MARIA VALERIA BAHAMONDES MAKUCH

ESTUDO PROSPECTIVO DA DENSITOMETRIA ÓSSEA DO ANTEBRAÇO EM USUÁRIAS DE LONGO TEMPO DO SISTEMA INTRAUTERINO LIBERADOR DE LEVONORGESTREL (SIU-LNG)

Dissertação de Mestrado

ORIENTADOR: Profª. Drª. ILZA MARIA URBANO MONTEIRO

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Dissertação de Mestrado apresentada à Pós-Graduação da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para obtenção do Título de Mestre em Tocoginecologia, área de Tocoginecologia

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Profa. Dra. Arlete Maria dos santos Fernandes
Profa. Dra. Cristina Aparecida Falbo Guazzelli

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BANCA EXAMINADORA DA DISSERTAÇÃO DE MESTRADO

Aluna: MARIA VALERIA BAHAMONDES MAKUCH

Orientadora: Profª. Drª. ILZA MARIA URBANO MONTEIRO

Membros:

1.

2.

3.

Curso de Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas

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Sumário

Símbolos, Siglas e Abreviaturas

AMPD – Acetato de medroxiprogesterona de depósito

DIUTCu380A – Dispositivo intrauterino de cobre.

DMO – Densidade mineral óssea

DP – Desvio padrão

E_2 – Estradiol sérico

HIV – Vírus da Imunodeficiência Humana

IL – Interleucina(s)

MAC – Método(s) anticoncepcional (is)

SIU-LNG – Sistema intrauterino liberador de levonorgestrel

TCLE – Termo de Consentimento Livre e Esclarecido

UNICAMP – Universidade Estadual de Campinas

Resumo

Introdução: A osteoporose é uma doença sistêmica que afeta principalmente as mulheres. Alguns dos fatores que aceleram a aparição desta doença são a idade e o uso, por longa data, de métodos anticoncepcionais com somente progestágenos. O sistema intrauterino liberador de levonorgestrel (SIU-LNG) é um método difundido para a contracepção e o tratamento de diversas patologias ginecológicas. Na literatura não foram identificados estudos longitudinais prospectivos, com usuárias de longa data deste método, que avaliem seus efeitos sobre a densidade mineral óssea (DMO). **Objetivos:** Avaliar a DMO em usuárias do SIU-LNG aos sete anos de uso e comparar com elas mesmas aos 10 anos de uso e com um grupo-controle de usuárias de método anticoncepcional não hormonal. **Sujeitos e métodos:** do total de 37 mulheres que realizaram DMO no antebraço aos sete anos de uso do SIU-LNG, foi avaliada a DMO novamente aos 10 anos de uso. Cada usuária foi pareada com uma usuária de DIU TCu380A, com o mesmo tempo de uso, por idade (± 1 ano), índice de massa corporal (IMC; kg/m^2) (± 1), cor da pele e número de gravidezes (± 1). A DMO foi avaliada no antebraço não dominante no rádio distal (*midshaft ulna*) e

no rádio ultradistal usando *double X-ray absorptiometry*. Os dados foram avaliados pelos testes *t* de Student pareado, Wilcoxon, Snedecor (ANOVA) e Índice de correlação múltipla. **Resultados:** A DMO das usuárias do SIU-LNG aos 10 anos de uso foi estatisticamente similar que aos sete anos e similar que os seus controles, usuárias de DIU TCu380A, mesmo quando pareadas por idade (± 1 ano), índice de massa corporal [IMC; kg/m^2, (± 1)], cor da pele e número de gestações (± 1). A maior DMO das usuárias do SIU-LNG aos 10 anos foi significativamente associada ao maior IMC (kg/m^2) e maior DMO aos sete anos de uso. **Conclusão:** As DMO dos antebraços distal e ultradistal foram similares entre as usuárias do SIU-LNG aos sete e 10 anos de uso, e também quando comparadas com um grupo de não usuárias deste contraceptivo.

Palavras-chave: Densidade óssea, anticoncepção.

Summary

Introduction: Osteoporosis is a systemic disease which mainly affects women. Some of the factors which provoke an acceleration of the initiation of this disease were age and use for a long-term of progestin-only contraceptive methods. The levonorgestrel-releasing intrauterine system (LNG-IUS) is widely introduced method for contraception and for the treatment of several gynecological pathologies. On the literature we were unable to identify prospective studies with long-term users of this method which evaluated their effect upon bone mineral density (BMD). **Objectives:** To assess prospectively the BMD of users of the LNG-IUS at the 7^{th} year of use and compare with the same women at the 10^{th} year of use and with a control group of users of a non-hormonal contraceptive method. **Materials and methods:** A total of 37 women who performed a forearm BMD at the 7^{th} year of use and again at the 10^{th} year of use. Each woman was paired with a woman who had been using a copper IUD TCu380A for at least the same length of time, who never use an LNG-IUS matched by age (±1 year), body mass index (BMI; kg/m^2) (±1), ethnicity, and number of pregnancies (±1). BMD was evaluated at the distal and the ultra-distal radius of the nondominant

forearm using double X-ray absorptiometry. The data was evaluated trough *t*-Student test for paired samples, Wilcoxon, Snedecor (ANOVA) and multiple logistic regression. **Results:** The BMD of LNG-IUS users at the 10th year of use was statistically similar than themselves when use at the 7th year as well as similar as controls users of the TCu380A IUD even when paired by age (± 1 year), body mass index (BMI; Kg/m^2, (± 1), race and number of pregnancies (± 1). Higher BMD of the LNG-IUS at the 10th year of use was significantly associated to a high BMI (Kg/m^2) and higher BMD at the 7th year of use. **Conclusions:** Forearm BMD at distal and ultra-distal radius was similar among users of the LNG-IUS at the 7^{th} and at the 10th year of use and was also similar when compared users with non-users of this contraceptive method.

Key Words: Bone density, contraception.

1. Introdução

Na maioria dos países a expectativa de vida tem aumentado, elevando a proporção da população idosa. Assim, as doenças associadas à terceira idade vão adquirindo relevância na saúde pública. Uma das doenças com alta prevalência é a osteoporose, que predispõe à ocorrência de fraturas – traumáticas e não traumáticas – do colo do fêmur, vértebras torácicas e lombares e parte distal do rádio (fratura de Colles) (1).

Segundo a Organização Mundial da Saúde (OMS), a osteoporose é uma "*doença sistêmica caracterizada pela diminuição da massa óssea e deteriorização da microarquitetura do tecido ósseo com consequente fragilidade e susceptibilidade a fraturas*" (2). Mais recentemente, a osteoporose foi definida como uma desordem esquelética caracterizada pela força óssea comprometida que predispõe a um risco aumentado de fraturas (3).

A osteoporose é a doença osteometabólica mais comum, responsável por um alto custo na saúde pública, sendo gastos, nos Estados Unidos da América, de 5 a 10 bilhões de dólares anuais (4). Metade das mulheres norte-

americanas com idade superior a 50 anos terá uma fratura associada à osteoporose durante sua vida. Além disso, como consequência, um de cada quatro indivíduos com fratura de colo de fêmur irá morrer no período de um ano após a fratura (5).

A osteopenia é uma precursora da osteoporose, e definida como a perda da densidade mineral óssea abaixo de um desvio padrão (DP) dos valores normais. Já a osteoporose caracteriza-se por uma massa óssea inferior a 2,5DP do valor médio de uma pessoa adulta jovem (2). Um dos métodos diagnósticos mais difundidos e utilizados é a densidade mineral óssea (DMO), que constitui um indicador de massa óssea do corpo, medida através de técnicas de Raios-X (densitometria) ou de ultrassom.

Em relação à osteopenia e osteoporose, as mulheres são mais suscetíveis que os homens a sofrer estas alterações nos ossos. Nelas, o estrogênio é um fator de equilíbrio da reabsorção e formação dos ossos. O hipoestrogenismo induz à acelerada remodelação do osso, onde a reabsorção ocorre mais rapidamente que a formação, levando à diminuição da massa óssea. Assim, os estados de hipoestrogenismo, como amenorreia de diversas causas, lactação exclusiva durante o pós-parto, e a pós-menopausa estão associados com o declínio da massa óssea (6; 7).

Entretanto, em mulheres, o principal efeito do estrogênio sobre a remodelação óssea é mediante o controle da síntese de citocinas pelos osteoblastos e osteoclastos, de forma autócrina ou parácrina. A remodelação óssea é um

processo contínuo de reabsorção do osso pelos osteoclastos e formação óssea pelos osteoblastos. Em adultos, aproximadamente 25% e 3% do osso trabecular e cortical, respectivamente, são reabsorvidos por ano. Por isso, a medida da DMO é mais importante no osso trabecular que no cortical (8).

Os osteoblastos são originados de uma célula mesenquimal pluripotente da medula óssea e os osteoclastos são derivados de uma unidade formadora de colônia granulocítica-macrofágica (origem na linhagem hematopoiética). Foi descrita a presença de receptores de estrogênio em osteoblastos ou células de linhagem osteoblástica (9). Embora os receptores de estrogênio estejam, predominantemente, nos osteoblastos, a principal ação deste esteróide está na inibição da reabsorção.

A ação do estrogênio é pela modulação de várias citocinas, como as interleucinas (IL) IL-1, IL-4, IL-6 e IL-11, que inibem a diferenciação dos osteoclastos, diminuindo a reabsorção óssea. Também atua através do fator de crescimento de transformação beta, que quando produzido pelos osteoblastos consiste em um potente agente mitogênico, mas que sobre os osteoclastos diminui o recrutamento e a atividade reabsortiva (10).

Entretanto, existem estados fisiológicos associados com o hipoestrogenismo. O exemplo mais comum é a amenorreia da lactação, a qual mostra variações para menos de 3% a 9% na DMO quando se comparam estas mulheres com as não lactantes. Não obstante, durante a lactação tardia (após os seis meses do

parto) ou depois do desmame, a DMO se recupera, mesmo que os intervalos entre as gravidezes e a lactação sejam curtos (11; 12).

Outros exemplos de mulheres jovens com hipoestrogenismo são aquelas afetadas por desordens do eixo hipotálamo-hipofise-ovário, como menarca tardia, amenorreia, anorexia nervosa ou hiperprolactinemia, as quais também apresentam perda óssea precoce e, consequentemente, aumento do risco de fraturas (13).

Já na pós-menopausa, um dos determinantes de perda de massa óssea e, consequentemente, de osteopenia e osteoporose é a massa óssea adquirida na adolescência e no início da vida adulta. Mulheres saudáveis com atividade ovariana normal atingem o pico de massa óssea na terceira década de vida, porém, o maior ganho de massa óssea entre as mulheres ocorre entre 11 e 14 anos de idade, com queda acentuada do ganho (observado na DMO realizada na coluna e no colo do fêmur) após os 16 anos ou dois anos após a menarca. Após a menopausa, a reabsorção óssea predomina sobre a formação óssea, resultando em uma perda óssea acelerada, decorrente principalmente do hipoestrogenismo (14; 15; 13). Este processo resulta em uma perda óssea ao redor de 15% nos primeiros cinco a 10 anos. Após esse período, a perda óssea ocorre mais lentamente (16).

Por outro lado, a DMO também depende de múltiplos fatores que ocorrem durante a vida reprodutiva ou na pós-menopausa. Dentre eles, um fator controverso é a utilização de métodos anticoncepcionais (MAC) hormonais

que poderiam, de alguma forma, ter algum efeito sobre a DMO (17). As mulheres necessitam de MAC por um período prolongado da vida, em média, por 28 a 32 anos, considerando de forma teórica que a idade média na primeira relação sexual seja aos 17 anos, que a menopausa ocorra aos 50 anos e que a mulher tenha em média dois filhos, amamentando exclusivamente por seis meses cada um.

Os MAC oferecem muitos benefícios à saúde, porém também podem apresentar alguns riscos. Um deles seria a perda de densidade mineral óssea, que poderia resultar em osteoporose no futuro, aumentando a possibilidade de fraturas (17). Entretanto, este é um tema controverso. Aparentemente, o único MAC hormonal com efeito deletério sobre a DMO durante o seu uso é o acetato de medroxiprogesterona de depósito (AMPD); embora este seja ainda um tema controverso (18; 19). Entretanto, após a descontinuação do mesmo, a DMO mostra recuperação aos níveis anteriores mesmo entre adolescentes (20).

Quanto aos progestogênios, eles exercem sua atividade através de um receptor específico intracelular. A ação dos progestogênios no osso parece resultar em uma proteção contra a perda óssea. Este efeito é mediado pela expressão dos receptores de progesterona nos osteoblastos e glicocorticóides, diminuindo a influência negativa dos glicocorticóides. Não há evidência de que os progestogênios tenham um efeito antagonista aos estrogênios no osso (21).

O sistema intrauterino liberador de levonorgestrel (SIU-LNG) é um MAC que libera 20µg diários de levonorgestrel (LNG). O SIU-LNG é uma estrutura de

polietileno em forma de “T”, que possui em suas hastes vertical e horizontal 32mm de comprimento e largura, e um cilindro que contém uma mistura de polidimetilsiloxano e 52mg de LNG. Este cilindro é revestido por uma membrana de polidimetilsiloxano (Silastic) que regula a liberação contínua de LNG para a cavidade uterina (22) (Figura 1).

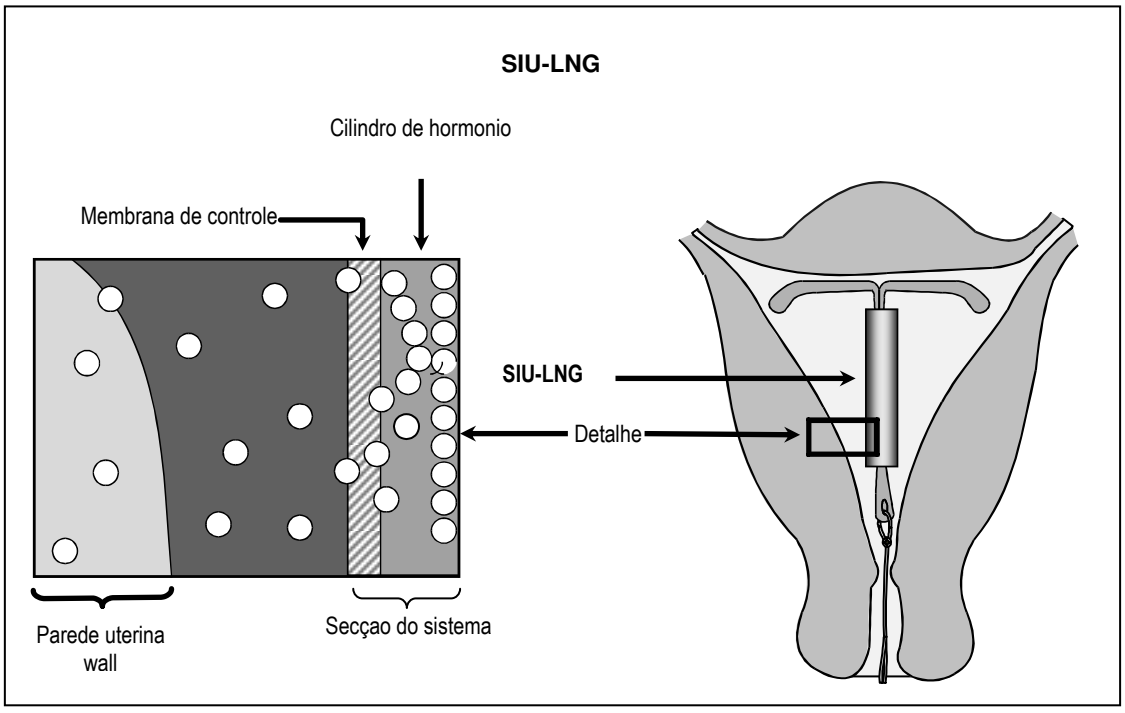

Figura 1. *Detalhe do sistema intrauterino liberador de levonorgestrel (SIU-LNG).*

Este MAC está muito difundido, já que seu uso foi aprovado em 122 países (23), em pouco mais de 100 como tratamento do sangramento uterino aumentado (metrorragia) e na mesma proporção de paises como protetor endometrial durante a terapia estrogênica contínua na pós-menopausa. No Brasil foi aprovado como contraceptivo e na terapêutica da metrorragia.

É um MAC altamente eficaz, com taxas de gravidez acumuladas aos sete anos de uso entre 0,0 e 0,1 por 100 mulheres/ano (24). Entretanto, um dos efeitos do uso é a atrofia do endométrio, o que leva à falta de sangramento ou amenorreia. Ao final dos 12 meses de uso do SIU-LNG, aproximadamente 80% das usuárias estarão em amenorreia, e 25% apresentarão oligomenorreia (25). O fato de induzir à amenorreia tem levado a que seja utilizado em diversas situações (26) como terapêutica da metrorragia idiopática (27), em mulheres com doenças hematológicas ou em usuárias de drogas anticoagulantes (28), no controle da dor em mulheres com endometriose (29; 30; 31), adenomiose (32), proteção endometrial em terapia estrogênica na pós-menopausa (33), hiperplasia de endométrio (34) e como contracepção em mulheres portadoras de HIV (35; 36).

Este MAC não produz hipoestrogenismo e tem sido observado que as usuárias apresentam níveis de estradiol (E_2) com grandes variações; entretanto, mantendo os padrões normais para a fase folicular do ciclo, entre 104,6 a 128,4pg/ml, aos sete anos de uso. Quando avaliado o nível de E_2, após 28 meses de uso em mulheres que apresentaram folículos ovarianos persistentes, este se mostrou mais elevado, em média de 165pg/ml, sendo que, após os folículos terem reduzido o seu tamanho, os níveis de E_2 diminuíram, ficando em níveis normais (37).

O fato de não provocar hipoestrogenismo deve ser a variável mais importante que levou a que em um estudo de corte transversal, comparando usuárias de SIU-LNG aos sete anos de uso com um grupo de nunca usuárias

do SIU-LNG, a DMO no rádio distal (*midshaft ulna*) e ultradistal foi similar nos dois grupos de mulheres (38).

A avaliação da DMO entre usuárias do SIU-LNG por longo período de uso e que inclusive já tenham trocado por um segundo dispositivo, seria de grande utilidade como informação para médicos e usuárias, já que a perda de massa óssea com o uso deste MAC não tem sido avaliada durante o uso contínuo do mesmo.

Algumas das mulheres, já avaliadas aos sete anos de uso, atualmente estão usando um segundo SIU-LNG por maior tempo após a troca e, além disso, estão mais próximas à idade da menopausa, idade em que ocorrem o hipoestrogenismo e os riscos de osteopenia, osteoporose e fraturas traumáticas e não traumáticas aumentam só pelo fator idade, os quais poderiam ainda estar agravados pelo uso do SIU-LNG. Além do mais, seria de utilidade proporcionar esta informação às usuárias de um método anticoncepcional de longo uso, que poderia não acarretar risco de perda de massa óssea pelo seu uso.

2. Objetivos

2.1. Objetivo geral

Avaliar a densidade mineral óssea em usuárias de SIU-LNG aos 10 anos de uso e compará-las com as mesmas usuárias de SIU-LNG que avaliaram a DMO aos sete anos de uso e com um grupo-controle de usuárias de método anticoncepcional não hormonal.

2.2. Objetivos específicos

- Determinar e comparar a DMO em usuárias de SIU-LNG aos 10 anos de uso com a DMO das mesmas usuárias de SIU-LNG aos 7 anos de uso.

- Determinar e comparar a DMO em usuárias de SIU-LNG aos sete anos de uso com a DMO de usuárias de um MAC não hormonal há no mínimo sete anos, pareadas por idade (± 1 ano), índice de massa corporal [IMC; kg/m^2,(± 1)], cor da pele e número de gestações (± 1).

- Determinar e comparar a DMO em usuárias de SIU-LNG aos 10 anos de uso com a DMO de usuárias de MAC não hormonal com, no mínimo, o mesmo tempo de uso, pareadas por idade (± 1 ano), índice de massa corporal [IMC; kg/m^2, (± 1)], cor da pele e número de gestações (± 1).

- Determinar que variáveis (se houver) estão significativamente associadas a maior ou menor DMO aos 10 anos de uso do SIU-LNG.

3. Sujeitos e Método

3.1. Desenho

Foi realizado um estudo de coorte prospectivo no período de agosto de 2005 a agosto de 2009.

3.2. Tamanho da amostra

Na literatura somente foi encontrado um estudo que avaliou a DMO em usuárias de longa data de SIU-LNG (38). Entretanto, tratou-se de um estudo-piloto com 53 mulheres, razão pela qual não se utilizou esta publicação para o calculo do tamanho da amostra. Entretanto, para calcular o tamanho da amostra deste estudo foi usado como indicador a estimativa do DP da DMO no rádio distal em mulheres usuárias de implantes subdérmicos contraceptivos (Implanon e Jadelle) (39), devido a que estes implantes liberam progestágenos na circulação sistêmica e um deles (Jadelle) libera também levonorgestrel igual ao SIU-LNG. A diferença aceitável entre as medidas da DMO no início e após 18 meses de uso

do Implanon foi calculada pelo erro tipo I ou α= 0,05, e erro tipo II ou β= 0,20. Esta diferença foi calculada em -0,021g/cm², e o tamanho da amostra foi estimado em 37 mulheres para cada grupo, totalizando 148 avaliações de DMO.

3.3. Variáveis

São apresentadas as variáveis estudadas, com suas respectivas definições e categorias. Todas as variáveis foram categorizadas durante a elaboração do projeto, os valores apresentados não se referem a resultados.

3.3.1. Variável dependente

Densidade mineral óssea: relação entre o conteúdo mineral ósseo e a área do osso avaliada, expressa em g/cm² (inicial aos sete anos de uso) e a diferença aos 10 anos de uso do SIU-LNG em relação à medida inicial, medido com um equipamento de densitometria tipo *double X-ray absoptiometry* (DEXA), marca Osteometer (Rodovre, Dinamarca). Normal, 0,481g/cm^2; Osteopenia, perda de massa óssea de 1DP; Osteoporose, perda de massa óssea inferior a 2,5DP do valor médio de uma pessoa adulta jovem.

3.3.2. Variáveis independentes

Tempo de uso do SIU-LNG: período, em meses, desde o momento da inserção do SIU-LNG até o momento da avaliação da DMO, referido na ficha de atendimento do ambulatório, entre 84 e 132 meses.

Tipo de contraceptivo: método utilizado para evitar a gravidez ao momento da avaliação da DMO. SIU-LNG ou DIU TCu380A (MAC não hormonal).

3.3.3. Variáveis de controle

- *Idade:* tempo, em anos completos, transcorrido a partir da data de nascimento até a data da avaliação da DMO, referido pela mulher - 35 a 52 anos.

- *Cor da pele:* coloração da *dermis* da mulher, classificada pelo pesquisador em branca ou não branca.

- *Escolaridade:* nível de aprendizado, ensino ou educação atingida, referida pela mulher - nenhuma, 1° grau completo, 1° grau incompleto, 2° grau completo, 2° grau incompleto, superior, outro.

- *Ocupação:* atividade de trabalho exercida fora da casa, no momento da avaliação da DMO, referida pela mulher -sim ou não.

- Peso: quantificação da unidade de volume de um corpo, expresso em quilogramas, medido em uma balança antropométrica Filizola – 40kg a 90kg.

- *Altura:* dimensão do corpo, a partir do extremo inferior até o seu extremo superior, expressa em centímetros exatos, medida em escala antropométrica Filizola- 1,45 a 1,75 metros.

- *Índice de massa corpórea:* critério de avaliação do grau de obesidade de um indivíduo, calculado pelo pesquisador, resultado do valor do peso em quilograma dividido pela altura, em metros, elevada ao quadrado e expressa em kg/m² - <20 abaixo do peso; 20-25 peso ideal; 26-30 sobrepeso; 31-35 obesidade moderada; ≥36 obesidade severa.

- *Idade na menarca:* número de anos completos na ocasião da primeira menstruação, referida pela mulher- 10 a 18 anos.

- *Menstruação regular:* período regular de cada menstruação, entre 25 e 32 dias - sim ou não.

- *Tempo de amenorreia:* tempo, em meses, em que a mulher não menstrua, segundo a data da última menstruação (DUM) até o momento da avaliação da DMO, referido pela mulher- 0 a 20 meses.

- *Número de gestações:* número de vezes que a mulher ficou grávida, referido por ela – Nuligesta: 0 gestações, Primigesta: 1 gestação, Secundigesta: 2 gestações; Tercigesta: 3 gestações; Multigesta: ≥4 gestações.

- *Número de partos:* número de partos, por via vaginal ou cesárea, referido pela mulher – Nulípara: 0 partos; Primípara: 1 parto; Secundípara: 2 partos; Tercípara: 3 partos; Multípara: ≥4 partos.

- *Número de abortos:* número de gestações terminadas antes de 22 semanas de idade gestacional, referido pela mulher- 1, 2, 3 ou ≥4 abortos.

- *Número de filhos que foram amamentados*: quantidade de filhos que a mulher amamentou - 0 a 6 filhos.

- *Tempo de amamentação exclusiva*: lactação, sem suplementação alimentícia, obtido pela soma dos meses em que cada filho só foi alimentado com leite materno, referido pela mulher - 0 a 80 meses.

- *Tempo de amamentação parcial*: definida como pelo menos um episódio de mamada ao peito por dia, expresso em número de meses, somado o período para cada filho, referido pela mulher - 1 a 42 meses.

- *Hábito de fumar:* foi considerada tabagista a mulher que fumava pelo menos um cigarro por dia, no mínimo há um ano, referido pela mulher- sim ou não.

- *Hábito de tomar café*: ingestão de pelo menos uma dose por dia de café (50ml/dia) há pelo menos um ano, referido pela mulher- sim ou não.

- *Ingestão de bebida alcoólica*: definida como ingestão semanal de pelo menos uma dose de bebida alcoólica (300 ml), em um período mínimo de um ano, referido pela mulher-sim ou não.

- *Atividade física*: desenvolvimento de alguma atividade física regularmente, referido pela mulher- sim ou não.

- *Lavagem de roupa manualmente*: avaliado se a mulher lava qualquer quantidade de roupa manualmente, referido pela mulher- sim ou não.

- *Uso de MAC hormonal prévio*: último MAC hormonal, usado pela mulher antes da inserção do SIU-LNG ou do DIU TCu380A, referido pela mulher- nenhum, anticoncepcional oral (ACO), injetável combinado mensal, acetato de medroxiprogesterona de depósito (AMP-D).

3.4. Seleção das mulheres

As mulheres do estudo foram recrutadas entre aquelas que frequentaram o Ambulatório de Planejamento Familiar, Departamento de Tocoginecologia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), usuárias de SIU-LNG, após 10 anos de uso, e usuárias de DIU TCu380A. Estas mulheres habitualmente têm retorno a cada seis meses e por livre demanda, segundo as queixas que apresentem.

Às mulheres usuárias do SIU-LNG que avaliaram a DMO aos sete anos de uso (38) e que trocaram por um novo SIU-LNG, foi oferecido realizar uma nova avaliação da DMO aos 10 anos de uso, por ocasião de uma das visitas de controle.

As usuárias de SIU-LNG foram pareadas com as usuárias de DIU TCu380A por idade (± 1 ano), IMC (kg/m^2) (± 1), cor da pele, número de gestações (± 1) e tempo de uso do MAC (sendo o mínimo o mesmo tempo de uso do SIU-LNG) ao momento da avaliação da DMO.

Neste estudo foram avaliadas 37 mulheres usuárias do SIU-LNG, que mediram a sua DMO em duas ocasiões (aos sete e 10 anos), e também 74 mulheres usuárias de DIU TCu380A que realizaram uma única medida de DMO, totalizando 148 avaliações de DMO.

3.4.1. Critérios de Inclusão

- Usuárias de SIU-LNG que participaram previamente do estudo aos sete anos de uso.
- Dez anos de uso mínimo de SIU-LNG e que previamente avaliaram a sua DMO aos sete anos de uso.
- Uso de DIU TCu380A, para o grupo-controle.

3.4.2. Critérios de Exclusão

- Gravidez e lactação nos 12 meses prévios à entrada no estudo.

- Doenças crônicas como diabetes *Mellitus*, insuficiência renal crônica, hiper ou hipoparatiroidismo, hiper ou hipotiroidismo, hepatite, câncer ou doença hipofisária.

- Uso de alguns medicamentos como: cálcio, vitamina D, anticonvulsivantes, corticosteróides, diuréticos tiazídicos, hormônios tiroideanos.

- Prática de atividade física regular por mais de 1 hora/dia.

3.5. Técnica, testes e/ou exames

No momento em que a mulher chegou ao Ambulatório, foi feita a avaliação do peso e altura. Para isso foram usadas uma balança e escala antropométrica marca Filizola.

Logo, foi avaliada a DMO no antebraço não dominante, medida com um equipamento de densitometria tipo double X-ray absoptiometry (DEXA), marca Osteometer (Rodovre, Dinamarca). Para realizar o procedimento, a mulher sentou-se em uma cadeira próxima ao equipamento e colocou o antebraço no mesmo. O procedimento durou aproximadamente 3 minutos. Os valores normais para mulheres em idade reprodutiva são de 0,481g/cm^2. Duas medidas de DMO foram realizadas em cada mulher e em cada momento do estudo: (1) no rádio distal (*midshaft ulna*), onde o osso cortical é predominante, situado a 8mm da ulna e (2) no rádio ultradistal, perto da articulação dos ossos do carpo, em que o osso trabecular é o predominante.

3.6. Instrumento de coleta de dados

A ficha de coleta de dados já foi utilizada em estudos prévios similares realizados no Ambulatório de Planejamento Familiar (Anexo 1). No início deste estudo essa ficha foi pré-testada novamente, não sendo necessária a modificação da mesma para atender aos objetivos propostos.

A ficha consta dos seguintes itens:

- Identificação do sujeito no estudo.
- Iniciais da mulher.
- Número da ficha de planejamento familiar (PF).
- Antecedentes pessoais.
- Hábitos de vida.
- Antecedentes gineco-obstétricos.
- Antecedentes clínicos.
- Densidade mineral óssea.
- Quem aplica o questionário.
- Quem realiza a densitometria mineral óssea.

3.7. Coleta de dados

Um grupo de mulheres avaliou sua DMO aos sete anos de uso de SIU-LNG. As que continuaram seu uso trocando pelo mesmo método estão hoje com 10 anos de uso ininterrupto do mesmo método.

Estas mulheres compareceram por livre demanda ao Ambulatório e foi oferecida a avaliação da DMO. O questionário foi aplicado pela pesquisadora ou por enfermeiras do Ambulatório de Planejamento Familiar, treinadas para tal fim. Logo, foi avaliada a DMO.

3.8. Análise de dados

A análise de dados foi realizada primeiro comparando as variáveis sociodemográficas e a DMO nas duas seções do antebraço, entre usuárias do SIU-LNG e do DIU com cobre, mediante o teste *t* de Student para amostras emparelhadas, teste de Wilcoxon ou Snedecor quando correspondia. Também foi utilizada a regressão logística simples para avaliar que variáveis estavam significativamente associadas à perda ou não de massa óssea aos 10 anos de uso. Os dados são apresentados como média ± erro padrão da média (EPM).

3.9. Aspectos éticos

O projeto de pesquisa foi aprovado pelo Comitê de Ética em Pesquisa (CEP) da Faculdade de Ciências Médicas da UNICAMP (Anexo 3) e todas as mulheres assinaram um Termo de Consentimento Livre e Esclarecido (TCLE) antes de entrar no estudo (Anexo 2).

4. Publicação

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> Subject: Human Reproduction - Manuscript ID HUMREP-09-1085
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Prospective study of the forearm bone mineral density of long-term users of the levonorgestrel-releasing intrauterine system

M. Valeria Bahamondes, Ilza Monteiro, Sara Castro, Ximena Espejo-Arce and Luis Bahamondes.

Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas (UNICAMP) and National Institute of Hormone and Women Health, 13084-971,Campinas, Brazil

Running title: Bone mineral density in users of the LNG-IUS

Corresponding author:

M. Valeria Bahamondes

Caixa Postal 6181, 13084-971

Campinas, SP, Brazil.

E-mail: vbahamondes@cemicamp.org.br

Abstract

BACKGROUND: This study compared bone mineral density (BMD) in levonorgestrel-releasing intrauterine system (LNG-IUS) users and copper intrauterine device (IUD) users. **MATERIALS AND METHODS:** Forearm BMD was evaluated in 37 women (25-48 years old) at 7 years of use when a second LNG-IUS was inserted and again at 10 years of use. Women were paired with IUD users for time of use, age, body mass index (BMI), ethnicity and number of pregnancies. BMD was evaluated at the midshaft ulna and ultra-distal radius of the nondominant forearm using dual-energy X-ray absorptiometry. **RESULTS:** Mean age of LNG-IUS and IUD users at the 7^{th} and 10^{th} years was 34 and 38 years, respectively. Mean BMI was 25 in both groups, increasing to 26 at the 10^{th} year. Amenorrhoea occurred in 51.3% and 91.9% of LNG-IUS users at the 7^{th} and 10^{th} years, respectively. BMD was 0.460 ± 0.009 at the midshaft of the ulna and 0.400 ± 0.011 at the ultra-distal radius in LNG-IUS users at the 7^{th} year of use and 0.456 ± 0.009 and 0.399 ± 0.010, respectively, at the 10^{th} year of use. There were no statistically significant differences between the two measurements or between LNG-IUS and IUD users. Higher BMI and BMD at the 7^{th} year and amenorrhoea were predictors of higher BMD at the 10^{th} year of use. **CONCLUSIONS:** Forearm BMD at the midshaft ulna and ultra-distal radius remained unchanged between the 7^{th} and the 10^{th} years of use of the LNG-IUS and similar to that of IUD users.

Key Words: Bone mineral density, levonorgestrel-releasing intrauterine system, Mirena, contraception.

Introduction

Long-term contraceptive methods are an attractive option for many women, particularly those methods that, like subdermal implants, intrauterine devices (IUD) and the levonorgestrel-releasing intrauterine system (LNG-IUS), do not involve having to remember to use the contraceptive method daily. Many women require contraception for many years and long-acting contraceptive methods avoid problems such as forgetfulness or incorrect use. The LNG-IUS is a relatively new contraceptive method that has already been approved in more than 120 countries worldwide. This rapid expanse was due to the high contraceptive efficacy of the method, few side-effects and the fact that it may be used continuously for periods of up to five years following one single intervention (Luukkainen *et al*., 1990; World Health Organization, 2004).

One of the characteristics of the LNG-IUS is that it induces amenorrhoea in a high percentage of women at different moments during use, this being provoked by the antiproliferative effect of LNG on the endometrium (Luukkainen *et al*., 1990; Ronnerdag and Odlind, 1999; Hidalgo *et al*., 2002). In view of this effect, the LNG-IUS has also been approved in almost 120 countries as a medical treatment for women suffering from menorrhagia or heavy uterine bleeding, thus constituting an alternative to hysterectomy (Monteiro *et al*., 2002; Hurskainen *et al*., 2004; Kaunitz *et a*l., 2009), and as endometrial protection in postmenopausal women during oestrogen therapy (Sitruk-Ware, 2007). In addition, although off-label, the device has also been used in women with endometriosis-related pain (Lockhat *et al*., 2005; Petta *et al*., 2005; 2008). However, although much information is available on the contraceptive efficacy and health benefits of the LNG-IUS, only one study so far has evaluated the bone mineral

density (BMD) of users of this contraceptive method and this study was carried out by our group of investigators (Bahamondes *et al*, 2006a).

The importance of evaluating BMD in users of the LNG-IUS resides in the fact that it is a progestogen-only (p-only)-releasing contraceptive method. P-only contraceptive methods are in use worldwide and the effect of current and past use on BMD remains a medical concern (d'Arcangues, 2006), principally in the case of users of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) (Guilbert *et al*., 2009) because of the transient hypoestrogenism DMPA may induce (Bahamondes *et al*., 2002), this constituting the most important factor associated with bone loss (Bagger *et al*., 2004).

As stated above, amenorrhoea is common in users of the LNG-IUS and its prevalence depends on the method of evaluation (Ronnerdag and Odlind, 1999; Hidalgo *et al*., 2002). Nevertheless, despite this characteristic, plasma oestradiol (oE_2) levels in users of the LNG-IUS are similar to those found during the follicular phase of the menstrual cycle (Luukkainen *et al*., 1990), even in long-term users of the same device (Hidalgo *et al*, 2009). Consequently, if serum oE_2 levels are normal, the LNG-IUS would not be expected to affect BMD, however, this should be confirmed, particularly in long-term users of the device. Therefore, the aim of this study was to evaluate forearm BMD in users of a second consecutive LNG-IUS in whom BMD was measured at the 7^{th} year of use, and compare findings with the BMD measurements of the same women at the 10^{th} year of use. In addition, this cohort of women was compared with women who had been using a non-hormonal contraceptive method, a copper intrauterine device (IUD), for at least the same length of time.

Materials and methods

This prospective cohort study was conducted at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, Brazil. The Institutional Review Board approved the study, and all participants signed an informed consent form prior to admission.

The subjects consisted of a group of women in whom forearm BMD was evaluated at the 7th year of use of an LNG-IUS (Bahamondes *et al*, 2006a) inserted between April and September, 1998 when these women participated in an acceptability study of the LNG-IUS (Mirena®, Bayer Schering Pharma Oy, Turku, Finland) in Brazil (Diaz *et al*., 2000; Hidalgo *et al*., 2002). At the end of the approved 5-year lifespan of the device, the women were invited to continue using the same device for a further 2 years. At the 7-year follow-up visit, the first 51 women who returned for a control evaluation underwent evaluation of forearm BMD as previously described (Bahamondes *et al*, 2006a). The women who had the LNG-IUS removed and a new one inserted on the same day were invited to undergo another BMD evaluation at the 10th year of use. Therefore, 37 women of 25-48 years of age were evaluated at the 7th and 10th years of use. The non-users group consisted of 37 women who had been in use of the TCu380A IUD (Optima, Injeflex, São Paulo, Brazil) for at least the same length of time and who had never used any kind of hormonal contraceptive. Women in the non-users group were paired with the LNG-IUS users according to age (±1 year), BMI (kg/m^2) (±1), ethnicity, and number of pregnancies (±1).

Women were excluded from the study if they were using calcium, vitamin D, anticonvulsants, corticosteroids, thiazide diuretics or drugs for the treatment of thyroid disease. Women with chronic diseases such as diabetes mellitus, chronic renal failure,

hyperthyroidism or hypothyroidism, hyperparathyroidism or hypoparathyroidism, hepatitis, cancer or pituitary diseases were also excluded.

Definition of variables

BMD was the dependent variable and was defined as the relationship between bone mineral content (g/cm^2) and the area of the bone measured. The independent variable was the use of the LNG-IUS or copper IUD at the 7^{th} and 10^{th} years. The control variables included age at the time of the first BMD measurement, ethnicity, number of pregnancies and deliveries, duration of exclusive and partial breastfeeding, weight, height, BMI (kg/m^2), exercise habits, smoking habits and patterns of coffee and alcohol consumption.

2. 2. Bone mineral density measurement

BMD was measured at the nondominant forearm using dual-energy X-ray absorptiometry (DXA) (DTX-200; Osteometer Meditech A/S, Rodovre, Denmark). The normal mean value for premenopausal women is 0.481 g/cm^2. Two BMD measurements were taken in each woman: (1) at the midshaft ulna (where the cortical bone predominates), at the point at which the radius is 8 mm from the ulna; and (2) at the ultra-distal radius near the articulation with the bones of the carpus (where the trabecular bone predominates).

2.3. Statistical analysis

Calculation of sample size was based on a previous study of BMD measurement carried out in users of the LNG-IUS (Bahamondes *et al*, 2006a) and a previous study of

users of LNG or etonogestrel-releasing contraceptive implants (Monteiro-Dantas *et al*., 2007), with an alpha of 5% and beta of 10%. Sample size was calculated at 37 women per group. Comparison between the groups of users and non-users with respect to demographic, anthropometric and obstetric variables and to BMD at both sections of the forearm was performed using Student's *t*-test for matched samples, and the Wilcoxon signed rank test or Snedecor's test (ANOVA) as appropriate. In addition, a multiple regression analysis was performed to evaluate whether BMD was significantly associated with any variables between the 7^{th} and 10^{th} years of use. All data are presented as means ± standard error of the mean (SEM).

Results

The 37 women in whom BMD was evaluated at the 7^{th} year of use were re-evaluated at the 10^{th} year of use. The mean duration of LNG-IUS use at the 7^{th} and 10^{th} years was 84.0 ± 0.0 months and 123.0 ± 0.8 months, respectively (range 116-121 months), while women in the control group had been using the TCu380A IUD for a mean of 112.5 ± 4.2 months (range 84-204 months) and 131.2 ± 4.7 months (range 120-240 months) at the 7^{th} and 10^{th} years of evaluation, respectively. The sociodemographic and obstetric characteristics of the two study groups are shown in Table I. The mean age of the LNG-IUS and copper IUD users at the 7^{th} and 10^{th} years of use was around 34 and 38 years, respectively. BMI (kg/m^2) at the same two time-points was around 25, with a slight increase after three years of use to around 26 in both groups of users. There were no statistically significant differences between the two groups with respect to this variable or to any of the other characteristics. White women comprised 75.7% of the

total sample, while smokers made up 8.1% and 24.3% of users of the LNG-IUS and IUD, respectively, at the 10^{th} year of use.

Other pertinent characteristics of the LNG-IUS group included the fact that 29 of the women (78.2%) had experienced menarche at 11-14 years of age; 31 (83.8%) declared that they had breastfed exclusively for a maximum of only two months; 35 (94.6%) had attended elementary or high school; only 14 (37.8%) worked in a job that involved strenuous physical activity; only one woman reported drinking alcohol more than just socially; and 32 (86.5%) declared that they drank coffee daily (data not shown). Amenorrhoea was reported by 51.4% and 91.9% of the 37 users of the LNG-IUS at the 7^{th} and 10^{th} years of evaluation, respectively ($p<0.001$). In the other women, bleeding consisted of only a few episodes of spotting.

BMD was 0.460 ± 0.009 at the midshaft of the ulna and 0.400 ± 0.011 at the ultra-distal radius in the LNG-IUS group at the 7^{th} year of use and 0.456 ± 0.009 and 0.399 ± 0.010, respectively, at 10 years of use. There were no statistically significant differences between the two evaluations. The values obtained for users of the TCu380A IUD were very similar to those of the LNG-IUS users, and there were no statistically significant differences between the two groups (Table II).

Table III shows the relationship between the different variables and BMD at the 10^{th} year of use in users of the LNG-IUS. With respect to age, 75% of the women were between 28 and 40 years of age. The number of participants with BMI (kg/m^2) < 25 was almost the same as the number of women in whom BMI was ≥ 25. Women with higher BMI had higher BMD at both sections of the forearm. Most of the women did not smoke and participated in no physical activity except for routine domestic activities. No

statistically significant differences were found between the two groups with respect to any of the other characteristics.

Multiple logistic regression analysis showed that higher BMD at the midshaft ulna and the ultra-distal radius at the 10^{th} year of evaluation were significantly associated with higher BMI (kg/m^2) and higher BMD at the 7^{th} year of evaluation and with a bleeding pattern of amenorrhoea (Table IV).

Discussion

In the present study, forearm BMD of users of the LNG-IUS was evaluated at the 7^{th} year of use of the LNG-IUS, at which time a new device was inserted. BMD was re-evaluated in these women at the 10^{th} year of use and no statistically significant differences were found between the two measurements. In addition, there were no statistically significant differences between the BMD measurements of these women and those of a cohort of non-users paired for age, BMI (kg/m^2), ethnicity and obstetric history. Moreover, BMD values (Z-score) were similar to the values expected for women in the same age-group (World Health Organization, 1994).

The findings of this study were to be expected due to the fact that the most important variable related to bone loss and resorption in women is the hypoestrogenism (Bagger *et al*., 2004) observed during the postmenopausal years, exclusive breastfeeding and during the use of some p-only contraceptives such as DMPA (Guilbert *et al.*, 2009). It was to be expected that the BMD of women in the LNG-IUS group would remain unaffected, since it is a very well-established fact that oE_2 levels in LNG-IUS users are similar to those of women in the follicular phase of the menstrual cycle (Luukkainen *et al*., 1990; Bahamondes *et al.,* 2003; 2006a), even when the women have been using the

same device continuously for up to nine years without renewal (Hidalgo *et al*., 2009). Values ranging from 100 to 400 pg/ml have been recorded at this time of use.

Although BMD measurements were similar in the users and controls, amenorrhoea was reported by almost 50% and 90% of LNG-IUS users, respectively, at the end of the 7^{th} and 10^{th} years of use. These figures are similar to previous findings (Ronnerdag and Odlind, 1999; Hidalgo *et al*., 2002) and may lead women and physicians to believe that this bleeding pattern could affect oE_2 levels and, consequently, the bone health of these women. Considering that the LNG-IUS is also widely used for non-contraceptive purposes (Bahamondes *et al*., 2008) and that as a p-only contraceptive it is an appropriate method for women who need to avoid the use of oestrogen, it is therefore important to show that the device exerts no effect on ovarian oE_2 production or BMD.

The LNG-IUS releases a 19 nor-progestogen which is considered to have a beneficial effect on BMD (Petitti *et al*., 2000) and may inhibit bone absorption in women of reproductive age (Volpe *et al*., 1997). In users of LNG-releasing implants (Norplant® or Jadelle®), no adverse effects have been found on BMD at the lumbar spine (L2–L4), femoral neck or distal radius where the trabecular bone is predominant (Naessen *et al*., 1995; Petitti *et al*., 2000; Bahamondes *et al*., 2006b). There is evidence that progestogens may stimulate osteoblasts through progesterone (Wang *et al.*, 2009) and androgen receptors (Wiren *et al*., 2006). Both receptors are expressed in osteoblasts and osteoclasts and their activation increases bone mass, principally due to a reduction in bone resorption.

Many factors may also affect peak bone mass acquisition. In addition to genetic factors, other variables affecting bone mass include diet, BMI, calcium intake, physical activity, and hormonal status (Sarfati and de Vernejoul, 2009). Nevertheless, in the group of LNG-IUS users, the other characteristics such as exclusive breastfeeding,

physical activity, and alcohol and coffee consumption did not appear to affect BMD results. In addition, coffee consumption appears to affect only DMPA users, no effect having been found in other groups of women (Wetmore *et al*., 2008).

This is the second report from our group (Bahamondes *et al.,* 2006a) on the effect of the LNG-IUS on the BMD of women using the device for contraceptive purposes and it is the first report to evaluate women using this contraceptive method for periods of up to 10 years that included the insertion of a second LNG-IUS. This fact should be considered the principal strength of the study. Nevertheless, there are some limitations that should be taken into account. The study population consists predominantly of young white women. These women were neither close to the menopause nor to adolescence, the age-groups in which the effect of p-only contraceptives could have a greater effect on BMD. In addition, BMD was not evaluated at the lumbar spine or trochanter; nevertheless, forearm BMD constitutes a good indicator of bone health (Marshall *et al*., 1996). Bone loss, however, is predicted by the difference between bone formation and bone resorption, and currently available markers, including BMD, are insufficient to calculate this balance. However, we are able to conclude that forearm BMD at the midshaft ulna and ultra-distal radius remained unchanged between the 7^{th} and the 10^{th} years of use of the LNG-IUS and similar to that of IUD users.

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Table I: Selected characteristics of women in the two contraceptive groups at the 7th and 10th years of use [n=37 pairs]

Variables	Duration of use					
	7 years		p-value	10 years		p-value
	LNG-IUS[¶]	IUD[@]		LNG-IUS[¶]	IUD[@]	
Age (years)	34.2 (0.15)	34.1 (0.131)	0.566*	37.9 (0.15)	37.9 (0.15)	0.689*
BMI (kg/m^2)	24.8 (0.09)	24.9 (0.09)	0.603*	25.9 (0.09)	25.8 (0.09)	0.471*
Number of pregnancies	2.1 (0.16)	2.0 (0.16)	0.549[•]	2.1 (0.16)	2.4 (0.16)	0.033[•]
White women (%)	83.8	75.7	>0.999[#]	83.8	75.7	>0.999[#]
Duration of use (months)	84.0 (0.0)	112.5 (4.24)	<0.001[•]	123.0 (0.87)	131.2 (4.71)	0.322[•]

LNG-IUS: Levonorgestrel-releasing intrauterine system; [@]Intrauterine device;

*Student's paired *t*-test; [•]Wilcoxon Signed Rank test; [#]McNemar paired test.

Table II: Bone mineral density according to the contraceptive method used, the section of the forearm evaluated and the moment of evaluation [n=37 pairs]

Length of use (months)	*LNG-IUS*[¶] *(N=37)*	*TCu380A IUD*[@] *(N=37)*	p-value[•]
84 months			
Midshaft ulna	0.460 (0.009)	0.448 (0.008)	0.133
Ultra-distal radius	0.400 (0.011)	0.394 (0.006)	0.588
120 months			
Midshaft ulna	0.456 (0.009)	0.469 (0.008)	0.172
Ultra-distal radius	0.399 (0.010)	0.406 (0.009)	0.507

LNG-IUS: Levonorgestrel-releasing intrauterine system; [@]IUD: Intrauterine device;

[•]Non-parametric Wilcoxon test for paired samples

Table III: Bone mineral density at both sections of the forearm at the 10th year of LNG-IUS use according to the different variables

Variables	N	Midshaft ulna (g/cm^2)	p-value	Ultra-distal radius (g/cm^2)	p-value
Age (years)			$0.751^{\$}$		$0.369^{\$}$
≤ 35	13	0.452 (0.012)		0.404 (0.017)	
36-40	15	0.464 (0.012)		0.409 (0.013)	
> 40	9	0.450 (0.025)		0.374 (0.024)	
BMI (kg/m^2)*			$<0.001^{+}$		0.002^{+}
< 25	19	0.426 (0.008)		0.371 (0.011)	
≥ 25	18	0.489 (0.011)		0.428 (0.014)	
Number of pregnancies			0.077^{+}		0.102^{+}
0-1	9	0.429 (0.016)		0.371 (0.018)	
≥ 2	28	0.465 (0.010)		0.408 (0.011)	
Smoker			0.275^{+}		0.452^{+}
Yes	3	0.424 (0.029)		0.374 (0.031)	
No	34	0.459 (0.009)		0.401 (0.010)	
Physical activity			0.496^{+}		0.991^{+}
Yes	4	0.474 (0.032)		0.399 (0.032)	
No	33	0.454 (0.009)		0.399 (0.010)	

*BMI: body mass index; $^{\$}$Snedecor test (ANOVA); $^{+}$ Student *t*-test for independent samples

Table IV: Variables associated with bone mineral density in users of the LNG-IUS at the 10th year of use according to multiple linear regression analysis [n=37].

Model/Variable	Coefficient	EP coefficient	p-value
Model 1: BMD at 10 years of use			
BMD midshaft ulna at the 7th year of use (g/cm^2)	0.798	0.050	<0.001
BMI (kg/m^2)	0.003	0.001	0.003
Amenorrhoea	0.024	0.011	0.033
Model 2: *BMD at the ultra-distal radius at 10 years of use*			
BMD at the ultra-distal radius at the 7th year of use (g/cm^2)	0.663	0.075	<0.001
BMI (kg/m^2)	0.005	0.001	<0.001

LNG-IUS: Levonorgestrel-releasing intrauterine system; *Dependent variable:* Bone mineral density (g/cm^2) (BMD) (at the 10th year of use of the LNG-IUS) in users of the LNG-IUS; *Model 1:* BMD at the midshaft ulna; *Model 2:* BMD at the ultra-distal radius; *Independent variables:* BMD (midshaft ulna or ultra-distal radius) at the 7th year of use; age (in years); BMI (kg/m^2); number of deliveries (<2/ ≥ 2); race (white/non-white); smoker (Yes/ No); physical activity (Yes/ No); occupation (physical/non-physical); age at menarche (age); bleeding pattern (amenorrhoea/spotting); exclusive breastfeeding (<2/≥ 2 months); schooling (elementary/other); coffee drinker (yes/no); alcohol consumption (yes/no); previous contraceptive method used (hormonal/non-hormonal).

5. Conclusões

– As densidades minerais ósseas do rádio distal (*midshaft ulna*) e ultradistal das usuárias do SIU-LNG aos 10 anos de uso foram estatisticamente similares às observadas aos sete anos de uso.

– A densidade mineral óssea do rádio distal (*midshaft ulna*) e ultradistal das usuárias do SIU-LNG aos sete anos de uso foi estatisticamente similar à de seus controles, usuárias de DIU TCu380A, mesmo quando pareadas por idade (± 1 ano), índice de massa corporal [IMC;kg/m^2, (± 1)], cor da pele e número de gestações (± 1).

– A densidade mineral óssea do rádio distal (*midshaft ulna*) e ultradistal das usuárias do SIU-LNG aos 10 anos de uso foi estatisticamente similar à de seus controles, usuárias de DIU TCu380A, mesmo quando pareadas por idade (± 1 ano), índice de massa corporal [IMC; kg/m^2, (± 1)], cor da pele e número de gestações (± 1).

– A maior densidade mineral óssea do rádio distal (*midshaft ulna*) e ultradistal das usuárias do SIU-LNG aos 10 anos esteve significativamente associada a um maior IMC (kg/m^2) e maior DMO aos sete anos de uso.

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7. Anexos

7.1. Anexo 1 – Termo de Consentimento Livre e Esclarecido

ESTUDO PROSPECTIVO DA AVALIAÇÃO DA MASSA ÓSSEA PELA DENSITOMETRIA EM MULHERES USUÁRIAS DE SISTEMA INTRAUTERINO LIBERADOR DE LEVONORGESTREL (SIU-LNG)

Nome da participante:_____

RG:_____

Endereço:_____

Telefone:_____

Eu fui informada que está sendo realizado o "Estudo prospectivo da avaliação da massa óssea pela densitometria em mulheres usuárias de sistema intrauterino liberador de levonorgestrel (SIU-LNG)". O objetivo deste estudo é avaliar a massa dos meus ossos do meu antebraço para saber se há a presença de uma doença que afeta os ossos, e que aparecer quando se usa um método para evitar gravidez que contém hormônios, como é o DIU com hormônio. Para participar da pesquisa terei que responder a questionário sobre meus dados pessoais, minhas gravidezes, partos, amamentação dos meus filhos, hábitos, atividade no trabalho e atividade física. Também irão tirar algumas medidas

como peso e altura. Terei que fazer um exame que libera raios- X e uma amostra de sangue será tirada do meu braço. O questionário e as medidas serão tirados uma única vez no dia de hoje.

Após receber toda a informação sobre o estudo, poderei perguntar todas as minhas dúvidas sobre a participação no estudo e sobre a doença que afeta os ossos, as consequências futuras e como evitá-la.

Também fui informada que não receberei pagamento ou ajuda financeira por participar deste estudo.

Fui esclarecida que no caso de não querer participar do estudo, a atenção que receberei no ambulatório, nesta consulta assim como em consultas posteriores, será a mesma sem nenhum prejuízo.

No caso de novas dúvidas, depois de ter ido embora, posso ligar ou procurar pessoalmente a pesquisadora responsável para esclarecê-las, Dra Maria Valeria Bahamondes Makuch, RNE: V099048-W, telefone: (19) 37887176, ou (19) 32892856, de segunda a sexta feira das 8:00 às 12:30 hs. Se tiver alguma dúvida sobre os aspectos éticos da pesquisa, também poderei contatar o Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da Unicamp pelo telefone (19) 37888936, em horário comercial.

Eu concordo voluntariamente em participar deste estudo.

Data _____/_____/_____

_____

Assinatura da voluntária

_____

Assinatura da pesquisadora

7.2. Anexo 2 – Instrumento

ESTUDO PROSPECTIVO DA AVALIAÇÃO DA MASSA ÓSSEA PELA DENSITOMETRIA EM MULHERES USUÁRIAS DE SISTEMA INTRAUTERINO LIBERADOR DE LEVONORGESTREL (SIU-LNG)

FICHA DE COLETA DE DADOS

Data: □□.□□.□□ **Nº no estudo : □□□-□**

□ SIU-LNG **□ DIU TCu380A** **Tempo de uso em meses:** □□

ANTECEDENTES PESSOAIS

Idade: □□ anos

Cor da pele: Branca □ Não branca □

Escolaridade: □ Analfabeta □ 1º grau completo □ 1º grau incompleto
□ 2º grau completo □ 2º grau incompleto □ Superior □ Outro ----------
Ocupação: Sim □ Não □
Peso □□□kg Altura □□□cm IMC: □□□

HÁBITOS DE VIDA

A senhora fuma?
Não □ Sim □ ⇨ Há quanto tempo? □□anos Quantos cigarros/dia? □□

A senhora toma café?
Não □ Sim □ ⇨ Há quanto tempo? □□ anos
Quantos cafés/dia? □□

A senhora consome bebidas alcoólicas?
Não □ Sim □ ⇨ Há quanto tempo? □□ anos
Quantas doses/dia? □□

Faz alguma atividade física (por ex. Ginástica): sim □ não□

Lava roupas manualmente? Sim □ não□

ANTECEDENTES GINECO OBSTÉTRICOS

Idade da menarca: □□ anos G□ P□ A□ C□

Tempo de amenorreia: □□ DUM: □□.□□.□□

Menstrua regularmente: Sim□ Não□

Quantos filhos foram amamentados: □□

Tempo total de **amamentação exclusiva** (no total de filhos): □□□ meses

Tempo total de **amamentação parcial** (no total de filhos): □□□ meses

USO ANTERIOR DE ANTICONCEPÇÃO HORMONAL

Método: AMP-D:□ Injetável mensal:□ ACO: □ Nenhum□

Por quanto tempo: □□□meses

ANTECEDENTES CLÍNICOS

Uso crônico de medicamentos: Não□ Sim□ Qual?_____

Doenças crônicas: Não□ Sim □ Qual?_____

DENSIDADE MINERAL ÓSSEA

DMO distal: □.□□□**g/cm^2** DMO ultradistal: □.□□□**g/cm^2**

OBSERVAÇÕES:_____

_____

_____

Questionário aplicado por: _____

Densitometria óssea aplicada por: _____

Iniciais □□□ PF □□□□□

7.3. Anexo 3 – Carta de aprovação do projeto CEP/FCM/Unicamp

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

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

CEP, 21/10/08.
(Grupo III)

PARECER CEP: N° 842/2008 (Este n° deve ser citado nas correspondências referente a este projeto)
CAAE: 0669.0.146.000-08

I - IDENTIFICAÇÃO:

PROJETO: **"ESTUDO PROSPECTIVO DA AVALIAÇÃO DA MASSA ÓSSEA PELA DENSITOMETRIA EM MULHERES USUÁRIAS DE SISTEMA INTRAUTERINO LIBERADOR DE LEVONORGESTREL (SIU-LNG)".**
PESQUISADOR RESPONSÁVEL: Maria Valeria Bahamondes Markuch
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 10/10/2008
APRESENTAR RELATÓRIO EM: 21/10/09 (O formulário encontra-se no *site* acima)

II - OBJETIVOS

Avaliar a densidade mineral óssea e os níveis de estradiol em usuárias do SIU-LNG aos 9 anos de uso e compará-los com os de usuárias de SIU-LNG aos 7 anos de uso e com um grupo controle de usuárias de método anticoncepcional não hormonal.

III - SUMÁRIO

Trata-se de um estudo será de coorte prospectiva. Serão selecionadas 37 mulheres com 9 anos de uso do SIU-LNG e igual numero de mulheres que usam o DIU TCu380A (pareadas por idade ± 1 ano e índice de massa corporal [Kg/m2] ± 1) que procuram o Ambulatório de Planejamento Familiar para seguimento. Nelas será medida a densidade mineral óssea (DMO) e colhida uma amostra de sangue para medir o estradiol sérico. Analise dos dados: os dados da DMO e do estradiol serão comparados entre ambos os grupos e entre usuárias de 7 e 9 anos e avaliados pelos testes t de Student para amostras emparelhadas, e Índice de correlação ou regressão linear.

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 estatística muito bem embasados por cálculos estatísticos. Os aspectos éticos estão bem discutidos no corpo do projeto e o Termo de Consentimento Livre e Eclarecido é claro e adequado às recomendações. O orçamento é detalhado e os gastos serão cobertos pelo Projeto temático FAPESP n°: 03/08391-7 já aprovado.

Recomendadmos que o telefone do Comitê de Ética em Pesquisa seja corrigido.

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, bem como ter aprovado o Termo do Consentimento Livre e Esclarecido, assim 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 X Reunião Ordinária do CEP/FCM, em 21 de outubro de 2008.

Profa. Dra. Carmen Sílvia Bertuzzo
PRESIDENTE DO COMITÊ DE ÉTICA EM PESQUISA
FCM / UNICAMP

7.4. Anexo 4 – Artigo de revisão bibliográfica

EXPERT REVIEWS

Levonorgestrel-releasing intrauterine system: uses and controversies

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Luis Bahamondes†, M Valeria Bahamondes and Ilza Monteiro

†Author for correspondence
Department of Obstetrics and Gynecology, School of Medicine, University of Campinas, Caixa Postal 6181, 13084-971 Campinas, SP, Brazil
Tel.: +55 193 289 2856
Fax: +55 193 289 2440
bahamond@caism.unicamp.br

This article provides a perspective on the use of the levonorgestrel-releasing intrauterine system as a contraceptive method and as therapy in different situations, as well as presenting the corresponding controversies and unresolved issues. All studies have reported high contraceptive efficacy, an improvement in menstrual blood loss in women with idiopathic menorrhagia, menorrhagia due to thrombophilic diseases and fibroids, and excellent endometrial protection during postmenopausal estrogen therapy. Moreover, the device is able to reduce pelvic pain and dysmenorrhea as well as improve the staging of endometriosis and adenomyosis, and to control, albeit partially, endometrial hyperplasia. The expectation is that in years to come the number of hysterectomies and female sterilizations will fall due to increased use of the device, including use by patients with endometriosis and HIV-positive women. It would also be desirable to develop a smaller device for postmenopausal women and nulligravidas.

KEYWORDS: levonorgestrel-releasing intrauterine system • LNG-IUS

Development of the levonorgestrel-releasing intrauterine system

Luukkainen and coworkers began development of the levonorgestrel (LNG)-releasing intrauterine system (LNG-IUS; Mirena®, Bayer Schering Pharma Oy, Turku, Finland) in 1970 [1]. It has been licensed in 120 countries as a contraceptive and in many countries as a treatment for menorrhagia and as endometrial protection during postmenopausal estrogen therapy (ET). There is evidence that it may also be useful in women with endometriosis, adenomyosis and endometrial hyperplasia [2].

The device releases LNG, a steroid used widely in combined oral contraceptives (COC) and implants. Early studies showed health benefits, including a reduction in menstrual blood loss (MBL) with a consequent improvement in dysmenorrhea and anemia [3]. Amenorrhea, or spotting, has been recorded in approximately 20% of users in clinical trials [4] and in up to 60% of users in other studies [5].

The device consists of a plastic, T-shaped frame impregnated with barium sulphate to render it radio-opaque, with a steroid reservoir around the vertical stem. The reservoir is a cylinder composed of a mixture of 52 mg LNG and one copolymer covered by a membrane that regulates the release of LNG to 20 µg/day (FIGURE 1).

Pharmacokinetics

The LNG-IUS releases the steroid into the uterus where it is rapidly absorbed by the capillaries of the basal layer of the endometrium and thereafter into the general circulation. LNG is detected in plasma 15 min following insertion [1] and plasma levels of 150–200 pg/ml were observed a few hours later, albeit with large individual variations [1]. Tissue levels of LNG in the myometrium, fallopian tube and fat ranged from 1 to 5 ng/g of wet tissue weight; nevertheless, LNG levels in the endometrium were high, ranging from 470 to 1500 ng/g, thereby explaining the potent effect of this progestin on the endometrium [1]. Despite the decline in LNG levels throughout the years of use, the device provides contraceptive protection for up to 5 [1] or 7 years [6,7], although 5 years is the regulatory agreement. Serum levels of LNG were significantly higher in anovulatory compared with ovulatory cycles, and amenorrhea was most often present in ovulatory cycles, thereby confirming the effect of LNG on the endometrium [1].

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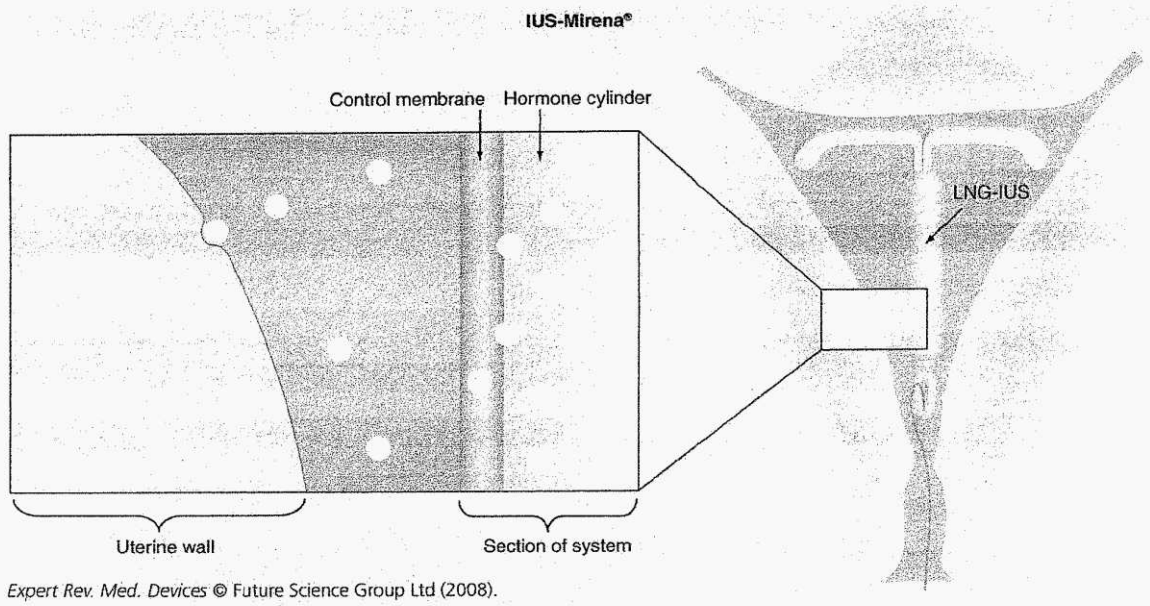

Figure 1. Details of the levonorgestrel-releasing intrauterine system.
LNG: Levonorgestrel; IUS: Intrauterine system.

Mechanism of action

Despite normal circulating estradiol (E2) levels, the LNG affects cervical mucus production, rendering it scanty and viscous [1] and possibly hampering sperm penetration of the zona pellucida [8]. The progestational activity of LNG [9] induces atrophy of the endometrial glands, the stroma undergoes a decidual reaction, and the mucosa and the epithelium become inactive [10,11]. Blood vessels become thick walled and fibrotic, often associated with suppression of spiral arterioles and thrombosis in capillaries [10]. An inflammatory reaction may occur, with leukocytic infiltrates, plasma cells and macrophages, and stromal necrosis [12]. The endometrium becomes insensitive to E2 mediated by the regulatory action of the high levels of LNG in the uterus.

The anovulation rate is almost 85% at the beginning of use and falls to less than 15% at the end of the first year [1]. E2 and progesterone levels are compatible with ovulatory cycles [1], even in long-term users, and are correlated with normal bone mineral density [13]. Ovarian function probably does not depend on serum LNG levels, which remain stable between the second and fifth years of use. Furthermore, a prevalence of functional ovarian cysts has been described in almost 19% of users, indicating normal follicular development. Most of these cysts disappear spontaneously [14,15].

Metabolic effects & other aspects of use

The effects of the LNG-IUS were evaluated in women with uncomplicated, insulin-dependent, Type 1 diabetes and showed that mean glycosylated levels, fasting-serum glucose levels, and daily insulin doses were unaffected even at the beginning of use [16]. Others evaluated hemoglobin, hematocrit, thrombelastography, tissue-type plasminogen activator (t-PA), urokinase plasminogen activator (u-PA), u-PA receptor (u-PAR), plasminogen activator inhibitor (PAI) -1/2, D-dimer, and von Willebrand factor (vWF) in blood and t-PA, u-PA and PAI-1/2 in endometrial tissue samples from women with menorrhagia of known pathological cause [17]. No changes occurred in the fibrinolytic/inhibitor systems or in VWF except for a decrease in u-PAR levels; however, significant increases in PAI-1/2 and u-PAR levels were observed in the endometrium, suggesting that systemic hemostasis was unaffected by the LNG-IUS.

Lower levels of high-density lipoprotein (HDL)-cholesterol and triglycerides were more likely in LNG-IUS users compared with nonusers, as were total and non-HDL-cholesterol levels [18]. Users presented an elevated risk of low HDL-cholesterol concentrations, reduced risks of high triglyceride and an unchanged total:HDL-cholesterol ratio [18]. However, high HDL-cholesterol levels were associated with a longer duration of use of the LNG-IUS, while the decrease in the release of LNG over time is apparently consistent with lower blood pressure, although one study has described a slight increase [19]. Consequently, users had at least equally favorable cardiovascular risk factors as nonusers [18].

No significant weight increase was reported at the end of 5 years of use [20] and there was no effect on the cervical smears or vaginal flora of long-term users [21,22]. However, the occurrence of pelvic inflammatory disease (PID) is controversial. The cumulative 36-month rate was found to be significantly lower among users of the LNG-IUS compared with users of a

copper intrauterine device (IUD) [23]; however, other investigators have failed to find any differences in the occurrence of PID between users of the LNG-IUS and the copper IUD [24,25]. The protective effect may be justified by the thickness of the cervical mucus, endometrial suppression and the reduction in MBL, which hampers the entry of bacteria into the upper reproductive tract [26].

Several publications have presented information on insertion during the postpartum, lactation or post-abortion periods. Insertion 6 weeks after delivery in breast feeding, amenorrheic women resulted in no differences being found between users and nonusers with respect to infant weight gain and growth, age of first teething, age at walking, and morbidity from infectious diseases. Moreover, no differences were found between the groups with respect to various metabolic parameters evaluated in these children [27]. LNG in the milk of breastfeeding women was approximately 25% of serum levels [28]. Insertion of the LNG-IUS at the time of first trimester elective abortion is a safe procedure and resulted in a 5-year cumulative gross pregnancy rate of 0.8 and an expulsion rate of 10.5, significantly better than rates found in a group of copper IUD users [29–31].

Side effects

Despite the low LNG plasma levels, hormonal side effects such as headache, mastalgia, nausea, acne, hirsutism, edema, lower abdominal and back pain, increased vaginal discharge, and mood changes are seen [1]; however, the overall incidence was low, peaking at 3 months of use and decreasing over time, and the discontinuation rate for these reasons is very low (almost 6–7/100 women per year) [1] if adequate counseling is provided [31]. Additionally, removals due to bleeding problems were 4.5/100 women per year [1]. The most common side effect and the most important reason for discontinuation is irregular uterine bleeding, prolonged spotting being the most frequent irregularity, principally in the first months following insertion [5]; however, a reduction in MBL is observed, a significant number of users becoming amenorrheic by the end of the first year of use [5,19].

LNG-IUS as a contraceptive method

The first randomized clinical trial (RCT) reported a 12-month pregnancy rate of 0.1 and 0.9 per 100 women for the LNG-IUS and copper IUD, respectively [32], while other investigators have reported a rate of 1.1 and no ectopic pregnancies at 7 years of use of a device loaded with 60 mg of LNG, releasing 20 µg/day [24]. A further RCT demonstrated no pregnancies among users of the LNG-IUS and 11 pregnancies with copper IUDs at 3 years of follow-up [25]. These results have been confirmed in other studies that have reported a Pearl index of 0–0.1 [33] or a 5-year Pearl rate of 0.1 [33,34], similar to that found with tubal ligation [35], or no pregnancies up to 7 years of use [5,6,36]. Pregnancy outcome was analyzed through questionnaires sent to 17,360 users, resulting in the identification of 64 pregnancies in which conception occurred with the LNG-IUS *in situ*. Among these, 33 pregnancies (51.6%) were ectopic [34]. This figure demonstrates that due to the high contraceptive efficacy of the device, the probability of ectopic pregnancy with the LNG-IUS *in situ* is very low and the rate of ectopic pregnancy is one of the lowest among users of different contraceptive methods [7], with a 5-year rate of 0.02/100 women per year, lower than that found with the Nova-T IUD (0.25) or among nonusers of other contraceptive methods (7.5–10.6/100 women per year) [33,36].

An important issue in contraceptive failure is inadvertent expulsion. An expulsion must be suspected if normal menstrual bleeding recommences in a previously amenorrheic woman, and it is important to counsel users in this respect. After removal of the device, the endometrium reverts to normal almost immediately and the return to fertility has been confirmed by a cumulative conception rate of 79.2 and 86.6 per 100 women after 12 and 24 months, respectively [37], similar to that of former users of the copper IUD.

Health benefits of LNG-IUS use for approved indications

Idiopathic menorrhagia

Idiopathic menorrhagia is defined as MBL of more than 80 ml without any pelvic or systemic disease; however, measurement of MBL is a complicated procedure in clinical practice [38]. The most common forms of treatment include hysterectomy, endometrial resection or ablation, oral medical therapy and the insertion of a LNG-IUS. Following insertion of LNG-IUS, the reduction in MBL is progressive, with a reduction of 97% by the end of the first year of use [39,40]. Comparison of the LNG-IUS and other medical treatments for menorrhagia has shown a 97% reduction in MBL at the end of the first year compared with a reduction of 44% with either flurbiprofen or tranexamic acid [40,41]. Similar results were observed when the LNG-IUS was compared with oral norethisterone [42], mefenamic acid [43] or with medical therapies in women awaiting hysterectomy [44]. After 6 months, 64.3% of women in the LNG-IUS group and 14.3% of the controls had cancelled surgery, and the 12-month continuation rate for the LNG-IUS was 47%.

Comparison with transcervical endometrial resection (TCRE), endometrial ablation and hysterectomy demonstrated that both the LNG-IUS and endometrial ablation significantly reduce MBL for up to 3 years [45–47]; however, endometrial ablation requires anesthesia, and the risk of complications is greater than with the LNG-IUS [47]. Comparison with thermal balloon ablation or TCRE demonstrated significantly less MBL in users of the LNG-IUS, although patient satisfaction was similar in the two groups [47,48]; however, costs were halved with the LNG-IUS and quality of life was better [49], although one study reported more side effects among users of the LNG-IUS [48].

When menorrhagic women were randomized receive to a LNG-IUS or hysterectomy [49,50], 48% of the women still had the LNG-IUS *in situ* at their 5-year follow-up and had avoided surgery. Almost 75% were in amenorrhea. Quality of life was found to be improved in both groups with respect to the domains of health, psychological well-being and patient satisfaction, and differences were not statistically significant. Costs were significantly higher in the hysterectomy group.

Endometrial protection during estrogen therapy

Although fertility decreases during the menopausal transition, contraception is still required; in addition, there is a risk postmenopause that ET may stimulate the endometrium through the presence of E2 without progesterone as an antagonist. The LNG-IUS is a good option for the period of menopausal transition and for nonhysterectomized postmenopausal women using ET [2,51,52]. Use of the LNG-IUS allows ET to be implemented, and the systemic effect of the progestin is very low. Studies on peri- or postmenopausal women using the LNG-IUS include data on almost 850 women [52,53]. Insertion of the LNG-IUS provokes a 'biochemical hysterectomy' and provides endometrial protection. Different estrogens, different doses and different routes of administration have been used with similar results over periods ranging from 6 months to 5 years.

After 6 months of use, amenorrhea ranged from 64 to 98% [53] and was correlated with an endometrial thickness of 2–3 mm [54] and with endometrial biopsies showing no proliferation or epithelial atrophy and no cases of endometrial hyperplasia or carcinoma [42,54–60] at 5 years, with a continuation rate of 80% [60], few menopausal symptoms [55], few steroidal side effects [52,53] and no increase in C-reactive protein [61].

Health benefits of LNG-IUS use for indications not yet approved

Sufficiently addressed issues

Endometriosis & adenomyosis

Of the medical and surgical treatments of endometriosis, GnRH analogues (GnRH-a) remain the gold standard [62], although the effect of the hypoestrogenism provoked by GnRH-a on bone mineral density is a concern that limits their use [62]. Many women with endometriosis wish to postpone pregnancy for a while and need long-term therapy for the relief of symptoms. The LNG-IUS is a new therapeutic option that has been used in endometriosis and adenomyosis [63]. Two studies have shown a reduction in MBL and in the visual analogue pain scale (VAS) at 12 months of use in women with severe dysmenorrhea following conservative surgery [64,65], while others have reported pain control and a reduction in lesions of the rectovaginal septum [66].

Comparison between the LNG-IUS and a GnRH-a [67] showed a significant reduction in VAS pain score throughout the 6 months of the study, the pain score improving faster in women with stage III or IV endometriosis. Amenorrhea was achieved faster with the GnRH-a compared with LNG-IUS; however, by 6 months 98% of the LNG-IUS patients were in amenorrhea. Hormonal side effects were similar in both treatment groups; however, LNG-IUS users reported more symptoms of breast tenderness [67]. These results were confirmed by others, who reported a continuation rate of 56% at the 3-year follow-up evaluation [68,69].

Reports on the use of the LNG-IUS in adenomyosis are sparse; however, all have confirmed the successful control of dysmenorrhea and MBL, and a reduction in the junctional zone thickness when evaluated by MRI [70]. Nevertheless, whether any reduction is achieved in uterine volume is still under debate, and the efficacy in reducing focal lesions remains to be confirmed [70].

Insufficiently addressed issues

Endometrial hyperplasia

The best treatment for endometrial cancer is surgery; however, there are several cases in which surgery is contraindicated for medical reasons. In these cases, insertion of a LNG-IUS may be an alternative and there have been reports of its use in a several cases of endometrial hyperplasia; however, no RCT has yet been published on this subject [71–75]. Most of the reports show complete histological regression of the hyperplasia irrespective of its pattern and show hypotrophic or atrophic endometrial mucosa with pseudodecidual reaction. Women with endometrial hyperplasia of the highest malignant potential were those who benefited most, the LNG-IUS proving better than oral progestin treatment [76].

In the aggregate, Gardner *et al.* randomized postmenopausal women with breast cancer who were using tamoxifen to a LNG-IUS or common endometrial surveillance [77]. A decidual response was found in users of the LNG-IUS and no new polyps developed. Similar results have been reported by others [78], with a 1-year continuation rate of 95%.

Thrombophilic diseases

Menorrhagia is a common complaint, occurring in 74 and 59% of women with von Willebrand's disease and factor XI deficiency, respectively [79]. The LNG-IUS is an excellent option because it offers high contraceptive efficacy with no need for daily pill taking and few systemic effects [80], as evaluated by MBL, quality of life and satisfaction in women with hematological disorders. The studies included women with menorrhagia, principally vWF, Factor XI deficiency or other hematological diseases and/or women receiving warfarin for a thrombotic disorder, in all of whom previous medical treatment had failed [81–84]. Following insertion of the LNG-IUS, spotting was observed at the beginning of use; however, amenorrhea or a significant reduction in MBL with an increase in hemoglobin levels was found in most of the enrolled patients.

Use in HIV-positive women

Use of the LNG-IUS in HIV-positive women is an interesting option because it offers effective contraception [85] with a reduction in MBL and a low rate of PID. Data are sparse [86]; however,

insertion of a LNG-IUS led to decreased MBL, with some women experiencing only spotting or no bleeding. The use of antiretroviral medication did not affect LNG levels or viral load.

Leiomyoma

Fibroids have been reported to be less common among users of the LNG-IUS compared with users of the copper IUD [24], and there is a hypothesis that the LNG-IUS has a protective effect. Although prospective studies are few [87–90], most have reported a reduction in MBL, an improvement in hemoglobin and a decrease in endometrial thickness [15]. The effect on the volume of the uterus and fibroids is controversial, some studies reporting a reduction in size and others reporting no improvement [15,89,90]. It would appear that the effect of the LNG-IUS is limited to a reduction in MBL due to effects on the endometrium and that it is not beneficial in reducing the size of the fibroids or the uterus. To the best of our knowledge, there is probably no effect.

Expert commentary & five-year view

Since the launch of the LNG-IUS, millions of women worldwide have used or are using the device for contraception or for other therapeutic purposes. Although its approved time of use is 5 years, there is evidence that the device may be effective for longer and although this limit cannot be changed, physicians and users must be assured that the time window around the 5-year mark is wide enough to permit replacement after that date. In many countries, introduction of the device occurred only a few years ago and many women are now approaching the time for replacing it. Although there is evidence that replacement of the device is a safe and simple procedure [19], a slight increase in the number of difficult insertions has been reported compared with the first insertion. One of the problems is that the LNG-IUS is 1 mm wider than the insertion tube of the copper IUD and it is hoped that the manufacturer may develop a new, thinner device. Although E2 levels were in the normal range [1,2], the fact that the target organ (the cervix) became insensitive to estrogens may explain the slight difficulty found in some cases at the second or third insertion.

One consequence of the use of the LNG-IUS may be the 75% decrease in tubal ligation observed in Newcastle (UK) over the past 9 years, with a corresponding increase in the use of the LNG-IUS and subdermal implants [91,92], both of which have the advantage of being reversible methods. In addition, the LNG-IUS has been found to be as effective as medical or surgical treatment for menorrhagia [49,50], even when MBL is caused by hematological diseases or the use of anticoagulant drugs; however, clotting factors have been studied less than MBL and it is essential to obtain more data since these women require long-term treatment.

In England, the beginning of a decrease in the number of hysterectomies coincided with the launching of the device [93]. We expect this pattern to be repeated in other countries, since the device is safe for women and less expensive for health services. We suggest that surgery be reserved only for women in whom medical treatments are unsuccessful; however, the LNG-IUS is approved in the USA only for contraception, its use for other purposes being off-label. In addition, in women with menorrhagia, the expulsion rate may be higher than in users of the device for contraception [39], and expulsion is more likely if it is inserted during heavy bleeding. In women with hematological diseases, it is important to prevent bleeding complications. MBL was controlled in HIV-positive women; however, the prevalence of HIV-positive women is highest in countries with poor medical care where the LNG-IUS is inaccessible to them. It is a challenge for physicians and stakeholders to try to influence policy makers to offer the LNG-IUS to low-income women for whom this device is important.

The use of the LNG-IUS as postmenopausal endometrial protection is under-report in the medical literature. Postmenopausal women benefit from the use of the device because it creates a 'chemical hysterectomy', providing excellent protection during ET, thereby avoiding the need for combined therapy with progestins [52]. The inconvenience is that insertion may be more difficult in women with an atrophic uterus who are not receiving ET. One strategy is to provide estrogen for a few days prior to insertion of the device. Small devices are desirable for postmenopausal women and are currently under evaluation [94], although one small LNG-IUS has been evaluated previously up to 5 years with similar excellent results to the existing device [95]. In addition, the use of the LNG-IUS is a good strategy for women in the menopausal transition when they start to experience menstrual irregularities, since it offers contraceptive efficacy and a reduction in MBL, while allowing ET to be initiated after the menopause.

One of the main concerns of the use of the LNG-IUS in postmenopausal women may be breast cancer [96,97]. However, these studies were conducted with oral or transdermal progestins. One study sent questionnaires to 23,885 women who had used a LNG-IUS [98]. The estimated incidence of breast cancer (with 95% confidence intervals) in the general female population was higher than that found among LNG-IUS users and there was no relationship between the duration of use and the incidence of breast cancer, hence there is probably no causal relationship. New studies are expected to confirm the findings of the previous one [98], thereby reassuring the millions of users of this device with respect to its safety. It should be noted, however, that the number of cancer cases detected among LNG-IUS users may be affected since users of this device habitually attend their gynecologist annually for follow-up visits.

Owing to the control of LNG-IUS upon pain and bleeding in endometriosis and adenomyosis, and due to the number of women with these diseases and the fact that many do not wish to conceive, it is expected that new studies will be published allowing a license to be issued for this indication. The main advantage is long-term use following a single intervention, representing a cost-effective treatment with no inconvenience and no effect on bone mineral density [13]. Owing to the epidemic of obesity occurring in many Western countries, the prevalence of endometrial hyperplasia may be increasing in young women.

Although surgery is the best treatment, for women with comorbid conditions or those who desire to preserve their fertility the LNG-IUS may represent a good option.

Although the LNG-IUS is an excellent method, the possibility of failure and hormonal side effects exists, and in some women MBL cannot be controlled, particularly in those suffering from menorrhagia. Expulsions are rare but may be followed by contraceptive failure and are more common in women with a distorted uterine cavity [99]. Counseling prior to insertion and during use is mandatory to avoid premature discontinuation and must make reference to the few hormonal side effects and expected bleeding patterns. Additionally, providers must be well trained before beginning insertions, since the technique is different from that used to insert the common copper IUD. Adequate training will avoid rare complications, such as perforation and expulsions.

Financial & competing interests disclosure

Luis Bahamondes has provided consultancies for Bayer Schering Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The levonorgestrel-releasing intrauterine system (LNG-IUS) is a contraceptive method with a very low pregnancy rate similar to that of tubal ligation.
- It dramatically reduces menstrual blood loss in users of the device for contraception, amenorrhea occurring at the end of the first year in many cases.
- Although bleeding disorders, side effects and hormonal side effects are few, physicians must counsel potential users regarding this issue.
- The LNG-IUS offers many noncontraceptive benefits, including a reduction in menstrual blood loss in menorrhagic women, leading to an improvement in anemia and iron deficiency similar to that obtained with other clinical and surgical treatments, while maintaining high contraceptive efficacy, even in women with hematological diseases.
- It is approved for use as endometrial protection in postmenopausal women on estrogen therapy.
- It reduces the incidence of dysmenorrhea in the general population, and chronic pelvic pain and dyspareunia in women with endometriosis and adenomyosis, also resulting in an improvement in the staging of endometriosis.
- Bleeding patterns improve in women with uterine fibroids, although it is debatable whether there is any reduction in uterine volume or in the fibroids.
- It may be used by women with endometrial hyperplasia, although only as a presurgical treatment or in women with contraindications to surgery.
- Its use has no effect on multiple variables in HIV-positive women under antiretroviral therapy and the pharmacokinetics of levonorgestrel are similar to those of nonusers of antiretroviral.

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Affiliations

- Luis Bahamondes, MD, PhD
Professor of Gynecology, Department of Obstetrics and Gynecology, School of Medicine, University of Campinas, Caixa Postal 6181, 13084-971 Campinas, SP, Brazil
Tel.: +55 193 289 2856
Fax: +55 193 289 2440
bahamond@caism.unicamp.br
- M Valeria Bahamondes, MD
MSc student, Department of Obstetrics and Gynecology, School of Medicine, University of Campinas, Caixa Postal 6181, 13084-971 Campinas, SP, Brazil
Tel.: +55 193 289 2856
Fax: +55 193 289 2440
vbahamondes@cemicamp.org.br
- Ilza Monteiro, MD, PhD
Associate Professor, Department of Obstetrics and Gynecology, School of Medicine, University of Campinas, Caixa Postal 6181, 13084-971 Campinas, SP, Brazil
Tel.: +55 193 289 2856
Fax: +55 193 289 2440
ilza@caism.unicamp.br