | 0.029W    |
| Orgasm       | 4.6 ± 1.4(4.8) | 4.6 ± 1.4(4.8) | 4.3 ± 1.2(4.4) | 3.3 ± 1.4(3.2) |
| P-value      | 0.786W    | 0.002W    | 0.323W    | 0.305W    |
| Satisfaction | 5 ± 1.2(5.4) | 5.2 ± 0.9(5.4) | 5.2 ± 0.9(5.2) | 4.1 ± 1.3(4.4) |
| P-value      | 0.201W    | 0.002W    | 0.156W    | 0.130W    |
| Pain         | 5.5 ± 0.7(6) | 5.5 ± 1(6) | 5.1 ± 1.3(6) | 4.3 ± 1.6(4.8) |
| P-value      | 0.759W    | 0.006T    | 0.050W    | 0.061W    |
| Total Score  | 28.9 ± 4.8(28.7) | 29.6 ± 4(29.8) | 27.1 ± 5.3(27.6) | 21.2 ± 6.9 (21.5) |
| P-value      | 0.289W    | < 0.001W  | 0.191W    | 0.006T    |

LNG: levonorgestrel intrauterine system; ENG: etonogestrel-releasing implant; CuIUD: copper intrauterine device; SIUD: silver intrauterine device. W paired samples Wilcoxon test, T Paired Student's t-test. Data presented as mean ± SD (median).
Table 5
Comparison of domain scores for Female Sexual Quotient (QS-F) questionnaire in the different stages of the study for the 4 types of LARCs evaluated.

| Domain          | LNG  | LNG  | ENG  | ENG  | CuIUD | CuIUD | SIUD  | SIUD  |
|-----------------|------|------|------|------|-------|-------|-------|-------|
|                 | Stage 1 | Stage 2 | Stage 1 | Stage 2 | Stage 1 | Stage 2 | Stage 1 | Stage 2 |
| Desire          | 21.3 ± 4(22) | 22.4 ± 4.1(22) | 20.6 ± 5.2(20) | 16.5 ± 6.5(16) | 21.3 ± 3.8(22) | 23.2 ± 3.4(23) | 19.7 ± 8.1(22) | 23.1 ± 4.6(24) |
| P-value         | 0.077T | 0.009T | 0.004T | 0.009T |
| Preliminary     | 9.6 ± 0.8(10) | 9.1 ± 1.4(10) | 9.2 ± 1.2(10) | 7.3 ± 2.6(6) | 9.2 ± 1.6(10) | 9.4 ± 0.9(10) | 9 ± 1.5(10) | 9.1 ± 1.3(10) |
| P-value         | 0.048W | 0.012W | 0.586W | 0.714W |
| Arousal         | 17.1 ± 2.5(18) | 17.1 ± 2.4(16) | 15.4 ± 3.8(16) | 12.1 ± 4.8(14) | 18 ± 2.3(18) | 18.1 ± 2.6(19) | 16 ± 4.2(18) | 17.2 ± 2.9(18) |
| P-value         | 0.921W | 0.006T | 0.790W | 0.060T |
| Comfort         | 15.9 ± 2.9(16) | 16.8 ± 3.1(18) | 15.8 ± 3.4(18) | 14.4 ± 4.8(16) | 16.6 ± 3.4(17) | 18.2 ± 1.7(18) | 14.2 ± 4.7(16) | 16.8 ± 3.5(18) |
| P-value         | 0.226W | 0.078W | 0.037W | 0.004W |
| Orgasm & Satisfaction | 16.5 ± 4.4(18) | 16.4 ± 4.2(18) | 14.5 ± 3.8(16) | 10.6 ± 4.7(10) | 15.4 ± 3.5(16) | 16.1 ± 2.8(16) | 14 ± 4.4(14) | 14.9 ± 3.9(16) |
| P-value         | 0.706W | 0.002W | 0.497W | 0.076T |
| Total Score     | 80.4 ± 11.5(84) | 81.8 ± 11.5(82) | 75.4 ± 14(78) | 60.8 ± 21.1(66) | 80.6 ± 9.8(81) | 85.1 ± 8.2(88) | 73 ± 18.4(74) | 81.1 ± 13.2(84) |
| P-value         | 0.325W | 0.003T | 0.017W | <0.001T |

LNG: levonorgestrel intrauterine system; ENG: etonogestrel-releasing implant; CuIUD: copper intrauterine device; SIUD: silver intrauterine device. W paired samples Wilcoxon test, T Paired Student’s t-test. Data presented as mean ± SD (median).

Discussion

The main finding of this study is the improvement in sexual function after the implantation of non-hormonal LARCs, especially SIUD, and the worsening of sexual function in patients after ENG implantation involving the use of two instruments. The QS-F was developed specifically for the Brazilian female population. However, the FSFI is an instrument consolidated internationally and the use of both tools increased the study reliability, since both instruments showed the same outcome.

Most women evaluated in this study consider it very or extremely important that the contraceptive method chosen does not change their libido or interrupt the sexual act. This, together with the effectiveness of the method, were the most important reasons for choosing the contraceptive method in the groups evaluated, reflecting the great importance given by patients to maintain sexual function. Assessing female sexual function is important, as it interferes with quality of life and is generally associated with general health issues (25). Abdo et al. (19) show that 49% of Brazilian women have some degree of sexual dysfunction, including decreased libido, dyspareunia, or dysfunctional orgasm. This study did not assess the prevalence of sexual dysfunction for the methods evaluated, but rather the sexual function changes resulting from LARC implantation.

Intrauterine devices that combine silver and copper began to be used in the USA in the 1970s, showing lower pregnancy rates when compared to devices only containing copper (26). The addition of silver to the device aimed at preventing corrosion (27), with copper release seeming to remain unchanged when silver is added (27, 28). Although the combined use of copper and silver is already well established in many countries, in Brazil, this device started to be marketed in 2016 under the name Andalan Silverflex®. To date, no
study was found comparing sexual function changes in SIUD and classic devices users without the incorporation of silver. Our study shows that non-hormonal devices improve sexual function when compared to hormonal devices, especially in the domain related to sexual desire, and SIUD seems to show even more significant improvement when compared to CuIUD, since it shows a statistically significant total score improvement of sexual function with both instruments used.

Despite studies showing that the use of contraceptives increases libido in women with decreasing concerns about an unwanted pregnancy (29), this study shows a worsened sexual function, including libido, with ENG. The literature presents conflicting results regarding the influence of ENG on sexual function. As described by Bason (2001), the female sexual response is complex, because it is influenced by a multifactorial factors including biological, psychological and sociocultural (30). The psychological factor was analyzed in a study that demonstrated decreased vitality and emotional function in patients in the first three months of ENG use (31). However, this study reported no worsening of sexual function in the group studied. The study by Bozalis et al. (2016), based on a large database (CHOICE), showed that ENG users reported the loss of sexual interest more frequently when compared to CuIUD users (9). Two studies evaluating the side effects of ENG use in women followed up for about two years show a prevalence of 2.5% and 1.6% decreased libido, respectively (32, 33). Decreased libido was associated not only with ENG, but also with depot medroxyprogesterone acetate (DMPA) injections, which may be related to systemic progestin release (9, 34). Estrogens have a fundamental role in female sexuality and their administration can be a recommended treatment for low libido and hypoactive sexual desire disorder (35). Systemic progestins can suppress ovarian function and consequently decrease the natural production of estrogen, resulting in loss of sexual desire (9). In addition, ENG is the device with the highest rate of discontinuation among LARCs users (36). In the present study, five (29%) of the 17 ENG users discontinued the method within six months after the second stage of the study (data not shown). Some studies associated the discontinuation of LARCs with sexual function changes (12, 37, 38), suggesting a negative effect of ENG on sexual function.

This study also correlated metabolic and hormonal parameters with sexual function findings. Total testosterone levels increased in non-hormonal LARCs users and remained constant in hormonal LARCs users. These results may be related to the fact that some women in this study were using combined oral contraceptive methods before starting LARC implantation, which is known to reduce total testosterone (39, 40). Since SIUD and CuIUD contain no hormones, their use would make it possible to re-establish the androgen production axis, whereas, for hormonal LARCs, this re-establishment could occur partially or not occur. The decreased SGBH in all groups in this study may also be due to the use of combined oral contraceptives prior to LARC implantation. The LARC agents are known increase the hepatic production of SHBG (39, 40). Many studies suggest that this is one of the reasons why the use of combined oral contraceptives reduce libido, since excess SHBG would decrease the free testosterone fraction in women, directly affecting sexual function (14, 15). In addition, the fact that the higher levels of total testosterone observed in users of non-hormonal LARCs could also be related to improved sexual function in these groups cannot be excluded.

The increased hemoglobin levels observed in women using the LNG and ENG progestin hormonal methods in this study corroborates other studies (41, 42). Likewise, reduced hemoglobin levels in CuIUD were already analyzed in many studies (43, 44). The SIUD group, however, presented a slight non-significant hemoglobin increase, which may mean a better SIUD response compared to CuIUD regarding blood loss. These data could be related to the smaller copper surface covering the SIUD, generating less inflammatory reaction and, therefore, less bleeding during the menstrual period (45).

This present study observed decreased prolactin levels in all groups evaluated, but with a statistically significant reduction only for non-hormonal LARCs. Once again, the use of combined oral contraceptives may have influenced these results. Prolactin levels has been studied for non-hormonal LARCs since the 1970s, and these studies report that these devices cannot influence the plasma levels of this hormone (46, 47). However, ethinyl estradiol and levonorgestrel oral contraceptives presented a considerably increased prolactin and macroprolactin plasma levels (48, 49). Thus, the discontinuation of oral contraceptives through the implantation of LARCs could re-establish baseline levels, especially with the use of non-hormonal LARCs. Another factor that could interfere with serum prolactin levels is pulsatility, since these levels vary within the normal range throughout the ovulatory cycle, reaching a maximum of 20 ng/ml near ovulation (50). Slightly increased T4 baseline levels were observed for LNG, but TSH levels remained unchanged in this group, suggesting that this change may be unimportant. Lipid parameters seemed to be stable after LARC implantation, which corroborates the literature (51).

Conclusion
This study assessed the influence of four long-term reversible contraceptive methods available in the market on female sexual response. The use of etonogestrel implants was associated with a worsened sexual response when assessed by the FSFI and QS-F.
instruments. Blocked ovarian function and a probable reduction in androgen and estrogen production may explain this result. The device containing silver, in addition to showing an important improvement in sexual function, seems to have no influence on hormonal parameters, not predisposing decreased hemoglobin levels.

**Abbreviations**

CuIUD: Copper Intrauterine Device; ENG: Etonogestrel Releasing Implant; FSFI Female Sexual Function Index; HDL: High Density Lipoprotein; LARCs: Long-acting Reversible Contraceptives; LDL: Low Density Lipoprotein; LNG: Levonorgestrel Intrauterine System; QS-F: Female Sexual Quotient; SIUD: Copper-Silver Intrauterine Device; SHBG: Sex Hormone-Binding Globulin; T4: Thyroxin WHO: World Health Organization

**Declarations**

**AVAILABILITY OF DATA AND MATERIALS**

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

All study participants signed an Informed Consent Form, after being informed about the project, understanding the terms, and clarifying possible questions about the research. This research project was approved by the Research Ethics Committee of the School of Medical Sciences of Minas Gerais (FELUMA) (CAAE: 796352418500005134) under opinion number 2928669. All procedures involved in this study are in accordance with the Helsinki Declaration of 1975, updated in 2013.

**CONSENT FOR PUBLICATION**

Not applicable.

**COMPETING INTERESTS**

None of the authors report any conflicts of interest.

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There was no funding source for this study, so the decision to publish and all aspects of this study are the responsibility of the authors alone.

**AUTHOR’S CONTRIBUTIONS**

IFAM: Conceptualization, investigation, data curation, formal analysis, writing and editing of the original draft. MPB and GRCM: Data curation, methodological supporting and revision of the original draft. AMA: Conceptualization, Formal analysis, Investigation, methodological supporting, project administration, supervision, validation and revision of the original draft. BAR: Conceptualization, Formal analysis, statistical analysis, investigation, methodological supporting, project administration, supervision, validation and revision of the original draft. All authors read and approved the final manuscript.

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**Study Limitations**
The main limitation of this study is the fact that the use of oral contraceptives was not assessed prior to LARC implantation. The previous use of these agents is believed to have influenced the study results, mainly the metabolic parameters. Another study limitation includes a small sample size. New studies with a larger sample are needed to confirm the findings of this study.

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**Figures**
Figure 1
Flowchart of participant inclusion.
Figure 2

Box diagrams for the total scores of the Female Sexual Function Index (FSFI - A) and Female Sexual Quotient (QS-F - B) instruments for the different types of LARC. The p-values refer to the paired Wilcoxon or Student’s t tests.