WALESKA OLIVEIRA MODESTO

AVALIAÇÃO DE ASPECTOS CLÍNICOS, DENSIDADE MINERAL ÓSSEA, COMPOSIÇÃO CORPORAL E PESO ENTRE USUÁRIAS DE CONTRACEPTIVOS DE SOMENTE PROGESTÁGENOS.

ASSESSMENT OF CLINICAL, BONE MINERAL DENSITY, BODY COMPOSITION AND WEIGHT AMONG USERS OF PROGESTIN-ONLY CONTRACEPTIVES.

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ASSESSMENT OF CLINICAL, BONE MINERAL DENSITY, BODY COMPOSITION AND WEIGHT AMONG USERS OF PROGESTIN-ONLY CONTRACEPTIVES.

Tese apresentada à Pós-Graduação em Tocoginecologia da Faculdade de Ciências Médicas da Universidade Estadual de Campinas para a obtenção do título de Doutora em Ciências da Saúde, área de concentração Fisiopatologia Ginecológica.

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ORIENTADOR: PROF. DR. LUIS GUILLERMO BAHAMONDES

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RESUMO

A diminuição da densidade mineral óssea (DMO), o ganho do peso e as alterações nos padrões de sangramento são frequentemente associados ao uso dos métodos de somente progestágeno. Aspectos não completamente elucidados quanto ao momento e tempo de ocorrência podem prejudicar a continuação e ocasionar descontinuação prematura ou induzir morbidades. **Objetivos**: Avaliar a DMO, ganho do peso e taxas de descontinuação por transtornos de sangramento dos métodos de somente progestágenos. **Sujeitos e Métodos**: realizaram-se quatro estudos sobre a influência do acetato de medroxiprogesterona de depósito (AMPD): A) sobre a DMO e a composição corporal (CC) de suas usuárias a partir dos 12 meses até os 23 anos de uso; B) sobre ganho de peso em usuárias do AMPD, do sistema liberador de levonorgestrel (SIU-LNG) e do dispositivo intrauterino com cobre (DIU) até 10 anos de uso, C) sobre a influência do implante liberador de etonogestrel (ENG) na DMO e na CC até 24 meses de seguimento e D) avaliamos a influência de diferentes orientações em relação aos distúrbios do sangramento nas taxas de continuação das usuárias de SIU-LNG, implante liberador de ENG e DIU. **Resultados**: a DMO, aos 12 meses de uso do AMPD, foi menor na coluna lombar quando comparadas a usuárias de DIU e, aos 10 anos de uso, 29,8% das usuárias do AMPD apresentaram osteoporose comparado a 2,4%

das usuárias de DIU. Na CC, observou-se que, aos 12 meses, ocorreu um aumento de 2kg de massa gorda e 2% na porcentagem de massa gorda nas usuárias de AMPD, porém, a longo prazo, não houve diferença na quantidade de massa gorda quando comparadas a usuárias de DIU. O peso aumentou ao final do primeiro ano em 1,3kg, 0,7kg e 0,2kg e, aos 10 anos, em 6,6kg, 4,0kg e 4,9kg nas usuárias de AMPD, SIU-LNG e DIU, respectivamente. Nas usuárias do implante liberador de ENG ocorreu uma diminuição da DMO da coluna lombar aos 12 meses e um aumento de 2% a 2,7% da massa gorda aos 12 e 24 meses comparadas a usuárias de DIU. Mulheres que receberam orientações de rotina ou intensivas quanto ao padrão de sangramento esperado não mostraram diferenças significativas nas taxas de descontinuação do SIU-LNG, do implante liberador de ENG e do DIUT. **Conclusões**: O uso do AMPD ocasionou uma diminuição na DMO no primeiro ano de uso, essa diminuição foi progressiva e aumentou a prevalência de osteoporose em longo prazo. Usuárias do AMPD, SIU-LNG e DIU apresentaram ganho do peso aos 10 anos de uso, sendo maior em usuárias de AMPD. A massa gorda aumentou no primeiro ano de uso do AMPD, porém não foi significante em longo prazo quando comparada a usuárias do DIU. Em usuárias do implante liberador de ENG foram encontrados ganhos do peso e da massa gorda aos 24 meses e diminuição da DMO após 12 meses. As estratégias de orientação de rotina e intensivas não apresentaram diferenças nas taxas de continuação das usuárias do implante liberador de ENG , SIU-LNG e DIU.

Palavras-chave: métodos contraceptivos, peso corporal, composição corporal, densidade óssea, progestágenos.

ABSTRACT

The decrease in bone mineral density (BMD), weight gain and changes in uterine bleeding patterns are often associated with the use of progestin-only methods. Aspects not still elucidated and the moment of occurrence could harm the continuation and provoke premature discontinuation or induce morbidities. **Objectives**: To evaluate BMD, weight gain and discontinuation rates for bleeding disturbances of progestin-only methods. **Subjects and Methods**: Four studies were conducted with depot medroxyprogesterone acetate (DMPA) users: A) regarding BMD and body composition (BC) from 12 months to 23 years of use; B) on weight gain among DMPA users, the levonorgestrel-releasing intrauterine system (LNG-IUS) and cooper-intrauterine device (IUD) up to 10 years of use; C) on the influence of the etonogestrel-releasing implant (ENG) upon BMD and BC up to 24 months of follow-up; and D) to evaluate the influence of two counseling strategies regarding to bleeding disorders in continuation rates of the users of the LNG-IUS, ENG-implant and IUD. **Results**: BMD after 12 months of DMPA use was lower at the lumbar spine compared to IUD users and 29.8% has osteoporosis among those women who had used DMPA for 10 years or more compared to 2.4% of IUD users. Regarding BC, at 12 months of use it was observed, an increase of 2 kg of fat mass and 2% in the percentage of fat mass in DMPA users; however, in

the long-term use, there was no difference in the amount of fat mass compared to IUD users. The weight increased at the end of the first year was 1.3kg, 0.7kg and 0.2kg and, at 10 years, was 6.6kg, 4.0kg and 4.9kg among DMPA-, LNG-IUS- and IUD-users, respectively. Users of the ENG-implant showed a decrease in BMD at lumbar spine after 12 months of use and an increase of 2% to 2.7% of fat mass at 12 and 24 months when compared to IUD-users. Women who received routine or “intensive” counseling about the expected bleeding patterns showed no significant differences regarding the rates of discontinuation of LNG-IUS, ENG-implant and IUD. **Conclusions:** Users of DMPA showed a decrease in BMD at the end of the first year of use, the decrease was progressive and an increased prevalence of osteoporosis in the long-term use was observed. DMPA, LNG-IUS and IUD users showed weight gain after 10 years of use, higher in DMPA users. Fat mass increased in the first year of DMPA use; however, was not significant in the long-term when compared to IUD-users. In ENG-implant users it was found a weight gain and increase of fat mass at 24 months and a reduction in BMD after 12 months of use. The routine and “intensive” counseling showed no differences in rates of continuation in ENG-implant, LNG-IUS- and IUD-users.

Key words: contraceptive agents, body weight, body composition, bone density, progestins.

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SIGLAS E ABREVIATURAS

ACOS – Anticoncepcionais combinados orais

AMPD – Acetato de medroxiprogesterona de depósito

CC – Composição corporal

DIU TCu380A – Dispositivo intrauterino com cobre

DMO – Densidade mineral óssea

DP – Desvio padrão

DXA – *Dual-photon absorptiometry*

ENG – Etonogestrel

FFM – Massa corporal livre de gordura

IMC – Índice de massa corporal

MACs – Métodos anticoncepcionais

LARC – *Long-acting reversible contraceptives*

SIU-LNG – Sistema intrauterino liberador de levonorgestrel

TBBM – Conteúdo mineral total

TBW – Total de água no corpo

UV – Ultravioleta

1. INTRODUÇÃO GERAL

Os contraceptivos reversíveis de longa duração (*Long-acting reversible contraceptives* [LARC]) incluem o dispositivo intrauterino (DIU) com cobre (dos quais o mais comum é o TCu380A), o sistema intrauterino liberador de levonorgestrel (SIU-LNG) e os implantes subdérmicos, dos quais o único disponível no Brasil é o liberador de etonogestrel (ENG) (1). São os métodos anticoncepcionais reversíveis mais eficazes, com a característica de serem convenientes, custo-efetivos e que precisam de uma única ação para início de uso (2). Estas características os tornam diferentes dos outros métodos que dependem da usuária, como contraceptivos orais combinados, anel vaginal, adesivo ou condom, que apresentam maior risco de falha do método. Os métodos LARC têm taxas de falha em "uso típico" similar às de "uso perfeito", entendendo como "uso típico" aquele que depende da mulher e "uso perfeito" aquele que não requer de atenção pela usuária (1).

Os métodos LARC são "livres de esquecimento", e sua alta eficácia é comparável à esterilização cirúrgica feminina com taxas de falha menores que 1% (3). Além da sua alta eficácia, os métodos LARC apresentam altas taxas de continuação. O implante liberador de ENG apresenta taxas de continuação de 67% a 75% no primeiro ano de uso (4-9) reduzindo para 44% a 69% no segundo

ano de uso (4,7-9). O DIU TCu380A apresenta 84% de taxa de continuação em um ano (10) e o SIU-LNG em torno de 90% (11-14). Quando as mulheres recebem sessões de orientação dos métodos contraceptivos, as usuárias de implante liberador de ENG atingiram 80% a 90% de taxa de continuação (15,16) enquanto as usuárias do SIU-LNG atingiram 90,3% (12,16).

Entre os métodos LARC, o SIU-LNG apresenta a maior taxa de satisfação variando de 56,3% a 89,7% (10,13,17), o DIU TCu380A com 65,6% e o implante liberador de ENG atinge 54,8% (10). Os principais fatores de descontinuação do SIU-LNG foram dores de cabeça, abdominal e lombar (6,7%) (13), problemas relacionados ao sangramento (entre 2,5% e 5,8%) (11,13) e aumento do peso (28,7%) (17). Enquanto para o implante liberador de ENG a descontinuação por irregularidades menstruais variou de 17,2% a 62,0% no fim de um a dois anos de uso (5-8,18), outros fatores de remoção citados, menos frequentes, foram: alterações de humor, ganho de peso, diminuição de libido, dor em baixo ventre e acne (7-9,18).

A associação entre uso de contraceptivos de somente progestágenos e irregularidade no sangramento menstrual está bem documentada. Alguns destes métodos, como o acetato de medroxiprogesterona de depósito (AMPD) - um contraceptivo injetável trimestral - apresentam taxas de irregularidade menstrual de 90% em usuárias após a primeira dose e 60% após a quarta injeção (19). No entanto, a principal queixa e fator de descontinuação do método é o aumento de peso de algumas usuárias (20). Assim, as orientações quanto ao uso do método parecem aumentar a tolerância das mulheres ao sangramento irregular e a outras

intercorrências do uso, sendo as orientações quanto à escolha do método um fator significante na sua continuação e satisfação (16,21).

1.1. Densidade Mineral Óssea

A avaliação da densidade mineral óssea (DMO) constitui um indicador da massa óssea do corpo e indiretamente do bem-estar ósseo. A DMO é avaliada através da incidência de um feixe de radiação, que é atenuado pelo osso, formando uma imagem projetada bidimensional, que corresponde à densidade da área óssea (22). As técnicas para medir a DMO têm aberto o caminho para o diagnóstico da osteoporose, mas também têm permitido fazer definições mais exatas das suas etapas precoces, como a osteopenia. A osteopenia é definida como uma DMO entre -1 e -2,5 desvios-padrão (DP) abaixo da média de uma pessoa adulta jovem. Já a osteoporose é definida por uma DMO inferior a -2,5 DP (23).

Entretanto, a DMO não é igual nas diversas partes do esqueleto. Desta forma, as medidas do quadril e do colo do fêmur são consensualmente usadas por apresentarem uma melhor capacidade preditiva de fraturas (22). Entretanto, os valores de diagnóstico e as medidas do quadril e colo do fêmur têm sido criticados por muitos autores já que se tem observado que há um aumento do risco de fraturas a partir de um DP abaixo da média e que, embora as medições da DMO possam prever risco de fratura, a sensibilidade e especificidade são realmente muito baixas (24,25). De fato a DMO é um *surrogate marker* e embora não seja a melhor ferramenta para avaliar a saúde óssea, atualmente continua sendo a mais adequada.

1.1.1 AMP-D e a perda de massa óssea

A DMO em mulheres depende de numerosos fatores que ocorrem durante a vida reprodutiva e/ou na pós-menopausa, incluindo atingir ou não o pico de massa óssea, peso corporal, fatores genéticos e hábitos de vida. Além dos fatores que apresentam relação bem estabelecida com o desenvolvimento de osteopenia/osteoporose, permanece controverso na literatura se a utilização e o tempo de uso de métodos anticoncepcionais (MACs) hormonais durante a vida reprodutiva influenciariam a DMO no momento de uso, se altera após a descontinuação ou, anos depois, na pós-menopausa.

Nos últimos anos foram publicados inúmeros estudos sobre contraceptivos hormonais, perda ou não de massa óssea, osteopenia e osteoporose, porém existem poucos estudos sobre o uso de MACs e risco de fraturas. O interesse deriva de que estes, frequentemente, são administrados por período prolongado e em uma fase da vida em que ainda não foi atingido o pico da formação de massa óssea, especialmente no caso do uso em mulheres adolescentes (26,27). A interferência dos MACs no pico ou perda precoce da massa óssea poderia resultar em osteoporose no futuro (22,28).

Em geral, quando combinados, estrogênio e progestagênio, em sua composição, os MACs mantêm e previnem a perda de massa óssea, e são compostos disponíveis na apresentação oral, injetável mensal, transdérmico e vaginal. Entretanto, discute-se que os anticoncepcionais combinados orais (ACOs), com baixa dose de estrogênio, poderiam não ser suficientes para manter a DMO (29,30,31), baseado no fato de que o estrogênio é um fator de equilíbrio entre a reabsorção e a formação dos ossos (32,33).

Dentre os MACs hormonais injetáveis, o acetato de medroxiprogesterona de depósito (AMPD) é o contraceptivo mais estudado em relação aos efeitos sobre a DMO. A preocupação com o efeito do AMPD na DMO iniciou-se logo após a aprovação do uso desta medicação pela Administração de Drogas e Alimentos dos Estados Unidos (*US Food and Drug Administration; USFDA*) em 1992 (34) e devem-se, fundamentalmente, ao estado de hipoestrogenismo induzido pelo método, chegando a valores de estradiol (E_2) plasmático na ordem de 30 pg/ml (35,36), valores compatíveis com pós-menopausa.

Os resultados dos estudos sobre uso do AMPD e DMO são conflitantes. Quinze estudos de corte transversal avaliaram a DMO em mulheres adultas usuárias de AMPD (26, 35,37-47) e dois estudos avaliaram adolescentes usuárias deste método (26,27). Estes estudos mostraram que o uso de AMPD geralmente esteve associado à diminuição da DMO, em média 0,5 DP dos valores da média da DMO entre as não usuárias. Porém, Perrotti *et al*., 2001 (44), mostraram que o uso de AMPD não afetou a DMO das usuárias e o estudo de Bahamondes *et al*., 1999 (40) mostrou que houve apenas diminuição na porção distal do rádio, onde o osso trabecular é menos presente que na porção ultradistal.

Sete estudos longitudinais prospectivos foram realizados com usuárias de AMPD (30,48-52). Na maioria destes estudos foi observada diminuição da DMO, em média de 1% ao ano. De outra forma, dois dos estudos, que avaliaram mulheres novas usuárias de AMPD mostraram perda maior, em torno de 2% a 3% ao ano (30,52). Ao final de um ano de seguimento, foi observada diminuição de 0,5% (48) a 3,5% (52) da DMO na coluna vertebral e de 1,1% (48) a 2,8% (50) no quadril de usuárias de AMPD. Ao final do segundo ano de seguimento, a DMO da

coluna declinou 5,7% entre as mulheres participantes no estudo de Berenson *et al*. 2004 (30) e 2,2% no estudo de Clark *et al.* 2004 (52). Por outro lado, a DMO é um resultado substituto (*surrogate endpoint*) para o risco de fratura, sendo que o resultado clínico de interesse (*clinical endpoint*) não obteve forte associação a um maior risco de fraturas entre usuárias *versus* ex-usuárias de AMPD (53).

1.1.2 Implante liberador de etonogestrel (ENG-implante) e a DMO

Estudos sobre a DMO em usuárias de implante liberador de ENG têm se mostrado conflitantes em alguns aspectos. Entretanto, tem se observado que o uso do implante liberador de ENG pode ocasionar uma diminuição da DMO de suas usuárias por mais de 18 meses. Esse dado é apontado por autores que mostraram em seus estudos uma diminuição da DMO na porção ultradistal da ulna após 18 e 36 meses de uso do método (54-56). Entretanto, a avaliação da DMO do rádio (ou *midshaft ulna*) apresentou resultados contraditórios nos quatro estudos disponíveis. Bahamondes *et al.*, 2006 (54) e Monteiro-Dantas *et al.*, 2007 (55), não encontraram diferenças significativas aos 18 e 36 meses de seguimento. Enquanto, Pongsatha *et al.*, 2010 (56) mostraram, em um estudo de corte transversal, que aos 24 meses de uso do implante liberador de ENG a DMO do rádio foi significativamente menor entre as usuárias de implante liberador de ENG quando comparadas a usuárias de métodos não hormonais. Por fim, Beerthuizen *et al.*, 2000 (57), relataram que após 24 meses de seguimento a DMO do rádio aumentou quando comparadas a usuárias de métodos não hormonais.

Em relação à avaliação da coluna lombar e colo do fêmur, os estudos mostraram que o uso do implante liberador de ENG por mais de 24 meses não

alterou a DMO dessas regiões quando comparadas a usuárias de métodos não hormonais (56,57).

1.2. Peso e AMP-D

O ganho de peso é frequentemente associado ao uso do AMPD (58) e uma das principais causas de descontinuação do método (20,59). Apesar de não existir evidências científicas sobre a associação entre o ganho de peso e o uso do AMPD (60), ele vem sendo descrito há décadas, e o mecanismo responsável pelo ganho de peso em determinadas mulheres ainda é desconhecido. Existe uma série de proposições que tentam elucidar o mecanismo de ganho de peso dentre elas. Pode-se citar: 1) o estilo de vida, pois mulheres em idade reprodutiva, e principalmente de baixa renda, usualmente optam por um estilo de vida sedentário (44). Estudos publicados sobre DMO e composição corporal (CC) em usuárias de AMPD que têm considerado a atividade física como variável de controle, mostraram que a frequência de mulheres que praticam alguma atividade física é sempre menor que a metade da amostra estudada (26,30,41,46,52,61-66).

Outra variável é a retenção de líquido causada por esteroides, fato constantemente citado como um efeito adverso do AMPD (67); embora o método não apresente efeito sobre o metabolismo de proteínas, os níveis plasmáticos de albumina aparecem ligeiramente diminuídos (68). Além disso, existe descrição sobre o aumento do apetite. O AMPD pode produzir um efeito estimulante no controle do apetite, no hipotálamo, o que provocaria uma maior ingesta calórica e, por sua vez, o aumento da deposição de massa gorda e do peso (69). Essa teoria ainda não está bem estabelecida, principalmente após alguns estudos que não

encontraram nenhum efeito significativo no aumento da ingesta calórica em usuárias de AMPD (70,71,72).

Os estudos sobre aumento de peso em mulheres usuárias do AMPD tiveram início na década de 60; o ganho de peso foi observado frequentemente como efeito colateral no decorrer dos anos; no entanto, não afetava todas as mulheres (73). Mulheres usuárias de MACs não hormonais também apresentam ganho de peso no decorrer dos anos, cerca de 0,6 kg/por ano, sendo esse aumento de peso consequência da idade, podendo estar associado com características étnicas, *status* marital, hábito de fumar, número de gravidezes e doenças crônicas degenerativas (74). Um ensaio clínico randomizado constatou aumento de peso em usuárias de AMPD de 4 a 13 kg após um ano de uso (75), porém, em outros estudos de curto prazo, não foi encontrado ganho de peso objetivo significativo após 12 meses de uso do AMPD (76,77). Outros dois estudos relataram ganho de mais de 4 kg aos cinco anos de seguimento comparado a 1,8 kg em usuárias de DIU TCu380A (20,59). Estes dados sugeriram que o ganho incomum de peso poderia ser proporcional ao tempo de uso do método (59).

1.3. Peso e Sistema Intrauterino liberador de Levonorgestrel (SIU-LNG)

O ganho de peso em usuárias do sistema intrauterino liberador de levonorgestrel (SIU-LNG) é citado como um dos efeitos adversos mais comuns (17,78), mesmo que esta associação apresente poucas evidências científicas. No entanto, as queixas representam baixo impacto na taxa de descontinuação das usuárias (10,78,79).

Estudos sobre o ganho de peso em usuárias de SIU-LNG são escassos, e quando comparadas com usuárias de DIU TCu380A, não têm sido encontradas diferenças significativas na variação do peso (13). A média do ganho de peso foi de 1,4 kg e 2,9 kg em usuárias de DIU TCu380A e SIU-LNG, respectivamente (80) e 1,0 kg em ambos os grupos durante 12 meses de seguimento (76). Outros estudos menos consistentes relataram ganho de peso maior que 2 kg em 30,5% das usuárias, porém não são específicos quanto ao tempo de seguimento ou taxas de descontinuação (17,81).

1.4. Peso e implante liberador de etonogestrel

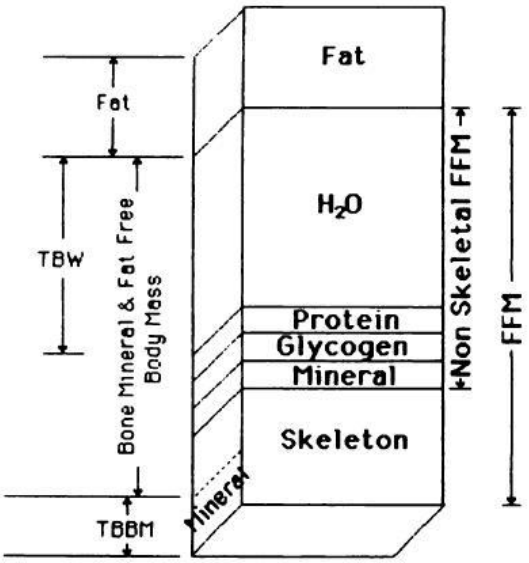
Estudos que avaliaram o peso de usuárias de implante liberador de ENG ainda são escassos e se concentram na prevalência das queixas do uso ou abandono do método. Segundo os estudos foram encontrados um ganho de peso de +2,1 kg após 12 meses de seguimento e +1,9 kg aos dois anos de uso **(**57,76). O ganho do peso é um efeito adverso frequentemente relatado por suas usuárias **(**6-8,16,18,57). No entanto, a porcentagem de abandono do método devido a este efeito adverso ainda é baixa (82).

Estudos mostraram que após seis meses de uso do método foram registradas queixas de ganho de peso de 9% a 24% entre as suas usuárias (4,18), de 12% aos 12 meses (6) e 10% a 21% aos 36 meses de uso do método (7,8).

1.5. Composição corporal

A análise da composição corporal (CC), feita através da *dual-photon absorptiometry* (DXA), tem sido amplamente utilizada para avaliar repercussões

nutricionais, metabólicas e de exercícios físicos em homens e mulheres. Na análise do DXA, pode-se mensurar a quantidade de massa gorda, massa magra, conteúdo mineral ósseo total, porcentagem de gordura, além dos valores regionais androide/ginecoide, braços, pernas e tronco (83). O DXA divide o corpo em três componentes: osso, massa magra e massa gorda (84).



Heymsfield, 1989

A figura representa como o DXA realiza a distribuição em compartimentos dos componentes corporais: quantidade de massa gorda (Fat), total de água no corpo (TBW) e o conteúdo mineral total (TBBM). O DXA associa a massa magra do corpo com a quantidade de água, proteínas e glicogênio, tornando a quantidade de fluidos do corpo uma importante variável confundidora ao estimar a massa magra. E, por fim, mede a massa corporal livre de gordura (FFM) (84).

O índice de massa corporal (IMC, kg/m^2) é um método amplamente utilizado e classifica os indivíduos como baixo peso (<18,5 kg/m^2), peso normal

(18,5-24,9 kg/m^2), sobrepeso (≥ 25-29,9 kg/m^2) ou obesidade (≥ 30 kg/m^2). A popularidade desta abordagem é devido à sua simplicidade e às correlações relativamente boas com a massa gorda (85). Entretanto, o DXA vem adquirindo uma grande importância clínica na estimativa da porcentagem de gordura e massa gorda, pois o reconhecimento da distribuição anatômica dessa gordura poderia, de fato, ser um importante indicador de doenças, como aumento do risco cardiovascular, diabetes e obesidade.

Até o momento não existe nenhum consenso sobre o ponto de corte ideal da porcentagem de gordura para determinar o risco de sobrepeso e obesidade (86). No entanto, alguns estudos propuseram uma estimativa para avaliar o risco de obesidade, doença cardiovascular e diabetes através do DXA. Um estudo japonês estimou uma porcentagem de massa gorda no limite de 24% em homens e 35% em mulheres, porém esse resultado pode ter sido superestimado, pois a amostra foi formada por pessoas com dislipidemia entre outros dos fatores de risco estudados (87). Li, 2009 (88) foi mais específico, sugerindo 41% de porcentagem de gordura para mulheres na categoria de IMC 25-29 kg/m^2 e 45% para mulheres na categoria 30-34 kg/m^2. Um manual publicado pela *American Society for Bariatric Physicians* sugere valores alarmantes sobre o percentual de massa gorda, em que portadores de valores maiores que 25% para homens e maiores que 30% de massa gorda para mulheres são considerados indivíduos obesos (89).

Não existindo consenso sobre os valores para risco da porcentagem de gordura, alguns autores enfatizaram que para interpretar o exame de composição corporal (CC) é necessário avaliar o indivíduo relacionando os seus resultados

com a idade e a etnia (90,91). Algumas variáveis clínicas também devem ser consideradas como *status* menopausal, dieta, exercício físico, história familiar de diabetes ou hipertensão arterial (87,88 92). O DXA pode ser usado como um poderoso instrumento na detecção do fator de risco de doenças, visto que o aumento do IMC ao longo do tempo tem pouca precisão nas mudanças da distribuição da gordura corporal (93). No entanto, deve-se entender que o DXA não está estabelecido como padrão-ouro para a avaliação da porcentagem de gordura, devido a variações com equipamentos de diferentes fabricantes. Logo, recomenda-se precaução na comparação de resultados de diferentes estudos (94).

1.5.1. Composição corporal e uso do AMP-D

Devido às frequentes queixas de aumento de peso por usuárias de AMP-D (64), novas pesquisas com avaliação da CC pela técnica de DXA estão sendo desenvolvidas a fim de elucidar os mecanismos de ganho de peso e se este fato é real ou restrito a algum grupo específico de mulheres. Clark *et al.*, 2005 (95) realizaram um estudo prospectivo com 30 meses de seguimento com 178 mulheres usuárias de AMPD. No estudo, foi relatado um ganho de peso igual ao de massa gorda de 6,1 kg, não encontrando alteração significativa da massa magra quando comparada ao grupo de controle. Berenson *et al.*, 2009 (71), acompanharam 240 mulheres durante 36 meses e encontraram um ganho de peso de 5,1 kg, aumento de massa gorda de 4,1 kg e um ganho de 3,4% na porcentagem de gordura, porém as análises da massa magra permaneceram sem variação significativa quando comparadas ao grupo de controle.

Os dois estudos citados são os únicos encontrados que avaliaram CC em usuárias de AMPD em idade reprodutiva maiores de 18 anos. Entretanto, eles apresentaram importantes problemas já que a perda de seguimento chegou a ser em torno de 80%. De acordo com os estudos, existe um aumento do peso e massa gorda significante nas usuárias de AMPD, que pode diminuir a aceitabilidade do método. Desta forma, sugere-se que essas informações devam ser ponderadas juntamente com a alta eficácia contraceptiva do método e a facilidade de uso.

1.6. Hábitos de vida e uso do AMPD

Hábitos comportamentais da mulher podem contribuir tanto para a variação da DMO como para CC. De acordo com Pinheiro *et al.,* 2010 (96), em mulheres brasileiras, os fatores mais importantes relacionados à fragilidade óssea foram idade avançada, menopausa prematura, sedentarismo, má qualidade de vida, *diabetes mellitus*, quedas recorrentes, uso crônico de medicamentos benzodiazepínicos e história familiar de fratura de quadril.

O estímulo à atividade física deve ser considerado como uma das medidas necessárias para a prevenção de fraturas na população (96). O exercício físico de impacto efetivado de forma regular apresenta um importante potencial osteogênico (97). A atividade física de impacto apresenta efeitos benéficos tanto na DMO do quadril como no colo do fêmur de mulheres na pré-menopausa quando feitos regularmente (97). Além disso, o exercício físico, em longo prazo, exerce efeito protetor contra fraturas de quadril em mulheres na pós-menopausa (98).

A prática de esportes como tênis e vôlei apresentam grandes potenciais osteogênicos tanto na coluna quanto no colo do fêmur, com ganhos maiores que 10% de massa óssea, enquanto uma caminhada regular três vezes por semana apresenta ganho de apenas 0,9% na coluna e 2% no fêmur (99,100,101).

Alguns estudos sobre DMO em usuárias de AMPD que utilizaram a atividade física como variável de controle não apresentaram correlação significativa entre os grupos de usuárias de AMP-D e não usuárias, em relação à aderência à atividade física ou à influência dos exercícios nos resultados sobre a DMO. Os estudos frequentemente mostraram que a quantidade de mulheres que aderiram à prática de atividade física é muito menor que a amostra estudada (26,30,41,46,52,61-66).

De forma semelhante ocorre com a ingestão de cálcio. Estudos mostraram que o consumo entre as usuárias de AMPD é menor do que a quantidade mínima diária exigida para a manutenção da DMO e outras atividades metabólicas corporais (30,41,50,52,61,62,64,66).

O Ca é fundamental para uma saúde óssea adequada. A quantidade mínima diária exigida é de 1000 mg para uma mulher adulta saudável, sendo que essa quantidade de Ca pode ser encontrada durante a ingesta de leite e derivados como iogurte e queijos (102). Uma ingestão de Ca na dieta abaixo de cerca de 700 mg por dia em mulheres foi associada ao risco aumentado de fratura e de osteoporose (103). No entanto, estudos com grandes coortes mostraram que a ingesta aumentada de Ca sozinha não reduz o risco de fraturas, pois as mulheres tendem a não consumir a quantidade necessária de vitamina D (104,105).

A manutenção dos estoques de vitamina D pode ser um artifício adicional eficiente no combate à perda de osso. A vitamina D é sintetizada através de processos fotoquímicos de ativação sob exposição solar (106), aumentando a absorção do Ca na alça intestinal, contribuindo para o aumento da DMO e diminuição do risco de fratura (100,107). Não existe consenso sobre quantidade de sol necessária para o organismo produzir vitamina D. Além disso, existe interferência de fatores individuais como idade, sensibilidade à luz solar, latitude geográfica onde se vive, estação do ano, hora do dia, tempo e tamanho da superfície corporal de exposição ao sol (106). Alguns estudos na Dinamarca e EUA sugeriram como benéfica a exposição ao sol durante 15-30 minutos, no período da tarde, no verão, sem o uso de protetor solar, pois este é responsável pelo bloqueio dos raios ultravioleta (UV), necessários para a ativação fotoquímica da vitamina D (106,108).

As mais conhecidas ações da vitamina D estão relacionadas à absorção de Ca pelo intestino. A vitamina D associada ao Ca diminui o risco de osteoporose, de fratura e melhora da força e função muscular (109,110). O aumento da força muscular reflete uma adaptação do osso para essa função; portanto, se a massa muscular diminui é também esperada uma diminuição da massa óssea, pois o músculo irá reduzir a carga aplicada ao osso (110,111).

2. OBJETIVOS

2.1 Objetivo Geral

Avaliar aspectos clínicos da DMO entre usuárias de AMPD e comparar com usuárias de método contraceptivo não hormonal (DIU com cobre), avaliar as variações de peso entre usuárias do SIU-LNG, de AMPD e de DIU com cobre, e os efeitos de duas estratégias de orientação no momento de escolha de DIU com cobre, do SIU-LNG e do implante subdérmico liberador de ENG nas taxas de descontinuação das usuárias por transtornos de sangramento e nas taxas de continuação.

2.2 Objetivos Específicos

- **Artigo 1** :Avaliar a influência das orientações quanto ao estilo de vida: exposição ao sol, consumo de Ca e atividade física em usuárias de AMPD durante 12 meses de seguimento após inicio do método;

- **Artigo 2:** Avaliar a evolução do peso de usuárias de AMPD, de SIU-LNG e DIU com cobre durante 10 anos de seguimento a partir do início de uso;

- **Artigo 3:** Avaliar a CC de usuárias de AMPD aos um, cinco, dez e quinze anos de uso;

- **Artigo 4:** Avaliar a prevalência de osteopenia e osteoporose em usuárias de longo prazo de AMPD e comparar com usuárias de DIU com cobre;

- **Artigo 5:** Avaliar a DMO e CC de usuárias de implante liberador de ENG após 24 meses de inserção;

- **Artigo 6** :Avaliar o efeito de duas estratégias de orientação no momento de escolha de DIU com cobre, do SIU-LNG e do implante liberador de ENG nas taxas de continuação das usuárias por transtornos de sangramento.

3. CAPÍTULOS

3.1 Artigo 1 – The effect of lifestyle counseling on bone mineral density and body composition in users of depot medroxyprogesterone acetate as a contraceptive method.

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Exploratory study of the effect of lifestyle counselling on bone mineral density and body composition in users of the contraceptive depot-medroxyprogesterone acetate

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ABSTRACT **Objectives** To compare variations in bone mineral density (BMD) and body composition (BC) in depot-medroxyprogesterone acetate (DMPA) users and nonusers after providing counselling on healthy lifestyle habits.

Methods An exploratory study in which women aged 18 to 40 years participated: 29 new DMPA users and 25 new non-hormonal contraceptive users. All participants were advised on healthy lifestyle habits: sun exposure, walking and calcium intake. BMD and BC were assessed at baseline and 12 months later. Statistical analysis included the Mann-Whitney test or Student's *t*-test followed by multiple linear regression analysis.

Results Compared to the controls, DMPA users had lower BMD at vertebrae L1 and L4 after 12 months of use. They also had a mean increase of 2 kg in total fat mass and an increase of 2.2% in body fat compared to the non-hormonal contraceptive users. BMD loss at L1 was less pronounced in DMPA users with a calcium intake ≥ 1 g/day compared to DMPA users with a lower calcium intake.

Conclusions DMPA use was apparently associated with lower BMD and an increase in fat mass at 12 months of use. Calcium intake ≥ 1 g/day attenuates BMD loss in DMPA users. Counselling on healthy lifestyle habits failed to achieve its aims.

KEYWORDS Depot-medroxyprogesterone acetate; Bone mineral density; Body composition

INTRODUCTION

Women's lifestyle habits may contribute to variations in both bone mineral density (BMD) and body composition (BC). Studies conducted to evaluate BMD and BC in users of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) have shown that most of them fail to adopt healthy lifestyle habits[1–12]. According to the European Consensus on

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Osteoporosis[13], calcium deficiency and a sedentary lifestyle augment the risk of osteoporosis. Furthermore, calcium is fundamental for healthy bones, with 1 g being the minimum daily amount required for a healthy adult woman. Dietary calcium intake of less than ~700 mg/day in women has been associated with a greater risk of osteoporosis and fracture[14]. Nevertheless, studies with large cohorts have shown that increasing calcium intake alone does not reduce the risk of fractures, since women tend to consume less than the necessary amount of vitamin D[15,16].

Indeed, the better-known effects of vitamin D are related to the absorption of calcium through the bowel[17]. Vitamin D associated with calcium reduces the risk of osteoporosis and fractures, and improves muscle strength and function[17,18]. Consequently, the combination of performing high-impact physical exercise on a regular basis, increasing calcium intake and ensuring good vitamin D levels has significant osteogenic potential[14,17,19].

Concern about possible bone mass loss and weight gain in DMPA users[11] has led to studies being developed to identify the causes of these changes. The hypothesis behind this study was that women, who receive counselling to (i) practise physical activity, (ii) increase their calcium intake, and (iii) expose themselves more to sunlight, will suffer less BMD loss. Therefore, the objective of the study was to compare variations in BMD and BC in two cohorts of women: new DMPA users and new users of a non-hormonal contraceptive method. All women in both groups were advised to practise physical activity, to increase their calcium intake and to expose themselves to sunlight as an adjuvant to vitamin D. They were followed up for 12 months after initiating use of the contraceptive method.

MATERIALS AND METHODS

This exploratory study was conducted at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas, Brazil. The Ethical Committee approved the study and all participants signed an informed consent form prior to enrolment. The investigation was registered at ClinicalTrials.gov under reference number NCT01527526.

The study was conducted between February 2011 and February 2013. The women enrolled were between 18 and 40 years of age and had a body mass index (BMI) $< 30\ kg/m^2$. They were divided into two groups according to the contraceptive they were about to use: 29 new users of the injectable DMPA (150 mg of which was to be administered intramuscularly, three monthly) and 25 new users of the copper releasing-intrauterine device (Cu-IUD) TCu380A. Exclusion criteria consisted of breastfeeding in the six months prior to enrolment; chronic diseases including diabetes mellitus, hyper- or hypothyroidism, hyper- or hypoparathyroidism, pituitary diseases, hepatitis, cancer, chronic renal failure; and a history of bariatric surgery or organ transplantation. Women using anticonvulsants, corticosteroids, thiazide diuretics, drugs for the treatment of thyroid disease or postmenopausal hormone therapy were also excluded. Measurements of weight and height were recorded prior to BMD evaluation.

At baseline and 12 months after initiating the contraceptive method bone mineral density and BC were measured by means of dual-energy X-ray absorptiometry (DXA), using a Lunar absorptiometer (GE Healthcare, Lunar Corporation Madison, WI, USA). BMD was measured at the lumbar spine and femoral neck. BC was evaluated according to total fat mass, percent body fat and total lean mass. Lifestyle counselling was provided every three months to all participants. Recommendations included exposure to sunlight, walking and calcium intake, as follows: (i) Minimal exposure to sunlight should be 15 min a day, three times a week, without the use of sunscreen and exposing at least 30% of the body to sunlight. This was sorted as [< 20 min; < 3 times/week]; [≥ 20 min; < 3 times/week] and [≥ 20 min; ≥ 3 times/week], with the latter being considered adequate exposure to sunlight. (ii) Walking for 30 min three times per week; divided into [< 150 min/week] or [≥ 150 min/week]. (iii) Increased calcium intake; categorised as [< 1 g/day] and [≥ 1 g/day]. The calcium intake was evaluated based on the past-three day record of food intake and the information was entered into the software *Diet win* that estimated the amount of calcium intake. We analysed the intake of calcium at baseline and up to 12 months.

Data analysis

The Mann-Whitney non-parametric test or Student's *t*-test was used to compare BMD at baseline and

at 12 months. The possible effect of the control variables on the relationship between DMPA use, lifestyle habits, BC and BMD was evaluated using multiple linear regression analysis. Significance was established at $p < 0.05$ and all the values were shown as means ± standard error of the mean (SEM). The SPSS statistical software programme version 20 was used to analyse the data.

RESULTS

Seventy-one women were invited to participate in the study: 44 DMPA- and 27 Cu-IUD users, but only 54 women completed the entire study protocol: 29 DMPA- and 25 Cu-IUD users because 15 (34%) and 2 (7%) women belonging to the DMPA- and non-hormonal groups, respectively, discontinued their participation in the study or were lost to follow-up. Nevertheless, the characteristics of the women who stopped partaking in the study were quite similar to those who continued it. We did not calculate the sample size because it was an exploratory study. However, we estimated the power of our sample with alpha of 5% and beta of 20%, and found it to be appropriate for the studied variables. There were no significant differences between the social and demographic characteristics of the two groups, except for the fact that DMPA users had fewer children ($p = 0.006$) and more years of schooling ($p = 0.016$) than Cu-IUD users (Table 1).

In the period between baseline and 12 months after initiating the contraceptive method, a significant drop in BMD occurred in DMPA users compared to the users of non-hormonal contraception, only at the first and the fourth lumbar vertebrae (L1 and L4). BC of DMPA users showed a rise in mean fat mass of 2 kg ($p = 0.015$) and one of 2.2% in the percentage of body fat ($p = 0.033$) compared to the Cu-IUD users (Table 2). Furthermore, six DMPA users and seven of the women who were fitted with a Cu-IUD presented osteopenia at baseline; at 12 months of follow-up the figures had changed to eight and five women, respectively. Osteoporosis was observed neither at baseline nor at 12 months of follow-up in either group.

Only seven DMPA users (24%) complied with the recommendations to augment their calcium intake. DMPA users whose calcium intake was ≥ 1 g/day had less BMD loss affecting L1 (-0.006 g/cm^2) than women belonging to the same group with a calcium intake of < 1 g/day (-0.049 g/cm^2) ($p = 0.038$). In addition, a calcium intake exceeding 1 g/day improved BMD at L1–L4 in participants in both the DMPA- and IUD groups when compared to women with a calcium intake of < 1 g/day. Although no significant correlation was found between exposure to sunlight and BMD, in 20 of the DMPA users (69%) sun exposure was deemed adequate. Only 11 of the DMPA users (37%) and six of the subjects wearing a Cu-IUD (24%) complied with the recommendation concerning physical activity. Multiple linear regression analysis showed that a greater calcium intake was associated with a rise in BMD at the lumbar spine in DMPA users compared to the users of the non-hormonal contraceptive method (Table 3).

Table 1 Characteristics of the study participants according to their contraceptive method.

Variables	*DMPA* (n = 29)*	*Copper-IUD* (n = 25)*	*p-value*
Age, years (mean ± SEM)	29.9 ± 0.9	28.7 ± 1.0	0.388
BMI, kg/m^2	23.9 ± 3.5	24.4 ± 2.7	0.627
Number of children; 0–1 (%)	20 (69%)	7 (28%)	0.006
Ethnicity (white), *n* (%)	12 (41%)	10 (40%)	1
Years of schooling > 8 years, *n* (%)	21 (72%)	9 (36%)	0.016
Non-smokers, *n* (%)	22 (76%)	19 (76%)	1
Alcohol consumption, *n* (%)	5 (17%)	5 (20%)	1
Coffee consumption < 200 mL/day, *n* (%)	23 (79%)	17 (68%)	0.343

*DMPA, depot-medroxyprogesterone acetate; IUD, intrauterine device.

Table 2 Mean variation in the different measurements of bone mineral density (BMD) and body composition according to type of contraceptive method.

	Contraceptive Method		
	DMPA (n = 29)	*Copper-IUD (n = 25)*	
Variable	*Mean ± SEM*	*Mean ± SEM*	*p-value**
Δ BMD L1, g/cm²	− 0.038 (0.009)	0.008 (0.009)	< 0.002**
Δ BMD L4, g/cm²	− 0.058 (0.011)	0.015 (0.010)	< 0.001
Δ BMD L1-L4, g/cm²	− 0.047 (0.008)	0.006 (0.007)	< 0.001
Δ BMD FN, g/cm²	− 0.022 (0.010)	− 0.003 (0.008)	0.152
Δ Percent body fat[a]	2.252 (0.777)	− 0.038 (0.666)	0.033
Δ Total fat mass, kg[a]	2.090 (0.646)	− 0.096 (0.548)	0.015
Δ Lean mass, kg[a]	− 0.033 (0.320)	− 0.209 (0.183)	0.635

*Student's *t*-test for independent samples; **Mann-Whitney non-parametric test for independent samples; Δ = (Measurement at 12 months − baseline measurement). [a]Data missing for one IUD user.

DMPA, depot-medroxyprogesterone acetate; IUD, intrauterine device; L1, 1st lumbar vertebra; L4, 4th lumbar vertebra; FN, femoral neck.

Table 3 Multiple linear regression analysis for the variation of different measurements of bone mineral density (BMD) and body composition.

Dependent variable / Associated variables	*Coefficient*	*Standard error of the coefficient*	*p-value*
Δ *BMD L1, g/cm²*			
Type of contraceptive method (DMPA)	− 0.049	0.009	< 0.001
Dietary calcium at 12 months (≥ 1g per day)	0.046	0.015	0.003
Δ *BMD L4, g/cm²*			
Type of contraceptive method (DMPA)	− 0.058	0.011	< 0.001
Δ *BMD L1 − L4, g/cm²*			
Type of contraceptive method (DMPA)	− 0.055	0.008	< 0.001
Dietary calcium at 12 months (≥ 1g per day)	0.030	0.013	0.023
Δ *Percent body fat*			
BMI, kg/m²	− 1.151	0.286	< 0.001
Weight, kg	0.321	0.107	0.004
Constant	9.370	3.757	0.016
Δ *Total fat mass, kg*			
Type of contraceptive method (DMPA)	2.090	0.579	< 0.002

Independent variables: type of contraceptive method (DMPA/TCu380A IUD); physical activity at 12 months (active/sedentary); sun exposure at 12 months (adequate/inadequate); dietary calcium at 12 months (< 1 g per day/≥ 1 g per day); age (years); weight (kg); BMI (kg/m²); schooling (≤ 8 years/> 8 years); skin colour (white/other); social class (A/B/C/D); number of pregnancies (≤ 1/> 1); number of deliveries (≤ 1/> 1); smoking (non-smoker/smoker or previous smoker); alcohol consumption (< 1 dose/≥ 1 dose); coffee consumption (< 1 cup/day/≥ 1 cup/day).

DMPA, depot-medroxyprogesterone acetate; L1, 1st lumbar vertebra; L4, 4th lumbar vertebra; BMI, body mass index.

DISCUSSION

DMPA treatment for 12 months was associated with a slight drop in BMD at the lumbar spine; however, this was attenuated in women receiving this injectable progestin whose calcium intake was greater than 1 g/day. Only 24% of DMPA users followed the recommendations regarding calcium intake, but this small sample was sufficient to produce significant results regarding this attenuation of the decrease in BMD. Be that as it may, a possible limitation was that calcium intake was only evaluated through a previous three-day record of food intake before each interview and this could have been influenced by the inaccuracy of the women's recall.

No significant correlation was found between sun exposure and BMD. Yet, there was less bone loss in 69% of the women in whom sun exposure was deemed satisfactory, probably because their calcium absorption increased, thus reducing bone wastage. Even so, it must be noted that in Brazil exposure to the sun is almost constant throughout the year, as there are only a few days during which the sun does not shine. Previous studies have shown the poor compliance of DMPA users in terms of adopting healthy lifestyle habits[1–12].

In addition, we observed a gain of 2 kg in mean fat mass in DMPA users at 12 months of follow-up and a gain of 2.2% in the percentage of body fat. These findings are in line with those of other researchers[20], who reported a gain of 1.78 kg in fat mass after 12 months of DMPA use compared to a gain of only 0.09 kg in users of a non-hormonal contraceptive method. Two other teams of investigators[20,21] published results similar to ours, with the lean mass remaining unchanged or diminishing, and no significant differences between non-users of DMPA. The latter finding may have been due to the poor compliance with physical activity by the volunteers in these studies, since an increase in lean body mass is associated with intense muscle activity. A decrease in muscle mass is also expected to go along with a drop in bone mass, since the muscle will reduce the force applied to the bone[17,22].

Our body reflects what we eat and what we do, with many factors causing gains or losses in fat mass and BMD. The adverse effects of DMPA used for contraception, namely, the increase of the fat mass and the loss in BMD, can apparently be overcome by adopting a healthy lifestyle. We observed that the reduction in BMD characterising DMPA users was clinically irrelevant among those who had adopted healthy habits. Providing counselling on how to adopt a healthy lifestyle is a good recommendation for the general population and could be an effective method to reduce the adverse effects caused by DMPA.

Limitations of the study

Not having closely monitored compliance, nor provided oral calcium supplementation to women whose intake was insufficient, or motivated the women to initiate or intensify their physical activities, could be considered a limitation of this study.

Although physical activity has a strong osteogenic potential[19], it was not possible in the present study to compare the effect of physical activity as a tool to prevent bone loss in DMPA users. The study population came from the underprivileged strata of the Brazilian society and it is not easy for these women to practise physical activities. Other limitations were the high drop-out among DMPA users, the problems encountered with the 'lifestyle counselling', the difficulties affecting the measurement of calcium intake which we already mentioned, and the absence of randomisation of the women to either group. Additionally, a study conducted with Caucasian women showed that high levels of physical activity are prejudicial to bone health, suggesting that the hypo-oestrogenism caused by DMPA use may reduce the effects of physical activity on bone turnover[23]. This could explain why physical activity had little influence on bone health among DMPA users, in our study.

Unanswered questions and future research

We evaluated the influence of calcium and vitamin D, but not that of physical activity, on bone health of users and non-users of DMPA. However, the high drop-out among the former, the small sample size, the difficulties encountered when attempting to measure calcium intake and the lack of randomisation of the women to DMPA- or non-hormonal contraceptive use affect the study. Future research will need to assess whether physical exercise has beneficial effects on BMD of women relying for contraception on this progestin-only injectable.

CONCLUSION

An increase in fat mass and a decrease in BMD are observed after 12 months of use of DMPA. However, counselling on adequate calcium intake and regular sun exposure appears to attenuate BMD loss. Further studies involving DMPA users should investigate the effect of physical activity on their BMD, the long-term increase in their fat mass, and their general health.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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3.2 Artigo 2

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Weight variation in users of depot medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine system and a copper intrauterine device for up to ten years of use

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Weight variation in users of depot-medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine system and a copper intrauterine device for up to ten years of use

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Running title: Weight variation in users of contraceptives

Keywords: Weight, Levonorgestrel-releasing intrauterine system, Depot-medroxyprogesterone acetate, Copper IUD.

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ABSTRACT

Background and objective Data on record regarding weight variation in depot-medroxyprogesterone acetate (DMPA) and levonorgestrel-releasing intrauterine system (LNG-IUS) users are controversial. To date, no studies have yet evaluated weight variation in DMPA and LNG-IUS users in up to ten years of use compared to non-hormonal contraceptives users.

Materials and methods A retrospective study analysed weight variations in 2,138 women using uninterruptedly DMPA (150 mg intramuscularly, three-monthly; n=714), the LNG-IUS (n=701) or a copper-intrauterine device (Cu-IUD; n=723).

Results At the end of the first year of use, there was a mean weight increase of 1.3 kg, 0.7 kg and 0.2 kg among the DMPA-, LNG-IUS- and Cu-IUD users, respectively, compared to weight at baseline ($p<.0001$). After ten years of use, the mean weight had risen by 6.6 kg, 4.0 and 4.9 kg among the DMPA-, LNG-IUS- and Cu-IUD users, respectively. DMPA-users had gained more weight than LNG-IUS- ($p=.0197$) and than Cu-IUD users ($p=.0294$), with the latter two groups not differing significantly from each other in this respect ($p=.5532$).

Conclusion Users of hormonal *and* non-hormonal contraceptive methods gained a significant amount of weight over the years. DMPA users gained more weight over the treatment period of up to ten years than women fitted with either a LNG-IUS or a Cu-IUD.

INTRODUCTION

Weight gain in women is usually considered a consequence of age, while the epidemic of obesity that prevails in many countries today may be attributed to high calorie intake and sedentariness[1,2]. Nevertheless, a common complaint and often a reason for discontinuation among users of hormonal contraceptives is that the contraceptive method in use induces weight gain, despite the fact that several studies have shown no cause-effect relationship between these factors[3]. Yet, weight gain or weight variations in users of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) remain a subject of debate[4]. One randomised clinical trial (RCT) led to a weight gain of 4 to 13 kg in DMPA users after the first year of treatment[5] whereas other short-term studies failed to objectively show any weight gain after one year of use[6,7].

A weight increase is also observed in users of non-hormonal contraceptive methods. Women wearing a copper-intrauterine device (Cu-IUD) reportedly gained 0.6 kg/year over seven years of use[8]. Mean increases ranging from 1.8 to 4.9 kg were recorded at three and five years of uninterrupted use among subjects relying on this non-hormonal contraceptive, suggesting that weight gain was related to ageing[9-11].

Weight gain has also been mentioned as one of the most common complaints in users of the levonorgestrel releasing-intrauterine system (LNG-IUS)[12,13], although this complaint is not a major reason for discontinuation[12,14]. Few studies have explored weight variations in LNG-IUS users; so far no differences have been reported when compared to Cu-IUD users[15]. One team of investigators observed a mean weight gain in LNG-IUS- and Cu-IUD users of 2.9 kg and 1.4 kg, respectively, up to one year after insertion[16], while other investigators[6] recorded a weight gain of 1.0 kg in both these groups, also after one year of use. Others reported a weight gain of 3.1 kg in LNG-IUS users at five years of follow-up[10].

The use of long-acting reversible contraceptives (LARCs, including the Cu-IUD, the LNG-IUS, and contraceptive implants) and DMPA is increasing worldwide due to the high contraceptive efficacy of these methods[17]. Furthermore, women use contraceptives – whether hormonal or non-hormonal - for many years; therefore, it is important to assess weight changes affecting long-term users. We hypothesised that long-term users of DMPA, the LNG-IUS and Cu-IUD would present similar variations in weight over ten years of use. Consequently, we evaluated weight changes in three cohorts of women: users of (i) DMPA, (ii) the LNG-IUS and (iii) a Cu-IUD for up to ten years of uninterrupted use.

MATERIALS AND METHODS

A retrospective analysis was carried out at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medicine, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil. The study was approved by the Ethical Committee; informed consent was not required, since the study consisted of reviewing medical charts and the data were retrieved from the charts without the women being identified.

Weight was assessed in 2,138 women aged 18 to 40 years who started using one of the three contraceptives concerned in 1990 and continued relying on it uninterruptedly. Women wearing a Cu-IUD or a LNG-IUS were monitored annually at the clinic, while DMPA users attended the clinic every 90 (±7) days to receive a new intramuscular injection of 150 mg of the progestin. The women were weighed on scales, wearing only light clothing and being bare feet. In the city of Campinas, Brazil, where the study was conducted, the weather remains fairly stable throughout the year; consequently the type of clothing worn does not tend to vary. A total of 714 women

who elected to use DMPA (Depo-Provera®, Pfizer, São Paulo, Brazil), 701 who chose the LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) and 723 who opted for the TCu380A IUD (Optima®, Injeflex, São Paulo, Brazil) were evaluated. Subjects with chronic diseases including dyslipidaemia, diabetes mellitus, insulin-resistance, other metabolic syndromes, hyper- or hypothyroidism, and renal failure were excluded from the study, as well as those who had previously undergone bariatric surgery or organ transplantation. In addition, users of the LNG-IUS who elected to use the method for reasons other than contraception were also excluded.

Sample size was calculated based on the difference in weight between DMPA users and nonusers, by means of repeated measures ANOVA[11]. For an α error of 5% and a ß error of 20%, 700 subjects were required in each group. The final sample size power amounted to 90%. The values are presented as mean ± standard error of the mean (SEM) for the analysis of both socio-demographic characteristics and weight. The absolute differences and percentage variations between each annual visit and baseline were compared. Repeated measures ANOVA test was not performed; for this analysis the subjects should indeed have returned for evaluation every year during the ten years of follow-up, which would have markedly reduced the sample size. Thus, for comparison between the three groups we resorted to the Kruskal-Wallis test, followed by the Mann-Whitney test. When the distribution of the data was not normal, the Kolmogorov-Smirnov test was used. Furthermore, generalised linear mixed model (GLMM) was applied for the analysis of weight variation adjusted for years of schooling and number of children. Significance was established at $p<.05$. All analyses were performed using the SAS statistical software package, version 9.2.

RESULTS

The medical records of 2,138 women were evaluated. The main characteristics of the users of the three methods are shown in Table 1. Women being fitted with a Cu-IUD were significantly younger than those initiating use of either DMPA or a LNG-IUS, and DMPA users had less years of schooling, a lower BMI and more children when compared to users of the other two methods. Mean weight at baseline was 58.3±0.5; 66.1±0.5 and 62±0.4 kg among DMPA-, LNG-IUS- and Cu-IUD users, respectively.

Note to the Publisher: Insert Table 1 if possible here.

The users of all three contraceptives experienced an increase in weight over the ten years of observation. At the end of the first year of use, women treated with DMPA had gained on average 1.3 ± 0.2 kg, which was significantly greater than the increases experienced by the women fitted with a LNG-IUS or a Cu-IUD (0.7 ± 0.2 kg, p=.0209, and 0.2 ± 0.2 kg, p<.0001, respectively). After two years of use, the mean weight gain was 2.3 ± 0.3 kg among DMPA users, compared to 1.2 ± 0.3 kg and 0.3 ± 0.3 kg in LNG-IUS- (p<.0001) and Cu-IUD users (p<.0001), respectively. After ten years of use, the mean weight increase among DMPA users was 6.5 ± 0.6 kg, compared to 4.0 ± 1.0 kg and 4.9 ± 0.6 kg in women wearing a LNG-IUS (p=.0148) or a Cu-IUD (p=.0350), respectively (Table 2). A secondary analysis (Table 3) showed that – among subjects who relied on their chosen contraceptive method uninterruptedly for three years – only those treated with DMPA had experienced a significant weight gain when compared to those wearing a LNG-IUS (p= .0197) or a Cu-IUD (p=.029). The power of the sample at the end of ten years of evaluation was 90%.

Note to the Publisher: Insert Tables 2 and 3 about here.

DISCUSSION

Our study shows that the weight of the women assessed augmented throughout the ten years of observation irrespective of whether they were using a hormonal or non-hormonal contraceptive. Cu-IUD users were included as control group and compared with women relying on hormonal contraceptives with regard to weight changes. This strategy was used by several teams of investigators who have reported an annual weight increase of 0.6 to 1.4 kg in Cu-IUD users, further rising to 1.8 kg annually after three years of use[8,9,11,16]. Those findings are similar to ours: we observed a weight gain of 0.23 kg after one year of use and 1.36 kg three years following insertion of the Cu-IUD. There is no plausible reason why the presence of a Cu-IUD *in utero* would influence weight. Consequently, one may assume that the aforementioned weight gain is related to ageing and life circumstances, mainly sedentary life and excessive food intake. In fact, weight changes are a rarely reported reason for discontinuation of Cu-IUD use.

Reported weight changes women wearing a LNG-IUS vary greatly. Although some complain about a weight increase during use of this method, it is not a common reason for early discontinuation. Additionally, there is no evidence that weight increase observed in women fitted with a LNG-IUS differs from that associated with the use of non-hormonal contraceptive methods[12-15]. The weight gain of 0.7 and 1.2 kg we noted at the end of the first and second years of use of the IUS, respectively, was lower than that (1.0 to 2.9 kg) described previously after one year of use[6,16]. Furthermore, the weight gain we recorded in women using the LNG-IUS was significantly lower from that experienced by DMPA-users and was not significantly different from the increase observed in Cu-IUD users over the period of evaluation. These findings are in agreement with a previous report by our group[10].

Variations in the weight of DMPA users have been extensively studied over recent years, but findings have been conflicting. Some short-term studies showed no

evidence of any weight increase after 12 months of use[6,7] whereas others, following the same time interval, brought to light a mean weight gain of 1.5 kg (95% confidence interval, 1.3 to l.7 kg)[5]. With long-term follow-up investigators recorded mean weight increases of 5.1 to 6.1 kg after three years of treatment with the progestin-only injectable[18,19], and of 4.3 to 6.3kg after five years[9,11].

Not all DMPA users experience a substantial weight gain and identifying individuals at risk of gaining excess weight may enable prevention. In this study we were unable to identify which women were at risk of extra weight gain during use. But our group recently reported that DMPA users had a mean increase of 2 kg in total fat mass and an increase of 2.2% in body fat at the end of the first year of use when compared to Cu-IUD users. It appeared that only 37% of those women gave due consideration to the counselling on healthy lifestyle habits which they had been provided[20]. Another aspect of the present study that could be important pertains to the fact that DMPA users had a lower weight at baseline than the women from the other two groups. It is possible to argue that healthcare personnel refused to provide DMPA to women with a greater body weight; however, this is not a common practice in our clinic in which women have the right to choose the contraceptive they desire unless medically contraindicated. The finding that, over ten years of follow-up, there were no significant differences in weight gain between the LNG-IUS- and the Cu-IUD users is important: it proves the common belief that long-term use of a hormonal contraceptive *per se* is an indicator of future obesity (BMI $\geq$ 30 kg/m^2) to be wrong.

Strengths and limitations of the study

The major strengths of the study reside in the fact that (i) the three cohorts of women were followed up for as long as ten years after initiation of their chosen method of

contraception and that (ii) the DMPA- and the LNG-IUS users were compared with those of a non-hormonal contraceptive.

There study has some limitations, the main one being its retrospective nature, which does not permit evaluation of users' nutritional or lifestyle habits, factors that may certainly influence weight over the years. According to the Brazilian Ministry of Health[21], 45% of Brazilian women are overweight or obese and this figure tends to increase in women with few years of schooling and with ageing. In the United States of America, 36% of adult women are obese, while in the United Kingdom obesity affects 25% of women[22,23]. The persons concerned consume excessive quantities of saturated fat and devote less time to exercise. However, the few studies that evaluated food intake in users of different hormonal contraceptives have shown no variations in food intake and no association with weight gain[4,24].

The other limitation of the present study was that many women stopped using the contraceptive method; consequently, the number of users in each group, ten years after initiation of the method, was markedly smaller than at baseline. It could be argued that the discontinuers were the women whose weight increased or those who had their menopause, thus introducing a bias in the study's results. Additionally, women treated with DMPA had fewer years of schooling than Cu-IUD users and this could bias the final result because the life styles could differ and we cannot affirm that the weight increase is only method-related.

Implications for healthcare personnel

This study may provide valuable information to healthcare professionals, allowing them to counsel users and potential new users with respect to weight changes and contraceptive use.

Unanswered questions and future research

Prospective studies of long-term users of different contraceptive methods are needed to assess weight variations and to identify factors involved.

CONCLUSION

The users of DMPA, the LNG-IUS and the TCu380A IUD experienced an increase in weight over the ten years of observation. DMPA users gained more weight over ten years than did women fitted with either intrauterine contraceptive.

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Table 1. Some socio-demographic characteristics at baseline of the women in the three study groups

Variables	Group		
	DMPA n=714	LNG-IUS n=701	Copper-IUD n=723
Age at initiation of the current method, years*	29.2 ± 0.2	29.9 ± 0.2	27.2 ± 0.2
Years of schooling*	5.61 ± 0.2	8.8 ± 0.1	6.2 ± 0.1
BMI, kg/m^2 *	23.8 ± 0.2	25.9 ± 0.2	25.2 ± 0.1
Number of children*	2.4 ± 0.1	2.0 ± 0.04	2.0 ± 0.04
Number of children, n (%)			
0	220 (31)	40 (6)	4 (1)
1-2	200 (28)	577 (82)	553 (76)
3 or more	294 (41)	84 (12)	166 (23)

* Mean ± standard error on the mean. DMPA, depot-medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; IUD, intrauterine device; BMI, body mass index.

Table 2. Cumulative weight gain in users of DMPA, the LNG-IUS and the Cu-IUD after up to ten years of use.

Years of use	*Weight variation, kg*						DMPA vs. LNG-IUS	DMPA vs. Cu-IUD	LNG-IUS vs. Cu-IUD
	DMPA users		LNG-IUS users		Cu-IUD users				
	n	Mean ± SEM	n	Mean ± SEM	n	Mean ± SEM	*p*-value*	*p*-value	*p*-value
1	675	1.3±0.15	602	0.7±0.18	602	0.2±0.17	.0209	< .0001	.1719
2	704	2.3±0.16	666	1.2±0.20	666	0.9±0.19	< .0001	< .0001	.6356
3	526	3.1±0.21	537	2.4±0.24	576	1.4±0.23	.0053	< .0001	.0418
4	540	3.5±0.23	563	2.7±0.27	625	1.9±0.23	.0017	< .0001	.2310
6	359	4.6±0.32	213	2.5±0.53	346	3.3±0.36	< .0001	.0081	.1083
8	184	4.9±0.52	90	2.6±0.76	198	4.2±0.48	.0123	.2831	.0735
10	125	6.6±0.61	68	4.0±0.97	154	4.9±0.6	.0148	.0350	.3475
	Weight variation, %								
1	675	2.4±0.26	602	1.2±0.27	602	0.4±0.27	.0024	< .0001	.0952
2	704	4.2±0.27	666	2.0±0.29	666	1.5±0.29	< .0001	< .0001	.7012
3	526	5.8±0.37	537	3.7±0.38	576	2.3±0.36	< .0001	< .0001	.1128
4	540	6.7±0.41	563	4.3±0.41	625	3.2±0.37	< .0001	< .0001	.3941
6	359	8.7±0.58	213	4.2±0.78	346	5.6±0.58	< .0001	< .0001	.0899
8	184	9.3±0.88	90	4.5±1.12	198	7.1±0.75	.0011	.0375	.0699
10	125	12.1±1.13	68	6.8±1.37	154	7.9±0.93	.0027	.0020	.4612

The groups were compared using the Kruskal-Wallis test after which the two groups were compared using the Mann-Whitney test.
*The *p* value was adjusted by generalised linear mixed model for years of schooling and number of children.
DMPA, depot-medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; Cu-IUD, copper-intrauterine device.

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Table 3. Baseline and final weight and weight gain in users of DMPA, LNG-IUS and Cu-IUD after up to ten years of use.

	DMPA users		LNG-IUS users		Cu-IUD users		DMPA vs. LNG-IUS	DMPA vs. Cu-IUD	LNG-IUS vs. Cu-IUD
Years of use	n	Mean±SEM	n	Mean±SEM	n	Mean±SEM	*p*-value	*p*-value	*p*-value
				Weight, kg					
Baseline	714	58.3±0.5	701	66.1±0.5	723	62±0.4	< .0001	< .0001	< .0001
10	125	66.1±1.1	68	68.3±1.8	154	68.4±1.1	.2130	.0743	.6731
				Weight gain, kg					
10	125	6.6±0.6	68	4.0±0.9	154	4.9±0.6	.0148	.0350	.3475
				Weight gain, %					
10	125	12.1±1.1	68	6.8±1.4	154	7.9±0.9	.0027	.0020	.4612

DMPA, depot-medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; Cu-IUD, copper-intrauterine device; SEM, standard error on the mean.

3.3 Artigo 3

Journal of Family Planning and Reproductive Health Care

Body composition in long-term users of depot medroxyprogesterone acetate

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Keywords:	hormonal contraception, intrauterine devices

Body composition in long-term users of depot medroxyprogesterone acetate

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Keywords: body composition, weight, depot medroxyprogesterone acetate and copper IUD.

Running headline: Body composition in depot medroxyprogesterone acetate users.

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Abstract

BACKGROUND: Due to a worldwide epidemic of obesity, it is important to understand the causes of weight gain among women. The injectable contraceptive depot medroxyprogesterone acetate (DMPA) is considered responsible for the increased weight among short-term users; however, evidence of weight gain is still controversial. Thus, the aim of this study was to assess body composition (BC) among DMPA users and compare to copper-intrauterine users (Cu-IUD) up to 15 years of uninterrupted use.

METHODS: This was a cross-sectional study which evaluated BC (fat mass, percentage fat mass and lean mass) and weight gain among DMPA users who started their use at 18 to 40 years of age. The evaluation was performed at one, five, 10 and 15 years of uninterrupted use. BC was measured by dual-energy X-ray absorptiometry.

RESULTS: We observed that at the end of the first year of use, DMPA users showed a mean (± SD) non-significant higher weight of 64.4 ± 8.5 kg compared to 59.9 ± 6.4 kg among the Cu-IUD users (p= 0.069). The weight variation was of 2.2 ± 3.3 and 0.9 ± 4.9 kg among DMPA- and Cu-IUD users, respectively, up to the first year of use (p = 0.014). At long-term use of both methods, weight, fat mass, percentage fat mass, and lean mass did not show significant differences.

CONCLUSION: Users of DMPA were not significantly different regarding weight gain or increased lean and fat mass in the long term when compared to Cu-IUD users.

Key message points:

- Long-term use of DMPA is not associated with significant changes in BC, and changes in BC are probably more associated to a person's lifestyle.
- DMPA and Cu-IUD users at different years of observation presented a high percentage of fat mass (38-40%), which is considered obesity.
- There were no differences between the values of lean mass and fat mass of long-term DMPA users when compared to Cu-IUD users.

Introduction

Obesity and being overweight are considered a worldwide epidemic and public health problem.[1, 2] It is estimated that more than one billion adults worldwide are overweight, and another 300 million are obese.[1] In Brazil, according to national statistics[3], overweight people comprise almost 48% of the adult population; however, the prevalence is higher among men than women.[3] In the United States of America (US), 35.8% of adult women are obese. In the United Kingdom (UK), obesity affects 25% of women.[4, 5] Additionally, it has been reported that obesity consumes an average of 2% to 6% of the total financial resources for health in developing countries [6] because it is associated with the development of chronic diseases, such as blood hypertension, diabetes, cardiovascular disease, and many types of physical disability.[7]

Among the causes attributed to weight gain is excessive calorie consumption combined with reduced physical activity, which reflect the major changes in lifestyle of a significant part of the world's population.[6-7] Besides these causes, research also connects obesity and weight gain with other causes, like genetics, ethnicity, marital status, smoking habit, and reproductive history.[8] Additionally, many women claimed that the use of hormonal contraceptives was associated with weight increase, but this has proven to be a controversial issue.[9] Users of the hormonal contraceptive depot medroxyprogesterone acetate (DMPA) are probably the women who have often been associated with weight gain both by healthcare professionals (HCPs) and by users.[10]

Several authors provided some evidence that DMPA use is related to weight gain.[11, 12-17] However, in a recent systematic review[9], the authors found that there is no scientific evidence connecting weight gain with DMPA use. Furthermore, when it occurs, the greatest weight gain was observed in two to three years of method use; nevertheless, it is generally similar for users of non-hormonal contraceptives.

Beyond the controversy regarding weight variation, scarce evidence exists on body composition (BC) among short- and long-term users of DMPA. Some authors have suggested that weight gain was linked to an increase in central fat mass of the adiposity [11,13,17,18], can be caused by retention of fluids in the extracellular space, increased muscle mass, physiological consequences of the use of DMPA and/or increased fat deposits caused by a higher intake of calories.[19]

In fact, since 2005 when the World Health Organization (WHO) called for research on injectable contraceptives due to the preoccupation with decreased bone mass and increased obesity[20], several studies are being developed to clarify the pathophysiology and consequences of DMPA use among women at different ages and to assess its safety in order to provide valuable information to HCPs and potential users. The aim of this study was to assess BC among DMPA users and compare it with users of a non-hormonal contraceptive (copper intrauterine device; Cu-IUD) at one, five, 10, and 15 years of uninterrupted use.

Subjects and methods

This cross-sectional exploratory study was conducted at the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Campinas, Brazil. The Ethical Committee approved the study, and all the participants signed an informed consent form before entering into the study. We invited women to participate in the study who started DMPA use (150 mg intramuscular every 90 days) at 18 to 40 years of age and who have used the method uninterruptedly for one, five, 10, or 15 years.

The women were identified from the clinical database of the family planning clinic. We sent invitation letters to complete a sample size of 80 users and 80 non-users, 20 for each group according to how long they used their specific contraceptive method.

Women were excluded who had chronic diseases, including diabetes mellitus, hyperthyroidism or hypothyroidism, renal failure, corticoid use, and previous bariatric surgery or organ transplants, as well as Cu-IUD users who had previously used DMPA.

BC was evaluated through densitometry, and the measurements were performed in the morning. The women were instructed to fast before coming to the clinic to reduce the bias of BC. The BC was measured at total body fat, percent body fat and total lean mass using dual-energy X-ray absorptiometry (DXA) Lunar DPX (GE Healthcare, Lunar Corporation Madison, WI, USA).

Statistical Analysis

The dependent variables of the participants were presented using means and standard deviation (SD) for continuous variables: weight, body mass index (BMI; kg/m^2), fat mass, and lean mass. Frequencies were calculated for categorical variables: ethnicity, living with a partner, number of children, practice of physical exercise, alcohol consumption, and smoking habits. Differences of the categorical characteristics between the two groups were evaluated using χ^2 test (Pearson or Yates) or Fisher's exact test. To compare continuous variables between DMPA and Cu-IUD groups, we used a parametric *t*-test or the Mann-Whitney non-parametric test. The significance was established at $p < 0.05$.

Results

The mean age was similar in both groups as well as all the sociodemographic variables that can influence any changes in BC, such as ethnicity, practice of physical exercise, alcohol consumption, and smoking habit. More Cu-IUD users had two or more children

during the first year of using the method compared with DMPA users (p= 0.011) (Table 1). At the end of the first year of use, DMPA users showed a mean (± SD) non-significant higher weight of 64.4 ± 8.5 kg compared to 59.9 ± 6.4 kg among the Cu-IUD users (p= 0.069). Still, in the analysis of weight variation, our study showed that DMPA users had a weight gain in the first year of use when compared to Cu-IUD users 2.2 ± 3.3 and 0.9 ± 4.9 (p = 0.014). At five, 10, and 15 years of use of both methods, weight and BMI (kg/m^2) did not show significant differences (Table 2).

The users of the two contraceptive methods showed an increase in fat mass from the first year through the fifth year of use. However, there was no significant difference between both groups. The percentage of fat mass also remained constant across all the years of evaluation in both groups. At the first year of evaluation, DMPA users showed a significant mean (± SD) larger amount of lean mass compared to Cu-IUD users: 35.8 ± 2.7 and 33.2 ± 2.8, respectively, (p< 0.005) (Table 2). However, at five, 10, and 15 years of use of both contraceptive methods, there was no significant difference in lean mass between the two groups.

Discussion

Our data showed that weight, fat mass, percentage of fat mass, and lean mass were not significantly different when comparing DMPA users to Cu-IUD users at five, 10, and 15 years of use. Although there is no scientific evidence for weight gain in DMPA users[9], a myth persists among HCPs and women that DMPA use is associated with meaningful weight increase when compared to non-users. This fact reflects the findings of several studies in which the authors showed an increase in weight among DMPA users at 1.9 kg[21], 5.1 to 6.1 kg among users up to 30 months [11, 17] and 4 kg at three to five years of use, respectively.[22, 14] In a retrospective cohort study which assessed

weight variation for up to 10 years of DMPA use, the levonorgestrel-releasing intrauterine system (LNG-IUS) and Cu-IUD users, the weight increase was evident only in the first year of DMPA use. Evaluation at the other years of observation was similar to the weight of the Cu-IUD users.

Although no significant differences were observed on the studied variables between the groups of users, the women from both groups at different years of observation showed a high percentage of fat mass (38-40%). It is important to note that 30-35% of fat mass is scientifically considered obesity.[23, 24] This observation allows us to speculate that age and the contraceptive being used [25] were not the leading responsible variables for increases in weight and fat mass. Nonetheless, our study also showed that both DMPA and Cu-IUD users practiced similarly sedentary lifestyles. Sedentary lifestyle and inadequate food intake are most likely the main reasons for the development of weight gain and obesity and could not be related to DMPA use. Perhaps the best way to prevent weight gain, overweight status, and obesity – not only in users of DMPA but in users of other contraceptives – would be to focus more on appropriate recommendations for adopting healthy lifestyle habits, including adequate food intake.[26]

The weight gain in DMPA users is linked to increased fat mass.[11] Authors of previous studies showed a significant gain of 1.6 kg and 2.0 kg of fat mass among DMPA users after 12 months of follow-up [21, 26] and 6.1 kg and 4.1 kg after 30 and 36 months, respectively.[11, 17] Lean mass was higher in DMPA users in the first year of use, contrasting with other researchers who presented no difference in lean mass gain during use of this method.[11, 17, 21, 26] Fat mass gain at the end of the first year of DMPA use does not correlate to significant changes among women who used the

contraceptive for as long as 15 years. As a result, our study showed that the gain of fat mass and lean mass were similar in long-term users of DMPA and Cu-IUD.

There are strengths and limitations linked to this study. One strength is that we assessed BC changes in DMPA users, which is scarce in the literature. Another strength was that the evaluation covered up to 15 years of use for both methods. However, the limitations are the cross-sectional design of the study and the fact that the sample of DMPA users may have been constituted by women who have adapted well to the method with no major complaints about weight. It is conceivable to speculate that women who presented greater weight gain during DMPA use could discontinue the method prematurely and create a bias to the study. Another possible limitation was that we did not perform an assessment of the diets of all the users in different years, but there was no difference between the weights of the users of both methods in the various years of observation.

Our results reinforce the evidence that long-term use of DMPA is not associated with significant changes in BC, and changes in BC are probably more associated to lifestyle habits. In conclusion, the results of our study showed that DMPA users have a higher amount of lean mass when compared to Cu-IUD users at the end of the first year of use of both methods. However, there were no differences between the values of lean mass and fat mass of long-term DMPA users when compared to Cu-IUD users. Future studies are needed to investigate the evolution of lean mass and fat mass in long-term DMPA users and compared to non-users.

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Competing Interests

No declaration of competing interests

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Table 1 Demographic characteristics of the study participants according to the years of use

Variables	1 year			5 years			10 years			15 years		
	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value
Age (mean ± SD)*	32 ± 5.1	30.9 ± 5.1	0.520	38.9 ± 6.2	36.1 ± 5.7	0.147	42.3 ± 5.6	40.6 ± 6.6	0.402	47.9 ± 6.0	45.9 ± 4.1	0.232
Ethnicity (white) (n)[#]	7	8	0.999	2	6	0.235	3	8	0.157	10	10	0.999
Living with a partner[&]	7	12	0.350	17	18	1.0	14	20	0.020	14	18	0.235
Number of children[#]												
1	15	6	0.011	4	8	0.301	7	7	1.0	9	7	1.0
≥2	5	14		16	12		12	13		11	12	
Physical exercise (yes)[#]	8	7	1.0	2	5	0.407	5	5	1.0	4	4	1.0
Alcohol consumption[&]	2	4	0.661	4	5	1.0	4	3	1.0	3	3	1.0
Current smoker[&]	3	4	1.0	4	4	1.0	6	2	.235	5	4	1.0

DMPA: depot-medroxyprogesterone acetate; IUD: intrauterine device; *t-test; [#]χ^2; [&]Fisher exact test

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Table 2 Weight, BMI and BC among DMPA and Cu-IUD users according to years of use

Variables	1 year*			5 years*			10 years			15 years		
	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value	DMPA (n=20)	Cu-IUD (n=20)	*p*-value
Weight (kg)	64.4 ± 8.5	59.9 ± 6.4	0.069	68.1 ± 13.3	69.1 ± 13.6	0.807	65.2 ± 10.6	67.4 ± 10.7	0.524¶	67.3 ± 10.7	68.9 ± 12.7	0.675¶
Δ weight (kg)	2.2 ± 3.3	0.9 ± 4.9	0.014¶	5.7 ± 6.1	3.1 ± 6.2	0.220	8.8 ± 7.6	4.7 ± 6.4	0.572*	11.4 ± 8.2	8.2 ± 9.5	0.485*
BMI (kg/cm²)	24.8 ± 3.0	24.4 ± 2.6	0.714	27.9 ± 5.9	27.9 ± 5.4	0.829¶	26.6 ± 3.8	27.5 ± 3.9	0.474*	27.4 ± 5.1	28.1 ± 5.1	0.665¶
Fat mass (kg)	24.8 ± 7.3	23.0 ± 5.2	0.359	27.3 ± 10.8	26.9 ± 11.0	0.923	26.2 ± 7.8	27.7 ± 7.3	0.543*	27.3 ± 8.4	27.4 ± 10.3	0.871¶
Fat mass (%)	39.0 ± 7.1	38.7 ± 4.8	0.898	39.1 ± 8.4	38.7 ± 9.1	0.905	40.4 ± 7.1	41.3 ± 6.1	0.401¶	40.6 ± 6.7	39.3 ± 8.3	0.610*
Lean mass (kg)	35.8 ± 2.7	33.2 ± 2.8	0.005	37.6 ± 4.5	37.5 ± 4.7	0.913	35.1 ± 3.8	36.1 ± 4.7	0.766¶	36.3 ± 3.4	37.5 ± 3.5	0.267¶

DMPA: depot-medroxyprogesterone acetate; IUD: intrauterine device; BMI: body mass index; BC: body composition; *t-test; ¶Mann Whitney test

3.4 Artigo 4

JOURNAL OF
Women's Health

Prevalence of osteopenia and osteoporosis in long-term users of the injectable contraceptive depot medroxyprogesterone acetate

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Complete List of Authors:	Modesto, Waleska; UNICAMP, Women´s Health; UNICAMP, Bahamondes, Maria Valeria; UNICAMP, Women´s Health Bahamondes, Luis ; UNICAMP, Women´s Health; UNICAMP, Obst & Gynecol
Keyword:	bone health, reproductive health, contraception
Abstract:	BACKGROUND: Bone mineral density (BMD) loss among depot medroxyprogesterone acetate (DMPA) users is a controversial issue. Aspects under debate include whether the number of years of use has any effect on continuous BMD loss, whether this loss will stabilise over the years of use or if it will progress to osteopenia, osteoporosis and an increased fracture risk. The aim of this study was to assess the prevalence of osteopenia and osteoporosis in long-term DMPA users. METHODS: This was a cross-sectional study which evaluated BMD at the lumbar spine and femoral neck in 47 long-term DMPA users and 41 copper-intrauterine device (IUD) users as controls. BMD was measured by dual-energy X-ray absorptiometry. The participants were 27 to 57 years of age, had used either DMPA or an IUD uninterruptedly for at least ten years, had initiated use of the method prior to 40 years of age and had FSH values < 40 mIU/ml. RESULTS: Findings showed that 68.1% and 36.6% of the DMPA and copper-IUD users, respectively, had osteopenia and 29.8% and 2.4% of DMPA and copper-IUD users, respectively had osteoporosis. BMD decreased as the number of years of DMPA use increased. CONCLUSION: Long-term DMPA use was associated with osteopenia and osteoporosis in women who had used the method for ten years or more. Bone mass loss was a continuous process that intensified with the years of DMPA use.

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Prevalence of osteopenia and osteoporosis in long-term users of the injectable contraceptive depot medroxyprogesterone acetate

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Keywords: Bone mineral density, Depot-medroxyprogesterone acetate, Osteoporosis, Osteopenia, Contraception.

Running Title: Prevalence of Osteoporosis in DMPA users**.**

Word count: 2,098

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Abstract

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METHODS: This was a cross-sectional study which evaluated BMD at the lumbar spine and femoral neck in 47 long-term DMPA users and 41 copper-intrauterine device (IUD) users as controls. BMD was measured by dual-energy X-ray absorptiometry. The participants were 27 to 57 years of age, had used either DMPA or an IUD uninterruptedly for at least ten years, had initiated use of the method prior to 40 years of age and had FSH values < 40 mIU/ml.

RESULTS: Findings showed that 68.1% and 36.6% of the DMPA and copper-IUD users, respectively, had osteopenia and 29.8% and 2.4% of DMPA and copper-IUD users, respectively had osteoporosis. BMD decreased as the number of years of DMPA use increased.

CONCLUSION: Long-term DMPA use was associated with osteopenia and osteoporosis in women who had used the method for ten years or more. Bone mass loss was a continuous process that intensified with the years of DMPA use.

INTRODUCTION

Depot medroxyprogesterone acetate (DMPA) is a highly effective, safe contraceptive method that has been in use worldwide for several decades.[1, 2] However, there are controversies concerning long-time exposure and its effects on bone mineral density (BMD), not only during its use but also following discontinuation, after menopause and with respect to fracture risk.[3] There is also concern regarding the use of DMPA over several years by adolescent girls before they achieve peak bone mass, and whether this would affect BMD in the future.[4-7]

It has been well established that DMPA users develop hypooestrogenism,[8, 9] and that low endogenous oestrogen is one of the principal causes of bone loss.[1] It has also been reported that DMPA users may experience progressive BMD loss throughout the first five years of use;[10-12] however, after that period, the body may adapt to hypooestrogenism, reducing bone mass loss and stabilising bone turnover.[8] Furthermore, it has also been well established that the decrease in BMD is reversible following discontinuation.[1, 13]

Although it has been reported that long-term DMPA use does not increase the risk of osteopenia, [14] some studies have shown that use of this contraceptive method may increase fracture risk, principally in the fingers, toes, face and skull, and may increase the risk of multiple trauma compared to users of other contraceptive methods.[15] However, it is important to take into account that alcohol consumption and smoking habits could act as confounding factors.[16, 17]

Evidence that any loss of BMD is recovered after DMPA is discontinued remains a subject of debate as far as long-term uninterrupted use is concerned.[3, 6, 7] Due to the scarcity of data on the long-term use of DMPA and its effect on BMD, the objective of this exploratory study was to determine the prevalence of osteopenia and

osteoporosis in women who had used DMPA uninterruptedly for ten years or more. The design of the study was based on the hypothesis that the body does not adapt to the hypooestrogenism caused by DMPA and that bone loss during long-term DMPA use may result in damage to bone health.

METHODS

This was a cross-sectional study conducted at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas, Brazil. The Ethical Committee approved the study and all the women signed an informed consent form prior to admission. Following a search of the archives of the family planning clinic up to the year 2013, 93 DMPA users were identified. They had been using DMPA and Cu-IUD for at least ten years uninterruptedly and attended the clinic regularly. An invitation letter was sent to all these women. Forty-eight of them agreed to participate and came to the clinic for BMD evaluation.

Two groups were formed: (i) the group of DMPA users and (ii) a group of non-users. Women of 27 to 57 years of age, who had been using DMPA (Depo-provera®, Pfizer, São Paulo, Brazil) (intramuscular injection of 150 mg of the progestin) uninterruptedly for at least ten years (40 doses) or who had never used DMPA (non-users), who started using the method prior to 40 years of age and who had at least two consecutive (90 days apart) FSH measurements < 40 mIU/ml were enrolled to the study. Only one woman had FSH values > 40 mIU/ml and was excluded. The non-user group consisted of current users of the TCu380A intrauterine device (Cu-IUD) (Optima®, Injeflex, São Paulo, Brazil). Non-users had had regular menstrual cycles for the 12 months preceding the study, had never used DMPA and had not used any other hormonal contraceptive method for more than 6 months during their reproductive lives

or in the six months preceding the study. Exclusion criteria consisted of: chronic diseases (including diabetes mellitus, hyper or hypothyroidism, hyper- or hypoparathyroidism, hepatitis, cancer or pituitary diseases), and chronic renal failure. Women previously submitted to bariatric surgery or organ transplantation were also excluded from the study. Bone mineral density was measured at the lumbar spine and femoral neck by dual-energy X-ray absorptiometry (DXA) using a Lunar bone densitometer (GE Healthcare, Lunar Corporation Madison, WI, USA).

Based on a pilot study, for an alpha error of 5% and a beta error of 13%, sample size was calculated at 22 users and 22 non-users for the assessment of BMD at the lumbar spine and femoral neck. Considering this sample size, 47 DMPA users and 41 Cu-IUD users were enrolled, providing a power of over 80%. The demographic and clinical variables were compared using Student's *t*-test, the Mann-Whitney test, the χ^2 test, and Fisher's exact test. Comparison of mean BMD between the groups of DMPA users at the different years of use was performed using ANOVA. The statistical analysis was performed using the SAS statistical software package for Windows, version 9.2 and all results were reported as mean ± standard derivation (SD). Significance was established at $p < .05$.

RESULTS

There were no differences between the two groups with respect to their sociodemographic variables (Table 1), with homogeneity being found for age, body mass index (BMI; kg/m^2) and physical activity, all of which are factors that could be associated with BMD. No influence upon the results was observed regarding ethnicity. Albeit we did not obtain data about socioeconomic status of the women, the participants are patients from a clinic of Brazilian public service and they came from the low income

portion of the population. Thirty-three out of the 47 women in the DMPA group (68.1%) and 15 out of the 41 women in the Cu-IUD group (36.6%) were found to have osteopenia (p= .002). In addition, 14 of the 47 DMPA users (29.8%) and one of the 41 Cu-IUD users (2.4%) had osteoporosis (p=.0008).

No significant differences were found between the two groups with respect to whether osteopenia was present at the spine or the femoral neck. Comparing the site of osteoporosis, there was a trend towards a higher prevalence of osteoporosis at the spine (13 women; 27.6%) when compared to the femoral neck (1 woman; 2.4%) in DMPA users; however, this difference was not significant (p=1.0). The mean BMD at the lumbar spine (L1-L4) among DMPA users was 1.037±0.125 significantly lower than Cu-IUD users (1.192±0.109; p<.0001) and at femoral neck it was 0.9116±0.119 and 0.9925±0.128 among DMPA and Cu-IUD users, respectively (p=.0029) (Table 2).

Furthermore, comparison between DMPA users who had been using the method for ten years, 11-15 years or 16-23 years showed that BMD decreased as the number of years of DMPA use increased. Additionally, a significant decrease in BMD was found at the lumbar spine; however, no significant differences were found at the femoral neck over the years (Figure 1).

DISCUSSION

Our results showed that around 30% of the women who had used DMPA for ten years or more developing osteoporosis compared to only 3% of the non-users. These results are more significant if we take into account that the two groups were homogeneous, insofar as the risk factors for osteoporosis are concerned.

Investigators evaluating adolescent girls of 12 to 18 years of age after two years of DMPA use reported that bone mass loss was insufficient to provoke osteopenia.[14]

Nevertheless, longer periods of use, which obviously correlate with older age in users, may induce a reduction in BMD and could reduce the bone remodeling process, consequently provoking osteopenia and osteoporosis and increasing fracture risk. There is no clear evidence regarding the relationship between DMPA use and an increased risk of fracture[3] despite the fact that some studies have shown a high risk of fracture in DMPA users compared to non-users.[15-17] However, there are some confounders that were not properly taken into account in those study populations,[1,3] and it is possible that the greater number of fractures in DMPA users could be accounted for by differences in the behavior of users compared to non-users such as greater alcohol consumption, smoking and illicit drug abuse.[16,18] A firm association has been established between these habits and a higher incidence of fractures in the appendicular skeleton, but not with fragility fractures in the axial skeleton.[15]

Additionally, although the reduction in BMD in DMPA users has been well documented by some authors,[8, 10-12, 15, 19] other investigators failed to replicate those results.[20,21] A greater loss was described in the initial years of use, varying in the different reports from around 0.4%[10, 11] up to 3% per year.[12,19] Furthermore, some investigators suggested that BMD loss occurs in a linear fashion after a prolonged period of DMPA use,[8, 10, 22, 23] however, this loss can be recovered within a short time, with a gain in bone mass of almost 5% two years after DMPA discontinuation.[24] Moreover, a United Kingdom (UK)-based researchers suggested that there is a balance with respect to BMD loss in long-term DMPA users and it is reasonable to speculate that there is an adaptation to the hypooestrogenism present during use.[8]

However, our study showed that when DMPA was used uninterruptedly for very long periods of time, BMD loss failed to stabilise, as predicted in the study design. These results were in agreement with the findings of other researchers showing that in

long-term users of DMPA BMD was below the mean for the normal population, particularly at the lumbar spine,[8, 10] and that women with FSH values ≥ 25.8 mIU/ml were associated with reduced BMD, possibly indicating that these women were in the menopausal transition.[25] However, when the region analysed was the distal radius, no decrease in BMD was found in long-term users of DMPA.[20] In addition, attenuated rates of bone loss were found at the lumbar spine and femoral neck[26] and the decrease in BMD at the distal and ultradistal radius was only statistically significant in women who had used DMPA uninterruptedly for as long as 13 to 15 years.[20]

These data may have an impact on family planning programmes. It has been well established that DMPA is one of the most commonly used contraceptive methods in many settings; consequently, the impact of BMD loss with the resulting osteopenia and osteoporosis may constitute a public health problem. Nevertheless, scarce information is available to the health care professionals (HCPs) regarding the duration of DMPA use. The information currently available is derived from few studies that provide insight into the prevalence of long-term DMPA use around the world, since in many settings DMPA is administered in clinical, rather than research settings. Nevertheless, there is information from some countries in which women have used DMPA for extremely long periods. For example, women are reported to have used DMPA for as long as 27 years in New Zealand, 23 years in Brazil, 16 years in the UK, and 15 years in China.[8, 10, 26]

Therefore, the recommendation given to physicians by the United States Food and Drug Administration (USFDA) in 2004,[27] and then by the health authorities of the UK and Canada,[28, 29] indicating that DMPA users were at risk of developing osteopenia and osteoporosis, may be exaggerated. In fact, in the present study, an effect on bone mass was only found in long-term users, as previously reported.[20] Nevertheless, it is

important to take into account that in addition to DMPA use, other factors may affect BMD. Long-term users are older and many of these women are in the menopausal transition. In addition, calcium intake, sun exposure, coffee and alcohol consumption, and physical activity must be taken into account when BMD is evaluated.

In this respect, the present study has some limitations, since subjects' family history of osteoporosis, calcium intake, coffee consumption and sun exposure, well known variables associated with bone mass loss, were not evaluated. However, Campinas is a Brazilian city in which there is sunshine throughout almost the entire year; consequently, exposure to sunlight is fairly constant.

According to the American College of Obstetricians and Gynecologists (ACOG)[1] and the World Health Organisation (WHO),[30] DMPA is a safe and effective contraceptive. It also has some additional benefits related to the treatment of gynaecological disorders such as its ability to reduce heavy menstrual bleeding, dysmenorrhoea associated with endometriosis, the risk of ectopic pregnancy, sickle cell crises, and the incidence of bothersome perimenopausal symptoms. Nevertheless, the WHO guidelines regarding bone health and DMPA use suggested that the data are insufficient to determine whether the overall risks of continuing use of the method may outweigh the benefits in women over 45 years of age and in long-term users.[30] The UK National Institute for Health and Care Excellence (NICE) states that new studies are needed to evaluate BMD recovery following discontinuation after long-term DMPA use and the risk of bone fractures in older women.[31]

According to the ACOG and WHO recommendations, the benefits of DMPA use surpass the risks. Nevertheless, our findings showed that DMPA use for ten years or more has a deleterious effect on BMD, significantly reducing BMD and increasing the prevalence of osteopenia and osteoporosis compared to never users.

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Author Disclosure Statement

No competing financial interests exist.

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Table 1. Some socio-demographic characteristics of the women in the two groups at the time of evaluation

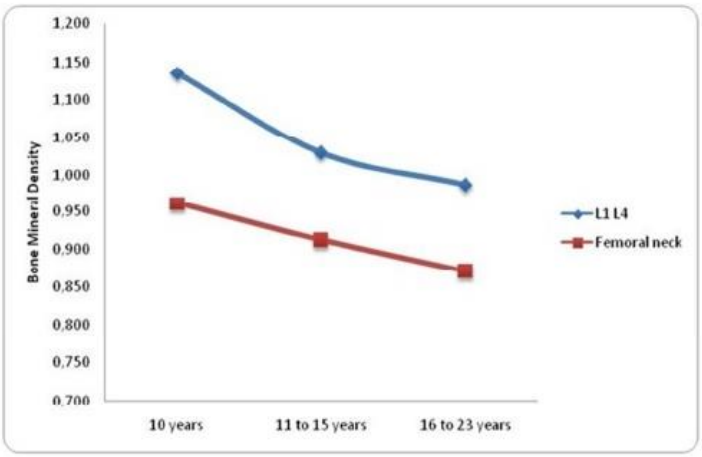
Variables	Contraceptive method in use		*p*-value
	DMPA (n=47)	Cu-IUD (n=41)	
Age, years *	45.7 ± 6.1	43.8 ± 6.1	.17
BMI; kg/m^2 *	27.3 ± 4.2	27.8 ± 4.4	.60
Years using the current method **	14.8 ± 3.8	15.3 ± 4.0	.49
Ethnicity (white women) ***	17 (36.2%)	18 (43.9%)	.54
Married or living with a partner	35 (74.5%)	39 (95.1%)	.0094
In paid employment	40 (85.1%)	27 (65.8%)	.04
Previous contraceptive method used			
Combined oral contraceptives	24 (51%)	18 (43.9%)	
Cu-IUD	8 (17%)	4 (9.7%)	
Condom, natural or no methods	12 (25.5%)	15 (36.5%)	
ENG-releasing implant	2 (4.2%)	0 (0%)	.46
Combined monthly injectable	1 (2.1%)	4 (9.7%)	
Years using the previous method **	3.7 ± 4.0	3.2 ± 3.6	.26
Physical activity ***	11 (23.4%)	9 (21.9%)	.91
Domestic chores ¶	42 (89.4%)	39 (95.1%)	.15
No alcohol consumption ¶	38 (80.8%)	35 (85.4%)	.46
No smoking ¶	35 (74.5%)	35 (85.4%)	.36

* Student's *t*-test; ** Mann-Whitney test; *** χ^2 test; ¶ Fisher's exact test

Table 2 Comparison between the BMD of DMPA and Cu-IUD users

Variable	Group	Mean ± SD	95% CI		*p*-value
L1-L4	DMPA	1.037±0.1	1.000	1.073	<.0001*
	Cu-IUD	1.192±0.1	1.158	1.227	
T score	DMPA	-1.2±1.0	-1.5	-0.9	<.0001*
	Cu-IUD	0.1±0.9	-0.2	0.4	
Femoral neck	DMPA	0.912±0.9	0.877	0.947	.0029*
	Cu-IUD	0.992±0.1	0.952	1.033	
T score	DMPA	-0.9±0.9	-1.2	-0.7	.0030*
	Cu-IUD	-0.3±0.9	-0.6	0.0	

**t*-test



161x105mm (96 x 96 DPI)

Fig 1 Bone mineral density in DMPA users

Anova test, L1-L4 (p=.007) Femoral neck (p=.244). 10 years:10 subjects; 11-15 years: 20 subjects, 16-23: 17 subjects.

3.5 Artigo 5

ANZJOG Proof

Body composition and bone mineral density in users of the etonogestrel releasing implant

Journal:	*The Australian and New Zealand Journal of Obstetrics and Gynaecology*
Manuscript ID:	Draft
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Keywords:	Etonogestrel-releasing implant, Body composition, Bone mineral density, Implanon

Body composition and bone mineral density in users of the etonogestrel releasing implant

Short title: Bone mineral density and BC in implant users

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ABSTRACT

Background: There is scarce information about bone mineral density (BMD) and body composition (BC) among users of the etonogestrel (ENG)-releasing implant. **Aims:** to evaluate BC and BMD in ENG-releasing implant users compared to TCu380A intrauterine device (Cu-IUD) users**. Materials and Methods:** A prospective study was conducted with 75 users of both contraceptive methods. BMD was evaluated at femoral neck (FN) and lumbar spine (LS) (L1-L4) and BC at baseline, 12, and 24 months of use. **Results:** For ENG-releasing implant and Cu-IUD users, respectively, the (mean ± SD) age was 30.4 ± 6.8 and 29.8 ± 8.4 years old and body mass index (kg/m^2) was 24.9 ± 4.1 and 24.6 ± 3.5.There was a significant decrease (p=0.052) in BMD in implant users at LS compared to Cu-IUD users at one year of use when compared with baseline values. BMD at the FN at 12 and 24 months of use of the ENG-releasing implant showed no significant differences. Furthermore, ENG-implant users had an increase in body weight at 12 months (p<0.001) and 24 months (p=0.05) and an increase of 2% and 2.7% in the percentage of body fat, respectively, when compared with Cu-IUD users. There was a significant increase in lean mass in ENG-implant users at 12 (p=0.020) and 24 (p=0.010) months. **Conclusions:** A small loss of BMD up to the 1st year of ENG-releasing implant use was observed, as well as an increase of weight and fat mass in ENG-releasing implant users when compared to Cu-IUD users.

Introduction

Long-acting reversible contraceptive methods (LARC) are used on a large scale due to their high effectiveness and convenience.[1-4] However, in recent years several studies have been published suggesting the possibility of bone mineral density (BMD) loss and fracture risk among contraceptive users. Interest in BMD and contraception arises because contraceptives are administered for prolonged periods and in a stage of life in which many women have not yet reached the peak of bone formation.[5, 6] Thus, some contraceptives might interfere with peak bone acquisition or induce early BMD loss, which could result in osteopenia or osteoporosis in the future.[7]

Studies of the effects of progestin-only contraceptive subdermal implants upon BMD are scarce and still inconclusive.[8, 9] Nevertheless, it was noted that BMD was significantly lower at 18 and 36 months of use at the midshaft of the ulna, although with no difference at the distal radius in which the bone is predominantly trabecular.[10, 11]

Additionally, body weight and body mass index (BMI; kg/m^2) are associated with BMD. Body composition (BC) is an important predictor of BMD, because both the fat and lean mass are important components of weight, which can be a protective factor in relation to BMD loss.[12] Studies of weight gain attributable to the use of subdermal contraceptive implants have been conflicting, and although some authors have suggested that weight increase was a frequently reported adverse effect among users,[13-18] the number of women reported to have discontinued for that reason was low.[19] Additionally, studies of BC changes are scarce among users of the ENG-releasing implant. Consequently, the aim of this study is to compare variations in BMD and BC in ENG-releasing implant users with those in a group of non-hormonal contraceptive method users after 24 months of insertion.

Materials and methods

This was a cross sectional study conducted at the Human Reproduction Unit, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas, Brazil. The Ethical Committee approved the study under number 07405112.9.0000.5404, and all the women signed an informed consent form prior to admission to the study. The study was conducted between August 2011 and August 2013. We invited women to participate who were beginning to use either an ENG-releasing implant or a TCu380A intrauterine device (Cu-IUD). The choice of contraceptive method was made exclusively by the women.

The women enrolled were between 18 and 46 years of age. Thirty-eight and 37 women, who had chosen an ENG-releasing implant or Cu-IUD respectively, were invited to participate. Exclusion criteria consisted of the following: breastfeeding in the six months prior to enrollment; chronic diseases, including diabetes mellitus, hyper- or hypothyroidism, hyper- or hypoparathyroidism, pituitary diseases, hepatitis, cancer, or chronic renal failure; or a history of bariatric surgery or organ transplantation.

Bone mineral density and BC were measured at baseline, 12, and 24 months after initiating the contraceptive method by dual-energy X-ray absorptiometry (DXA) (Lunar DPX, GE Healthcare, Lunar Corporation, Madison, WI, USA). BMD was measured at the lumbar spine (L1-L4) and femoral neck (FN). BC was evaluated according to total fat mass, percent body fat, and total lean mass.

Data analysis

The SAS statistical software program was used to analyse the data. To compare BC and BMD at baseline and at 12 and 24 months, either the Mann-Whitney non-parametric test or the Student's *t*-test was used. The level of significance was established at $p<0.05$, and all values are shown as mean ± standard derivation of the mean (SD).

Results

A total of 75 women were enrolled: 38 ENG-releasing implant users and 37 Cu-IUD users. Before the end of the first year of use of the method, two women removed the implant due to complaints of weight gain, five due to bleeding disturbances, and six for personal reasons (desire to become pregnant, the partner performed vasectomy, and treatment of disease). After the first year of implant use, another two women discontinued for bleeding disturbances, and three for personal reasons (Figure 1).

There were no significant differences between the two groups of contraceptive users as to their social and demographic characteristics (Table 1). In the 12 months following insertion, a significant decrease (p=0.052) in BMD occurred among ENG-releasing implant users (-0.010 ± 0.037), compared to the Cu-IUD users (0.014 ± 0.047), but only at the LS. The evaluation at the FN at 12 and 24 months of use of the ENG-releasing implant showed no significant differences (Table 2).

The analysis of BC showed a weight gain of 4.1 kg (p<0.001) and 0.9 kg (p =0.05) at 12 and 24 months after insertion, respectively, versus -0.1 kg and -2.0 kg at 12 and 24 months among Cu-IUD users, respectively (Table 2). The fat mass increased by 2.4 kg (p=0.034) and 2.9 kg (p=0.024), and the percentage of body fat by 2.0% (p=0.028) and 2.7%, at 12 and 24 months (p=0.028 and p =0.043), respectively, among the ENG-releasing implant users (Table 2). Regarding lean mass, the mean increase was significant after 12 months (36.5 ± 4.1) (p=0.020) and 24 months (36.9 ± 3.4) (p =0.010) among the ENG-releasing implant users when compared to the Cu-IUD. However, the analysis of variation at the end of 12 and 24 months did not show significant differences.

Discussion

The results of this study showed that weight, fat mass and percentage of fat mass in ENG-releasing implant users increased at 12 and 24 months of use. Weight gain was higher (4.1 kg after 12 months) than reported by two groups of researchers: 2.1 and 1.9 kg at 12 and 24 months, respectively, after insertion.[13, 20] However, Cu-IUD users showed a reduction in weight through the same period of follow-up. Although there are reports of weight gain among ENG-releasing implant users, [13, 20] early discontinuations due to this reason have remained low, and bleeding disturbance is still the most important cause for early discontinuation.[17, 21] In our study, only two women removed the implant before the end of the first year of use due a complaint of weight gain, and no one did so through the second year. Just as with weight gain, the fat mass and percentage fat mass showed a significant increase after 12 and 24 months of follow-up among the ENG-releasing implant users when compared to Cu-IUD users.

In addition, ENG-releasing implant use for 12 months was associated with a slight decrease in BMD at the LS, probably without clinical significance, and with no significant change at 24 months. Likewise, the FN showed no significant changes in BMD at 12 and 24 months of use. These results were in slight contrast to other studies that showed that the use of the ENG-releasing implant for more than 24 months did not change BMD at the LS and FN when compared to users of non-hormonal methods.[13,8] However, there was also observed a small decrease in BMD at the midshaft ulna after 18 and 36 months of use of the method.[8,10,11] According to these results, the use of the ENG-releasing implant seems to induce a slight decrease in BMD, becoming evident after 12 months of use, and mainly affecting the non-trabecular bone up to 24 months.[10,11]

Some users of the ENG-releasing implant presented habits which potentially exert a negative influence on BMD and BC, including high coffee consumption and a low level of physical activity, and this may be an important factor in understanding the findings of BMD loss, changes in BC, and weight gain. Additionally, we did not evaluate the daily diet or calcium intake, and these variables could also have influenced our results.

There are strengths and limitations to this study. The main strength is that we assessed BC of ENG-releasing implant users, with estimates of weight, fat mass, percentage of fat mass and lean mass, up to 24 months after insertion. Studies of all of these factors in relation to ENG-release implants continue to be scarce. In our study, there was a significant loss to follow-up at 24 months of the study, and this may have influenced our results, mainly with respect to the variation in BMD at LS of ENG-releasing implant users. In addition, the lack of consideration of exercise and other habits could influence the results. However, when assessing BC, even with the loss of follow-up, our results showed that users of the ENG-releasing implant maintained a weight gain at 24 months of follow-up.

Conclusion

In conclusion, the results of the present study showed that ENG-releasing implant users had an increase in weight, fat mass, and percentage fat mass after 24 months of use of the method, and a decrease in BMD at LS after 12 months of use. A study with a large number of women and with control of physical exercise and deleterious habits is necessary before making any definitive conclusions.

Conflict of interest

The authors declare no conflict of interest

Acknowledgements

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Table 1. Anthropometric characteristics of the two groups at the beginning of the study.

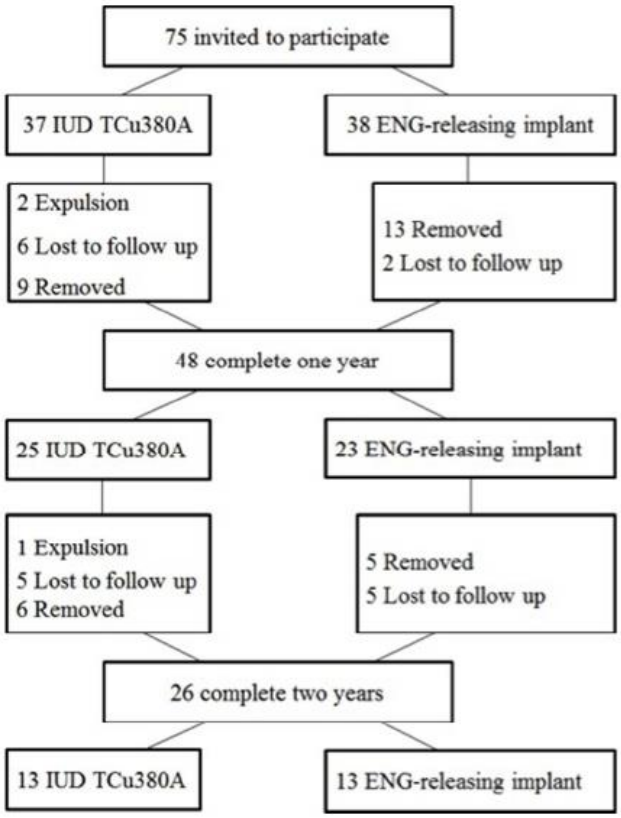
Variables	ENG-releasing implant (N=23)	Cu-IUD (N=25)	*p*-value
Age (mean ± SD) †	30.4 ± 6.8	29.8 ± 8.4	0.397
Ethnicity‡ white n (%)	11 (55)	14 (56.0)	0.999
Parity ‡ ≥2 n (%)	8 (40.0)	16 (64.0)	0.193
Regular physical practice‡ n (%)	6 (30.0)	4 (16.7)	0.472
Coffee consumption‡ n (%)	12 (60.0)	17 (70.8)	0.663
Alcohol consumption‡ n (%)	7 (35.0)	9 (33.3)	0.999
Smoking habits‡ n (%)	2 (10.0)	3 (12.5)	0.999

† Student-*t* test, ‡Mann Whitney test

Table 2. Body composition and bone mineral density at 12 and 24 months

Variables	ENG-releasing implant	Cu-IUD	*p*-value
Weight (kg)			
Baseline‡	67.2 ± 12.6	61.5 ± 8.9	0.101
12 months† (n=19)	70.2 ± 12.7	61.3 ± 10.2	0.016
24 months†	66.6 ± 18.3	62.4 ± 9.2	0.467
Δ 12 months†	4.1 ± 3.9	-0.1 ± 2.8	<0.001
Δ 24 months‡	0,9 ± 8.5	-2.0 ± 6.6	0.05
BMI (kg/cm2)			
Baseline	24.9 ± 4.1	24.6 ± 3.5	0.799
12 months‡	27.6 ± 7.6	24.6 ± 3.7	0.129
24 months†	25.4 ± 4.1	24.9 ± 3.1	0.735
Δ 12 months†	1.5 ± 1.5	-0.3 ± 1.1	<0.001
Δ 24 months‡	1.3 ± 1.4	-0.7 ± 2.5	0.01
BMD Femoral neck (g/cm2)			
Baseline†	1.007 ± 0.142	0.996 ± 0.999	0.753
12 months†	0.999 ± 0.142	1.004 ± 0.089	0.886
24 months†	1.023 ± 0.140	0.996 ± 0.870	0.556
Δ Femoral neck 12 months†	-0.007 ± 0.043	0.008 ± 0.048	0.238
Δ Femoral neck 24 months†	0.002 ± 0.058	0.013 ± 0.055	0.624
BMD Spine (g/cm2)			
Baseline†	1.192 ± 0.129	1.147 ± 0.119	0.213
12 months†	1.179 ± 0.135	1.161 ± 0.103	0.613
24 months†	1.191 ± 0.147	1.154 ± 0.128	0.500
Δ Spine 12 months†	-0.010 ± 0.037	0.014 ± 0.047	0.052
Δ Spine 24 months†	-0.009 ± 0.042	0.006 ± 0.056	0.422
Fat mass (%)			
Baseline‡	41.6 ± 8.8	40.1 ± 6.8	0.489
12 months†	44.2 ± 7.6	40.0 ± 7.3	0.059
24 months†	41.8 ± 8.1	42.4 ± 5.7	0.826
Δ Fat mass 12 months‡	2.0 ± 4.2	-0.1 ± 3.1	0.028
Δ Fat mass 24 months†	2.7 ± 5.4	-0.9 ± 3.1	0.043
Fat mass (kg)			
Baseline†	27.1 ± 9.6	24.1 ± 7.1	0.232
12 months‡ (n=22)	30.1 ± 9.1	24.3 ± 8.2	0.021
24 months†	27.8 ± 9.6	25.6 ± 6.7	0.516
Δ Fat mass 12 months†	2.4 ± 4.0	0.2 ± 2.9	0.034
Δ Fat mass 24 months†	2.9 ± 3.8	-1.2 ± 4.9	0.024
Lean mass (kg)			
Baseline‡	36.1 ± 4.4	33.9 ± 3.5	0.062
12 months†	36.5 ± 4.1	33.8 ± 3.5	0.020
24 months†	36.9 ± 3.4	34.1 ± 3.4	0.010
Δ Lean mass 12 months†	0.4 ± 1.4	-0.1 ± 1.3	0.277
Δ Lean mass 24 months†	0.1 ± 1.9	-0.1 ± 1.6	0.768

†Student-*t* test, ‡Mann Whitney test



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3.6 Artigo 6

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human reproduction ORIGINAL ARTICLE *Fertility control*

A randomized clinical trial of the effect of intensive versus non-intensive counselling on discontinuation rates due to bleeding disturbances of three long-acting reversible contraceptives

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STUDY QUESTION: Does intensive counselling before insertion and throughout the first year of use have any influence on discontinuation rates due to unpredictable menstrual bleeding in users of three long-acting reversible contraceptives (LARCs)?

SUMMARY ANSWER: Intensive counselling had a similar effect to routine counselling in terms of discontinuation rates due to unpredictable menstrual bleeding in new users of the contraceptives.

WHAT IS KNOWN ALREADY: Contraceptive efficacy and satisfaction rates are very high with LARCs, including the etonogestrel (ENG)-releasing implant, the levonorgestrel-releasing intrauterine system (LNG-IUS) and the TCu380A intrauterine device (IUD). However, unpredictable menstrual bleeding constitutes the principal reason for premature discontinuation, particularly in the cases of the ENG-implant and the LNG-IUS.

STUDY DESIGN, SIZE, DURATION: A randomized clinical trial was conducted between 2011 and 2013, and involved 297 women: 98 ENG-implant users, 99 LNG-IUS users and 100 TCu380A IUD users.

PARTICIPANTS, SETTING, METHODS: Women accepting each contraceptive method were randomized into two groups after the women chose their contraceptive method. Group I received routine counselling at the clinic, including information on safety, efficacy and side effects, as well as what to expect regarding bleeding disturbances. Group II received 'intensive counselling'. In addition to the information provided to those in Group I, these women also received leaflets on their chosen method and were seen by the same three professionals, the most experienced at the clinic, throughout the year of follow-up. These three professionals went over all the information provided at each consultation. Women in both groups were instructed to return to the clinic after 45 ($\pm$7) days and at 6 and 12 ($\pm$1) months after insertion. They were instructed to record all bleeding episodes on a menstrual calendar specifically provided for this purpose. Additionally, satisfaction with the method was evaluated by a questionnaire completed by the women after 12 months of use of the contraceptive method.

MAIN RESULTS AND THE ROLE OF CHANCE: There were no significant differences between the intensive and routine counselling groups on the discontinuation rates due to unpredictable menstrual bleeding of the three contraceptives under evaluation. The 1-year cumulative discontinuation rates due to menstrual bleeding irregularities were 2.1, 2.7 and 4.0% and the continuation rates were 82.6, 81.0 and 73.2%, for the ENG-implant, the LNG-IUS or the TCu380A IUD users, respectively. The main reasons for discontinuation of the methods were weight gain in users of the ENG-implant and expulsion of the TCu380A.

LIMITATIONS, REASONS FOR CAUTION: The main limitations are that we cannot assure generalization of the results to another settings and that the routine counselling provided by our counsellors may already be appropriate for the women attending the clinic and so consequently intensive counselling including written leaflets was unable to influence the premature discontinuation rate due to unpredictable menstrual bleeding. Additionally, counselling could discourage some women from using the LARC methods offered in the study and consequently those women may have decided on other contraceptives.

WIDER IMPLICATIONS OF THE FINDINGS: Routine counselling may be sufficient for many women to help reduce premature discontinuation rates and improve continuation rates and user satisfaction among new users of LARC methods.

TRIAL REGISTRATION NUMBER: The trial was registered at clinicaltrials.gov (NCT01392157).

STUDY FUNDING/COMPETING INTEREST(S): The study was partially funded by the *Fundação de Apoio a Pesquisa do Estado de São Paulo* (FAPESP) grant # 2012/01379-0, the Brazilian National Research Council (CNPq) grant #573747/2008-3 and by Merck (MSD), Brazil under an unrestricted grant. The LNG-IUS were donated by the International Contraceptive Access Foundation (ICA) and the copper IUD by Injeflex, São Paulo, Brazil. L.B. has occasionally served on the Board of MSD, Bayer and Vifor.

Key words: counselling / long-acting contraceptive methods / copper intrauterine device / implant / levonorgestrel-releasing intrauterine system

Introduction

The long-acting reversible contraceptives (LARCs) include the copper-intrauterine device (IUD), the levonorgestrel-releasing intrauterine system (LNG-IUS) and the levonorgestrel (LNG)- and the etonogestrel (ENG)-releasing subdermal implants (Peterson and Curtis, 2005). Contraceptive efficacy and continuation rate with these methods are high with the advantage that they are convenient and their efficacy depends on one single initial act (Winner *et al.*, 2012). In Brazil, some observers have called for a concerted effort to expand the use of LARCs (Ferreira *et al.*, 2014).

In Brazil, the only copper IUD available is the TCu380A and the only implant is the ENG-implant (Implanon®, Merck, Oss, The Netherlands). Despite its high contraceptive efficacy and minor (though many) side effects (Croxatto 2000, 2002), the ENG-implant is not widely used in Brazil. The reasons for this could be due to its lack of availability in the public sector, the lack of trained health care professionals (HCPs) in insertions and removals, and probably the lack of studies about women's opinions regarding its side effects, particularly those associated with bleeding disturbances. Regarding the LNG-IUS, similar local studies of bleeding disturbances have been conducted in Brazil (Diaz *et al.*, 2000; Hidalgo *et al.*, 2002). The main side effect of the ENG-implant is menstrual bleeding irregularities, including infrequent or frequent and prolonged bleeding without any previous symptoms, and this is the main reason for premature discontinuation (Mansour *et al.*, 2011). However, the possibility of the contraceptive method inducing amenorrhoea may be seen as an advantage. There is no way of predicting which women will go on to develop bleeding disturbances and there is no effective treatment prior to implant insertion to avoid menstrual bleeding irregularities. However, previous studies with other progestin-only contraceptive methods have shown that adequate and intensive counselling, in which the woman is provided with information on the bleeding profiles she can expect while using of the method, may contribute towards improving the continuation rate (Mansour *et al.*, 2011).

It is important to take into account that side effects induced by LARCs methods could lead to premature removals which in turn could influence continuation rates and user satisfaction and potentially increase unwanted pregnancies. First year continuation rates are high with LARC methods, with rates of 67–75% having been reported for the ENG-implant (Kalmuss *et al.*, 1996; Croxatto *et al.*, 1999; Smith and Reuter, 2002; Agrawal and Robinson, 2005; Lakha and Glasier, 2006; Harvey *et al.*, 2009), rates of 86–90% having been described for the LNG-IUS (Andersson *et al.*, 1994; Baldaszti *et al.*, 2003; Suhonen *et al.*, 2004; Sheng *et al.*, 2009; Bahamondes *et al.*, 2012; Ferreira *et al.*, 2014), and a rate of 84% being reported for the TCu380A IUD (Peipert *et al.*, 2011). Counselling is crucial and when intensive counselling has been given, 1-year continuation rates have reached 80–90% in users of the ENG-implant (Davie *et al.*, 1996; Rubenstein *et al.*, 2011) and 90% in users of the LNG-IUS (Baldaszti *et al.*, 2003).

The objectives of this randomized clinical trial (RCT) were to compare the discontinuation rates due to unpredictable menstrual bleeding and the 1-year continuation rates after women were allocated to either intensive counselling or the routine counselling provided at a Brazilian public sector clinic among new acceptors of the ENG-implant, the LNG-IUS or the TCu380A IUD.

Materials and Methods

This RCT was conducted at the Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, Brazil. The Ethical Committee approved the study and all the participating women signed an informed consent form. The trial was registered at ClinicalTrials.gov: NCT01392157. The study population included women of 18–40 years of age attending the family planning clinic and requesting any LARC method. According to the current practice at the clinic, all the women received unbiased counselling on all the contraceptive methods available at the clinic. All the contraceptive methods were offered at no cost to the women. The methods available at the time of the study were: the TCu380A IUD (Optima, Injeflex, São Paulo, Brazil), the ENG-implant (Implanon®, Merck, Oss, The Netherland) (only for research purposes), the LNG-IUS (Mirena®, Bayer Oy, Turku, Finland), the injectable depot-medroxyprogesterone acetate, once-a-month combined injectables, oral contraceptives, the vaginal ring, and the male and female condom.

After a brief counselling session and provision of information about the available contraceptive methods at the clinic, the women who chose the ENG-implant, the LNG-IUS or the TCu380A IUD were invited to participate in the trial and were randomly allocated (1:1) to one of two groups using sealed opaque envelopes prepared according to a computerized randomization program by a person who was not directly involved in the study. The women were included sequentially until there was a maximum sample size of 100 women in each contraceptive group.

The women allocated to Group I received the routine verbal counselling given at the clinic, which includes information on anatomy (mostly for those who chose the IUD and the LNG-IUS), mechanism of action, safety, efficacy, how and when fertility can return, side effects of the chosen methods, and the non-contraceptive benefits of the method, as well as information about scheduled and non-scheduled visits. In addition, women were provided with information on what to expect with respect to unpredictable bleeding disturbances. This session of counselling lasted ~15 min. The women in this group received the counselling from the nurses on duty and

the follow-up visits were attended by a person on duty that day at the clinic, including residents in training and medical students.

The women in Group II received 'intensive counselling' in which, in addition to the information provided to those in Group I, these women were given a leaflet on the chosen method developed specifically for the study and pre-tested. The leaflet contained a drawing showing the anatomy of the pelvis, in-depth explanation of changes in bleeding patterns that could occur during the use of the chosen LARC method, the mechanism of action of bleeding irregularities and the possibilities of treatment. This additional session of counselling lasted ~15 min. The women in this group were always attended to and counselled by the same three professionals who were the most experienced at the clinic, who went over all the information provided at each consultation throughout the year of follow-up. Only the women in Group II also received telephone calls as a reminder of the next scheduled visits.

All of the women were instructed to return to the clinic at 45 days (±7 days), and 6 and 12 months (±1 month) after insertion or at any time if needed and were also instructed to record any bleeding episodes in a menstrual diary specifically provided for this purpose. Satisfaction with the method was evaluated based on a questionnaire completed by the women after 12 months of use of the contraceptive method. All the women in both groups were instructed that they have the right to remove the chosen contraceptive method at any time and to receive a different one. The women did not receive any incentive to return for the visits or to choose a particular method.

Analysis of bleeding patterns

Bleeding patterns were analysed in accordance with the terminology proposed by the World Health Organization (WHO, 1989) in 90-day reference periods: 'amenorrhoea' was defined as no bleeding during the reference period; 'infrequent bleeding' as fewer than three bleeding episodes; 'frequent bleeding' as more than five bleeding episodes; 'irregular bleeding' as between three and five episodes with less than three bleeding-free intervals of 14 days or more in length; 'prolonged bleeding' as one or more bleeding episodes lasting 14 days or more; and 'none of the above' as a 'normal' bleeding pattern.

Statistical analysis

Sample size was calculated based on the assumption that 20% of new contraceptive users would opt to use either the ENG-implant, the LNG-IUS or the TCu380A IUD and that the continuation rate at the end of the first year after insertion would be 80% in each group of users. For an alpha of 5% (Type I error) and a Type II error of 20%, 91 women would have to be recruited to each group. Taking into account a possible loss to follow-up of 10%, it was decided to enrol 100 women to each contraceptive method.

Statistical analysis was performed using the SPSS statistical software package for Windows, version 20. Significant differences were established at $P < 0.05$. Analysis of variance (ANOVA) or the Kruskal–Wallis test was used to compare the sociodemographic characteristics between the groups. The χ^2 test was used to compare the qualitative variables. The cumulative continuation and discontinuation rates for each reason were calculated by life-table analysis and the Wilcoxon–Gehan test was used to compare the rates between the groups.

Results

Enrolment started on 2 August 2011 and ended on 5 June 2012. During that period, 1004 women consulted at the clinic requesting a contraceptive method. A total of 300 women agreed to participate in the study; however, due to the contamination of one LNG-IUS and two ENG-implants, analysis was conducted on 98 users of the ENG-implant, 99 users of the LNG-IUS and 100 users of the TCu380A IUD (Fig. 1). The characteristics of the subjects are shown in Table I. There were no significant differences in age between the groups; however, the ENG-implant users had had fewer children and had a lower body mass index (BMI; kg/m^2).

The return for each of the scheduled visits was at the same rate in both counselling groups. The continuation rates were 82.6, 81.0 and 73.2% for the ENG-implant, the LNG-IUS and the TCu380A IUD ($P = 0.214$), respectively (Table II). There were no significant differences in the number of women discontinuing the method due to bleeding or pain between the three contraceptive methods. However, significantly more ENG-implant users discontinued the method because of weight gain compared with the other two methods ($P = 0.022$), while discontinuation rates due to expulsion were higher with the TCu380A IUD when compared with the LNG-IUS users ($P = 0.008$) (Table II). (Women could request another insertion after expulsion but in that case, they were discontinued from this study.) There were no significant differences in the continuation rate at 12 months between the women who received intensive counselling and those who received regular counselling in any of the three groups. With respect to the ENG-implant and the LNG-IUS, over 80% of users continued using the method irrespective of whether they had received intensive or routine counselling. Of the TCu380A IUD users who received intensive counselling, 65.9% continued with the method compared with 70.0% of those who received only routine counselling. After 12 months of follow-up, the satisfaction rate among the continuing users was 90.0% with the ENG-implant, 91.0% with the LNG-IUS and 85.7% with the TCu308A IUD ($P = 0.612$).

Figure 2 compares the bleeding patterns for the three contraceptive methods from insertion up to 12 months of use in accordance with each 90-day evaluation period. For the ENG-implant users, the most common bleeding patterns were infrequent bleeding in the first 90-day evaluation period and amenorrhoea or infrequent bleeding in the following 90-day evaluation periods. For the LNG-IUS users, the two most common bleeding patterns were frequent or prolonged bleeding in the first 90-day evaluation period, and amenorrhoea, infrequent or normal bleeding in the fourth 90-day evaluation period. Finally, the most common bleeding pattern in users of the copper IUD was normal menstruation. In the first 90-day evaluation period, 50% of these users were menstruating normally and this proportion increased to almost 90% at 12 months. Bleeding patterns were similar in the women who had received intensive counselling and in those who had received routine counselling (data not shown).

Discussion

The main finding of our study was that the rates of premature discontinuation due to menstrual bleeding disturbances among the three groups of LARC users were very low and consequently the 1-year continuation rate ranged from 73% among copper IUD users to 83% among ENG-implant acceptors. Additionally, women randomly allocated to either intensive or routine counselling did not show any differences in the discontinuation rates due to unpredictable menstrual bleeding.

These results could be interpreted as the conundrum of whether the glass is half-empty or half-full. In one way, it could be argued that routine counselling is not an important tool to reduce premature discontinuations and to improve the continuation rate. However, in the opposite

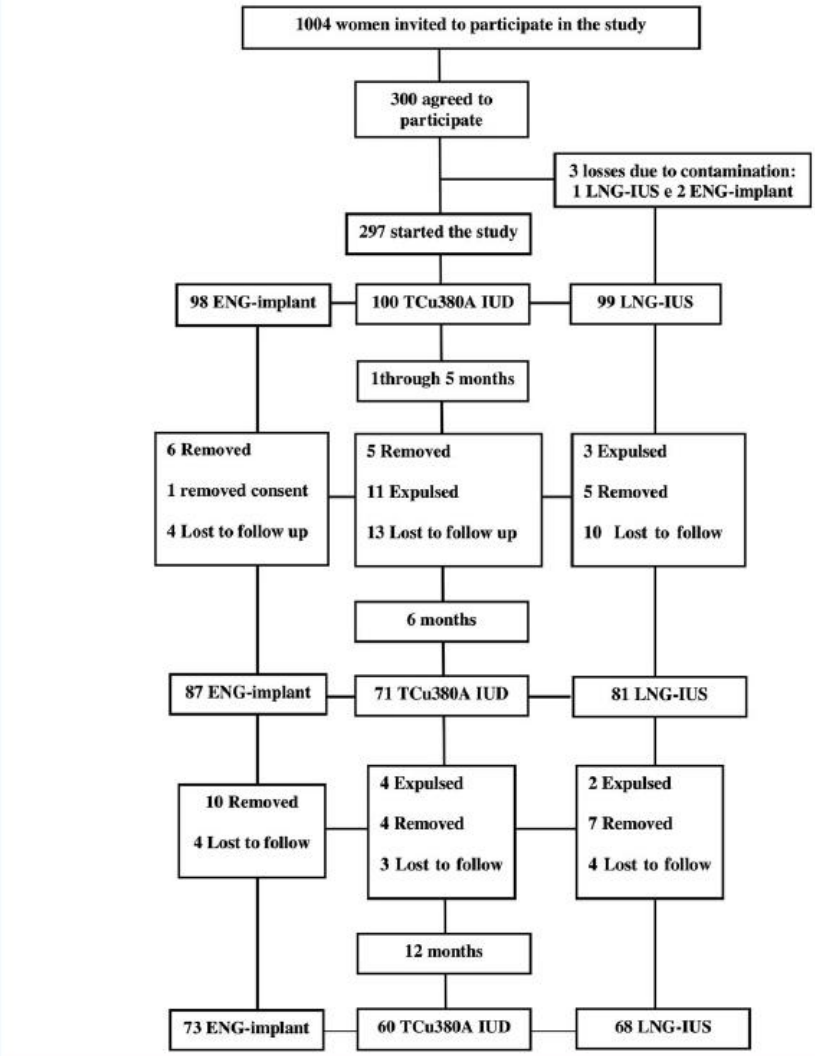

Figure 1 Flowchart depicting participation in the study (full analysis: all participating women). ENG-implant: etonogestrel-releasing implant; IUD: copper-intrauterine device; LNG-IUS: levonorgestrel-releasing intrauterine system.

direction it may be possible to conclude that routine counselling is enough to maintain the adherence of the women to the selected contraceptive method. Our centre is probably the largest Brazilian family planning clinic with >30 years of operation and >20 000 women attending per year, and consequently, the result that premature removals were equal in the two randomly allocated groups likely reflects that the routine counselling alone is adequate and fulfils the needs of the population who use our service. It may be speculated from our results that regarding the side effects induced by contraceptives, mainly those related to unpredictable menstrual bleeding which are unacceptable,

Table I Descriptive characteristics of the participants.

Variables	Copper IUD (n = 100)	LNG-IUS (n = 99)	ENG-implant (n = 98)	P-value
Age[a]	29.1 ± 6.0	30.8 ± 5.8	30.5 ± 6.1	0.092*
Number of children[a]	1.5 ± 0.8	1.5 ± 0.8	1.1 ± 0.8	0.004#
Body mass index (kg/m^2)[a]	27.5 ± 5.3	27.7 ± 6.2	25.3 ± 4.2	0.022#
Years of schooling[a]	10.7 ± 3.4	11.8 ± 3.1	11.7 ± 3.4	0.008#
Marital status, n (%)	79 (80.6)	75 (78.9)	70 (72.2)	0.331¶
Ethnicity (white); n (%)	75 (76.5)	84 (86.6)	79 (81.4)	0.194¶

IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; ENG, etonogestrel.
[a]Mean ± standard error of the mean.
*F-test (ANOVA); #Kruskal–Wallis test; ¶Pearson's χ^2 test.

Table II Cumulative continuation and discontinuation rates.

Reasons for discontinuation	Method			P-value*
	Copper IUD (n = 100)	LNG-IUS (n = 99)	ENG-implant (n = 98)	
Bleeding	4.0 (2.3)	2.7 (1.9)	2.1 (1.5)	0.853
Pain	1.1 (1.1)	4.6 (2.3)	0.0	0.069
Weight gain	0.0	1.3 (1.3)	6.9 (2.7)	0.022
Expulsion	8.6 (2.8)	5.8 (2.5)	0.0	0.008
Continuation rate	73.2 (4.8)	81.0 (4.2)	82.6 (4.0)	0.214

IUD, intrauterine device; LNG-IUS, levonorgestrel-releasing intrauterine system; ENG, etonogestrel.
*Wilcoxon–Gehan test; Standard error of the mean (SEM).

inconvenient or considered severe by the users, the women were probably influenced by either routine or intensive counselling this helps to avoid premature discontinuations.

Counselling provided to contraceptive users and potential users is a well-accepted strategy and tool to increase acceptance, adherence, continuation and user satisfaction. However, in some settings counselling is brief, incomplete or not provided at all (Davie *et al.*, 1996; Gemzell-Danielsson *et al*, 2011; Bitzer *et al.*, 2013). Counselling and unbiased information are crucial to facilitate the decisions of women in choosing a contraceptive method. However, counselling cannot be ended at the first consultation, and it must be a continuous activity performed on all of the follow-up consultations to counsel women about side effects, how to deal with these side effects and to reinforce the benefits of the method. It is well established that counselling which anticipates side effects could improve continuation rate (Backman *et al.*, 2002).

A recent Swedish-based study (Gemzell-Danielsson *et al*, 2011) evaluated a contraceptive education program which intended to encourage HCPs to counsel women seeking hormonal contraception about the available methods (combined oral contraceptives, patch and vaginal ring) and to assess the influence of counselling on women's contraceptive decisions. The authors observed that when structured counselling, including a free of choice of different combined hormonal contraceptives, was offered, significant changes were observed in the contraceptive selected by the women, in the fact that almost 96% were able to choose a preferred method and in the changes in attitudes of HCPs regarding the right of free choice of contraceptives by women.

Counselling is a crucial activity during contraceptive use to reduce premature discontinuations due to side effects, and to improve continuation rate and satisfaction. LARC methods are highly effective methods (Winner *et al.*, 2012); however, premature discontinuations reduce this effectiveness and in many cases could lead women to choose less effective methods or to discontinue prematurely, both of which increase the risk of unplanned pregnancy.

We observed that the main reasons for discontinuation were expulsion in the TCu380A IUD and LNG-IUS groups and weight gain in users of the ENG-implant. An increase in weight during the use of hormonal contraceptive methods has already been reported; however, this subject is still a matter of debate (Smith and Reuter, 2002; Agrawal and Robinson, 2005; Lakha and Glasier, 2006; Wong *et al.*, 2009). The main reasons described for discontinuation of the LNG-IUS have been weight gain (29%) (Sheng *et al.*, 2009), headache, abdominal pain and lower back pain (7%) (Suhonen *et al.*, 2004), and menstrual bleeding abnormalities (3–6%) (Andersson *et al.*, 1994; Baldaszti *et al.*, 2003; Suhonen *et al*, 2004). With the ENG-implant, the discontinuation rate due to menstrual bleeding irregularities has been reported as 17% at 1 year and 62% at 2 years (Croxatto *et al.*, 1999; Smith and Reuter, 2002; Agrawal and Robinson, 2005; Lakha and Glasier, 2006; Wong *et al.*, 2009), much higher than observed in this trial. In our study, users of the ENG-implant experienced high rates of amenorrhoea and infrequent bleeding at the end of the first year of use and it would appear that this type of bleeding pattern increases satisfaction and consequently ensures a high continuation rate.

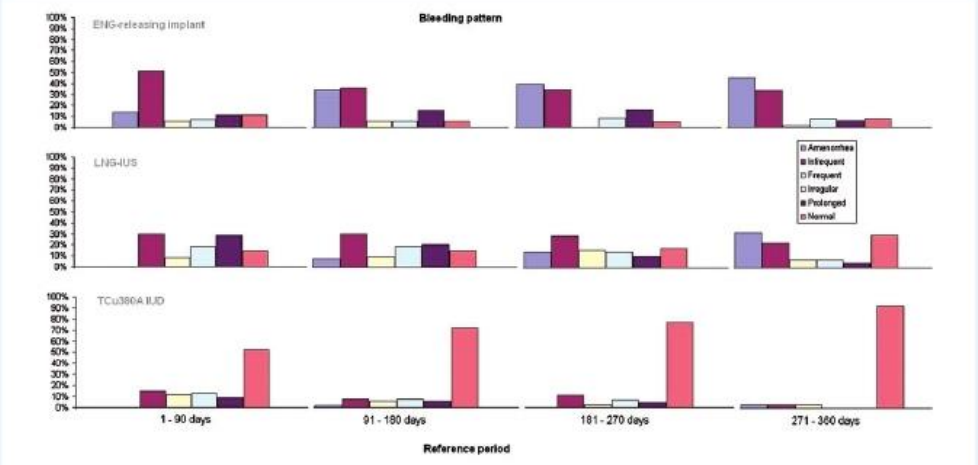

Figure 2 Bleeding patterns in the ENG-implant, the LNG-IUS and the TCu380A IUD users at 1 year of use. In the analysis between groups of 1 – 180 days, χ^2 $P = 0.000$. Invalid χ^2 test in the analysis of 181 – 360 days.

The continuation rate of users of the ENG-implant was higher (83%) than rates reported from other studies (Kalmuss *et al.*, 1996; Croxatto *et al.*, 1999; Smith and Reuter, 2002; Agrawal and Robinson, 2005; Lakha and Glasier, 2006; Harvey *et al.*, 2009); however, in the case of the LNG-IUS, the continuation rate was similar to those found in previous studies (Andersson *et al.*, 1994; Baldaszti *et al.*, 2003; Suhonen *et al.*, 2004; Bahamondes *et al.*, 2012; Ferreira *et al.*, 2014). With respect to the TCu380A IUD, the continuation rate at the end of the first year was 73.2%, slightly lower than that of 80% found in a previous study (Peipert *et al.*, 2011). Similarly, user satisfaction was also high with all three methods, with rates of 86% for the TCu380A IUD and 90% or over for the LNG-IUS and the ENG-implant. One explanation for these high continuation and satisfaction rates may lie in the counselling provided prior to insertion of the method. This assumption is reasonable, particularly because discontinuation rates were similar in the women who received intensive counselling and in those who were given routine counselling.

There are limitations and strengths associated with this study. The main limitation may be that information may have been exchanged between the women who received intensive counselling and those who were given only routine counselling, since they shared the same waiting room and could have discussed the information they were given during counselling. Another possible limitation is that the routine counselling provided by our counsellors is adequate for the women attending the clinic and premature discontinuation due to bleeding irregularities was already low. Consequently, intensive counselling did not, and was unlikely to, lead to further reductions in premature discontinuations due to unpredictable menstrual bleeding. Additionally, another limitation is that it may not be generalizable to less well-established and active settings.

The main strength of the study was the fact that the women were randomized to one of two counselling strategies. The message emerging from our results for low resources settings is that it is better strategies that focused on counselling about what to expect regarding bleeding disturbances and side effects is useful because it allows low rates of premature discontinuation, high rates of continuation and high user satisfaction. Furthermore, counselling potentially reduces unintended pregnancies and it is cost-effective mainly in the case of LARC methods.

In conclusion, both counselling strategies which included what to expect with respect to bleeding patterns when using an LARC method were followed by low rates of premature discontinuations and high rates of continuation and satisfaction in this cohort of Brazilian women.

Authors' roles

W.M. was responsible for the collection, analysis and interpretation of the data, for writing the first version of this article and for reviewing and approving the final version of the manuscript. M.V.B. and L.B. conceived the idea for the study and were responsible for its design. They were also responsible for inserting all the devices. L.B. was also responsible for analysing and interpreting the data and for writing and revising the final version of the manuscript.

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Access Foundation (ICA) and the copper IUD by Injeflex, São Paulo, Brazil.

Conflict of interest

L.B. has occasionally served on the Board of MSD, Bayer and Vifor.

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4. DISCUSSÃO GERAL

O uso do contraceptivo injetável AMPD e as possíveis alterações no peso são estudadas desde a década de 60 (73). No entanto, o uso de AMPD ganhou maior evidência a partir de 2004, quando a USFDA apontou riscos do uso de AMPD na diminuição da DMO, levando a OMS a fazer uma chamada para pesquisas sobre e as repercussões do uso de AMPD na DMO das usuárias (112).

Essa repercussão é reforçada pelo fato de AMPD ser um método seguro, eficaz, com boa aceitabilidade por parte das mulheres (42, 112WHO) e largamente utilizada em países desenvolvidos e em desenvolvimento (113). Assim, é necessário conhecer até que ponto os efeitos adversos do uso de AMPD podem contribuir para o aparecimento de morbidades como a osteoporose e a obesidade.

Estudos mostraram que existe uma diminuição na DMO nos primeiros 2-5 anos de uso do método (26,30,35,37-52). Especulava-se que essa diminuição da DMO estabilizava com o decorrer dos anos (35). Todavia, nota-se no presente estudo que a DMO continuou a diminuir com o passar dos anos. Essa diminuição pode ser devido ao hipoestrogenismo provocado pelo uso do AMPD ou ainda pode estar associada com as alterações de perda progressiva da massa óssea provocada pelo processo do envelhecimento. Isto acarretaria uma maior

prevalência de osteopenia e osteoporose em usuárias de AMPD de longo prazo quando comparadas a usuárias de DIU TCu380A.

Existem poucos estudos que analisaram o uso do AMPD a longo prazo (35, 42, 114-116), talvez por poucas mulheres utilizarem o método por longos períodos de tempo, como ocorre em países como os Estados Unidos, Tailândia, Reino Unido e o Brasil, ou por existirem poucos centros de pesquisa no mundo que acompanham as usuárias do método regularmente. O fato é que o AMPD exerce um efeito de diminuição da massa óssea que, de acordo com os nossos estudos, parecem ser progressivos em usuárias de longo prazo, e mesmo que não esteja clara a parcela da população mundial usuária de AMPD de longo prazo, os seus efeitos atingem uma porção ainda desconhecida da população, que sofrem com os danos causados pelo uso ininterrupto. É preciso entender ao certo a sua abrangência para elaborar orientações quanto ao manejo de atitudes preventivas e/ou terapêuticas para as usuárias de AMPD por muitos anos.

Como orientações preventivas e terapêuticas, algumas mudanças nos hábitos de vida poderiam diminuir os efeitos adversos provocados pelo uso do AMPD, como exposição ao sol para a síntese de vitamina D, que mantém a homeostase do Ca, e o aumento da ingesta de Ca maior ou igual a 1g/dia. Este estudo mostrou que as mulheres usuárias de AMPD que na sua dieta diária ingeriram uma quantidade maior ou igual a 1g/dia de Ca, durante 12 meses de seguimento, apresentavam uma perda menor da DMO quando comparadas a usuárias de AMPD que ingeriram menos de 1g/dia. A variável exposição ao sol não apresentou diferença significativa quando comparada à variação da DMO. No

entanto, é possível acreditar que a exposição ao sol aumentou a síntese do Ca influenciando nos seus resultados.

A prática da atividade física é outro hábito de vida capaz de proporcionar alterações significativas na DMO. A expectativa inicial do estudo foi que as usuárias de AMPD estimuladas à prática da atividade física não apresentassem importantes perdas da DMO ou até incrementassem a sua massa óssea, principalmente associada ao consumo de Ca e à exposição ao sol. No entanto, havia baixa adesão à prática de atividade física pelas usuárias de AMPD. Assim, não foi possível avaliar a influência da atividade física na variação da DMO ou no peso.

Essa baixa adesão a um estilo de vida saudável pode ser notado também em usuárias do SIU-LNG e do implante liberador de ENG, e os resultados deste estudo mostraram que além das usuárias dos métodos iniciarem os estudos com altas porcentagens de massa gorda, em torno de 40%, as usuárias do implante liberador de ENG apresentaram hábitos de vida, como alto consumo de café e baixa prática de atividade física, que influenciaram negativamente na DMO das usuárias após o primeiro ano de seguimento.

O comportamento das usuárias de AMPD e do implante liberador de ENG e SIU-LNG em nossos estudos mostra um retrato dos hábitos de vida pouco saudáveis adotados por uma parcela significativa da população brasileira, que oscila entre 26,7% e 78,2% de sedentários (117,118). A causa da alta prevalência de sedentarismo pode ser devido a barreiras pessoais, na dificuldade de modificar padrões de comportamento; dificuldade no acesso ao exercício, que pode ser financeira ou por falta de espaços estruturados à prática da atividade física; ou

ainda a falta de um investimento social em educação e promoção da saúde, tendo a prática da atividade física como um fator de prevenção e tratamento de morbidades.

As orientações no que dizem respeito ao aumento da DMO e a prevenção do ganho do peso devem ser realizadas no início do uso dos métodos contraceptivos e durante todo o seu seguimento de uso. Deve existir uma política de prevenção a morbidades por parte da equipe multidisciplinar formada por Fisioterapeutas, Nutricionistas, Médicos e outros, a fim de informar sobre o ganho de peso progressivo inerente ao processo do envelhecimento de toda mulher e uma possível perda da DMO provocada pela combinação de fatores de diminuição dos níveis de estrogênio e o sedentarismo. A partir do momento que novas usuárias de MACs absorverem os novos padrões preventivos de comportamento e adquirirem hábitos de vida saudáveis, os efeitos adversos provocados pelos métodos contraceptivos a curto e a longo prazo se tornarão menos agressivos à sua saúde.

Os MACs frequentemente são apontados como os vilões do aumento do peso por suas usuárias. Entretanto, de uma forma geral, os estudos divergem se de fato existe ganho de peso com o uso da AMPD (60) e perguntas como quais mulheres apresentariam um maior ganho de peso e o motivo de apenas um grupo de mulheres apresentarem um aumento abrupto do peso, ainda são objetos de dúvida. Na tentativa de contribuir com essa discussão, os nossos estudos mostraram um aumento de 2 kg de massa gorda após 12 meses de seguimento e um ganho de peso contínuo após 10 anos de uso, superior ao ganho de peso das usuárias do SIU-LNG e DIU TCu380A. Enquanto as usuárias de AMPD

apresentaram um ganho do peso de 0,6 kg/ano, as usuárias do SIU-LNG e de DIU TCu380A, durante o mesmo período de seguimento, mantiveram um ganho de peso similar de 0,4 kg/ano. No entanto, essa diferença de ganho anual de 0,2 kg entre os métodos parece não ter maior importância clínica, principalmente se compararmos com o ganho de peso anual estimado para mulheres com uso de MAC não hormonais de 0,6 kg/ano (74).

Desta forma, o aumento da concentração da massa gorda somado ao estilo de vida sedentário das usuárias de AMPD contribuiu para o ganho de peso da mulher. Talvez a forma mais adequada para lidar com as usuárias de AMPD seja oferecer um acompanhamento mais intensivo no primeiro ano de uso, e a atenção para perceber as grandes variações do peso e os cuidados a longo prazo, no que se diz respeito a orientações quanto ao ganho do peso e à diminuição da DMO.

Em relação às usuárias de implante liberador de ENG, apesar de ocorrer um aumento do peso importante de 4,1kg no primeiro ano de uso do método, maior do que os registrados anteriormente pela literatura de 2,1 e 1,9 kg (57,76), esse aumento parece não ser significativo nas queixas de abandono. Entretanto, orientações quanto à sua prevenção podem evitar o aparecimento de comorbidades agregadas ao aumento do peso.

As orientações para usuárias de MACs é uma ferramenta para melhorar a aderência aos métodos e aumentar a satisfação das suas usuárias (119). Assim, como as orientações podem ser usadas com sucesso para diminuir as taxas de descontinuação por efeitos adversos provocados pelos métodos, as orientações podem aumentar a aderência de usuárias de implantes contraceptivos, de SIU-LNG e de DIU com cobre, pois possibilitam à mulher um conhecimento mais

aprofundado sobre o que esperar no tocante aos transtornos possíveis ocasionados pelos métodos, incluindo o sangramento menstrual anormal.

Mulheres usuárias de métodos LARCs apresentam taxas de continuação de 60%-80% no primeiro ano de uso (4-10,14). Quando submetidas a orientações mais intensivas, as taxas de continuação chegam até 90% no primeiro ano de uso (12,15). Os resultados encontrados neste estudo se assemelham aos resultados de altas taxas de continuação encontrados na literatura, não apresentando diferenças quanto ao tipo de orientações que receberam, sejam elas “intensivas” ou rotineiras.

As orientações do presente estudo foram concentradas principalmente nos distúrbios de sangramento, frequentes principalmente nos primeiros meses de uso, e maior causa de descontinuação por parte das usuárias do implante liberador de ENG e do SIU-LNG (5-8,11-13,18).

O padrão de sangramento mais comum entre as usuárias do DIU com cobre foi “menstruações regulares”, que variou de 50% no primeiro período para quase 90% ao final dos 12 meses. Com relação às usuárias do SIU-LNG os dois padrões de sangramento mais comuns foram “sangramento prolongado” e “sangramento infrequente” nos primeiros 90 dias de avaliação e “amenorreia” e “sangramento regular” no quarto período de avaliação de 90 dias. Finalmente, as usuárias do implante liberador de ENG apresentaram padrões de sangramento mais comuns compatíveis com “sangramento infreqüente” nos primeiros 90 dias de avaliação e “amenorreia” e “sangramento infrequente” no quarto período de avaliação de 90 dias.

Certamente, as altas taxas de amenorreia e sangramento infrequente colaboraram para que o implante liberador de ENG apresente altas taxas de continuação. Em contrapartida, o SIU-LNG parece ser um método que exige maior tolerância nos primeiros meses por parte das suas usuárias, pois os períodos de sangramento irregular aparecem mais frequentemente. Nesse aspecto, mesmo os métodos que agregam características de maior conveniência para as usuárias, maior eficácia e possibilidade do uso prolongado, as orientações adequadas, intensivas ou não, têm o papel fundamental de aumentar a tolerância e manter a continuação do método.

O conjunto de estudos desta tese mostra que, as orientações, seja no âmbito do estilo de vida ou para auxiliar no controle de efeitos adversos provocados pelos métodos, exercem um papel fundamental na adesão e na continuidade dos MACs, além de prevenir futuras morbidades que as usuárias podem vir a desenvolver pelo o seu uso. Portanto, esta tese corrobora uma postura mais atuante do profissional de saúde no processo de educação e promoção da saúde das usuárias dos MACs de longa duração.

5. CONCLUSÃO GERAL

- As orientações quanto ao estilo de vida, promovendo a ingestão adequada de Ca e a exposição solar regular parecem ter um efeito na atenuação da perda da DMO, após 12 meses de seguimento. Em contrapartida, a prática da atividade física não foi aderida pelas pacientes, não podendo ser avaliada por este estudo.

- As usuárias de AMPD, de SIU-LNG e do DIU com cobre tiveram um aumento de peso ao longo dos 10 anos de observação. No entanto, as usuárias de AMPD ganharam mais peso em até 10 anos de uso quando comparadas com o SIU-LNG e o DIU com cobre.

- As usuárias de AMPD apresentaram maior quantidade de massa magra quando comparadas às de DIU com cobre ao final do primeiro ano de uso do método. No entanto, não houve diferenças entre os valores da massa magra e massa gorda em usuárias de AMPD e DIU em cinco, dez e quinze anos de uso dos métodos.

- As usuárias de longo prazo de AMPD apresentaram maior prevalência de osteopenia e osteoporose quando comparadas às usuárias de DIU com cobre;

- As usuárias do implante liberador de etonogestrel apresentaram diminuição na DMO após 12 meses de uso e ganho do peso e massa gorda após 24 meses de seguimento;

- As estratégias de aconselhamento, intensiva ou de rotina, que incluíram o que esperar com relação a padrões de sangramento após a inserção do DIU com cobre, do SIU-LNG e do implante liberador de ENG, não apresentaram diferenças significativas nas taxas de continuação e foram seguidos por uma baixa taxa de descontinuação por transtornos de sangramento.

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7. ANEXOS

7.1 Anexo 1 – Orientações para prevenir a Osteoporose

Prevenção da perda de DMO para pacientes em uso de AMP-D

Orientações para prevenir a Osteoporose

Banho de sol

Vitamina D - Onde conseguir?

ou depois das 16:00h

Com braços e pernas amostra

Sem o uso do protetor solar

Caminhada

30
minutos
3 vezes por semana

Dieta

- Casca de ovo. Pode ser utilizado a água de cozimento do ovo ou torrar a casca e dissolver no suco ou comida;
- 2 copos de leite por dia ou 1 iogurte;
- 1 fatia média de queijo branco;
- Peixes em geral: sardinha em lata;
- 3 colheres de sopa cheia de verduras verde escuro;
- Diminuir o consumo do café e refrigerante.

7.2 Anexo 2- Orientações quanto ao sangramento para as usuárias de DIUTCu380A

Para quem é indicado o DIU com cobre ou TCu-380?

- Mulheres que buscam contracepção em longo prazo;
- Mulheres com dificuldade de adesão a outros métodos;
- Mulheres que buscam intervalos entre as gestações.

Informações

- Rápida inserção sem necessidade de internação;
- Eficácia de mais de 98%;
- Dura até dez anos, mas em mulheres maiores de 35 anos de idade pode ficar até a menopausa
- Após a retirada do método, rápido retorno à capacidade de engravidar.

Sangramento.

- Muitas mulheres que usam o DIU TCu-380 podem ter menstruações aumentadas e cólicas, principalmente nos primeiros três meses;
- Este sangramento pode ser aumentado em quantidade ou em numero de dias
- Isto não afeta o seu desempenho contraceptivo, nem é causa para retirada prematura
- Não interfere nas relações sexuais.

7.3 Anexo 3 – Orientações quanto ao sangramento para as usuárias de implantes subdérmicos liberador de etonogestrel

Para quem é indicado o implante Implanon?

- Mulheres que buscam contracepção em longo prazo;
- Mulheres com dificuldade de adesão a outros métodos;
- Mulheres que buscam intervalos entre as gestações.

Informações

- Rápida inserção sem necessidade de internação;
- Eficácia de mais de 99%;
- Após a retirada do método, rápido retorno à capacidade de engravidar.

Sangramento.

- Muitas mulheres podem apresentar sangramento irregular, entretanto, geralmente é de pouca monta embora possa ser tipo "manchado", ou seja, sem aviso prévio, isso não faz mal e normalmente diminui ou desaparece nos 6 primeiros meses. Sua forma pode ser:

  Sangramento: requer mais de um absorvente por dia

  Sangramento escuro em pequena quantidade (mancha): requer no máximo um absorvente por dia
- Algumas mulheres que usam Implanon param de menstruar, isso não é prejudicial para a sua saúde e não há necessidade de menstruar todo mês;
- Não interfere nas relações sexuais.

7.4 Anexo 4 – Orientações quanto ao sangramento para as usuárias de sistema intrauterino liberador de levonorgestrel

Para quem é indicado o Mirena?

- Mulheres que buscam contracepção em longo prazo;
- Mulheres com dificuldade de adesão a outros métodos;
- Mulheres que buscam intervalos entre as gestações.

Informações

- Rápida inserção sem necessidade de internação;
- Eficácia de mais de 99%;
- Após a retirada do método, rápido retorno à capacidade de engravidar.

Sangramento.

- Muitas mulheres podem apresentar sangramento irregular, entretanto, geralmente é de pouca monta embora possa ser tipo "manchado", ou seja sem aviso prévio, isso não faz mal e normalmente diminui ou desaparece nos 6 primeiros meses. Sua forma pode ser:

  Sangramento: requer mais de um absorvente por dia

  Sangramento escuro em pequena quantidade (mancha): requer no máximo um absorvente por dia
- Algumas mulheres que usam Mirena param de menstruar, isso não é prejudicial para a sua saúde e não há necessidade de menstruar todo mês;
- Não interfere nas relações sexuais.

7.4 Parecer do Comitê de Ética.

7.4.1 Publicação: Body composition in long term DMPA users; Prevalence of the Osteoporosis in DMPA users and Weight variation in DMPA, LNG-IUS and IUD users.

FACULDADE DE CIENCIAS MEDICAS - UNICAMP (CAMPUS CAMPINAS)

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Composição corporal de usuárias de medroxiprogesterona de depósito comparadas a usuárias de dispositivo intrauterino (DIU) TCu380A após um, cinco, dez e quinze anos de uso. Estudo piloto.

Pesquisador: Luis Guillermo Bahamondes

Área Temática:

Versão: 2

CAAE: 12639113.9.0000.5404

Instituição Proponente: Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - CAISM

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 256.594

Data da Relatoria: 12/04/2013

Apresentação do Projeto:

A obesidade e o sobrepeso são considerados uma epidemia mundial e um problema de saúde pública. Entre os diversos estilos de vida atribuídos como causa da obesidade, o método contraceptivo (MAC) com acetato de medroxiprogesterona de depósito (AMPD) tem sido frequentemente associado ao ganho de peso, tanto por médicos como pelas usuárias. No entanto, evidências científicas não foram constatadas sobre a associação entre o ganho de peso, uso de AMPD e alterações da sua composição corporal (CC). o presente estudo pretende investigar esta questão em usuárias de AMPD.

Objetivo da Pesquisa:

Avaliar a composição corporal de mulheres usuárias de AMPD e comparar com nunca usuárias deste MAC (usuárias de DIU TCu 380A) após um,cinco, dez e quinze anos de uso de forma ininterrupta.

Objetivo Secundário:

1. Comparar a diferença de valores de massa gorda entre usuárias de AMPD e DIU TCu 380A ao longo do tempo;
2. Comparar a diferença de valores de massa magra entre usuárias de AMPD e DIU TCu 380A ao

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UF: SP **Município:** CAMPINAS
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longo do tempo.

Avaliação dos Riscos e Benefícios:

Segundo informações do TCLE, o exame de densitometria corporal é indolor, não provoca danos tampouco necessita de preparo especial pra ser realizado.

Não haverá benefícios diretos para as participantes do estudo.

Comentários e Considerações sobre a Pesquisa:

Trata-se de estudo de corte transversal, onde a CC será aferida através do exame de densitometria de duplo feixe (DEXA), em 20 usuárias de AMPD de cada grupo com um, cinco, dez e quinze anos de uso. 20 usuárias do DIU TCu380A servirão como grupo controle, com o mesmo período de uso que o AMPD.

Na análise dos dados serão calculadas as freqüências absolutas e relativas, média,desvio-padrão e mediana dos resultados.

Considerações sobre os Termos de apresentação obrigatória:

Folha de rosto e respectivas assinaturas estão adequadas.

foram apresentados o protocolo de estudo originale o o gerado pela plataforma brasil. Adequados.

O TCLE foi corrigido e esta versão atualizada apresentase de acordo comas recomendações da Resolução de 196/96. Autores informam que os dados serão guardados durante 5 anos, após encerramento do estudo.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Pendências atendidas. TCLE adequado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

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7.4.2 Publicação: A randomized clinical trial of the effect of intensive versus non-intensive counselling on discontinuation rates due to bleeding disturbances of three long-acting reversible contraceptives

CEP, 06/06/11
(Grupo III)

PARECER CEP: N° 431/2011 (Este n° deve ser citado nas correspondências referente a este projeto).
CAAE: 0369.0.146.000-11

I - IDENTIFICAÇÃO:

PROJETO: **"ACEITABILIDADE E CONTINUAÇÃO DE USO DO IMPLANTE CONTRACEPTIVO LIBERADOR DE ETONOGESTREL (IMPLANON) COMPARADO AO SISTEMA INTRAUTERINO LIBERADOR DE LEVONORGESTREL (SIU-LNG) E O DISPOSITIVO INTRAUTERINO (DIU) TCU380A NO SETOR PÚBLICO BRASILEIRO".**
PESQUISADOR RESPONSÁVEL: Waleska Oliveira Modesto
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 12/05/2011
APRESENTAR RELATÓRIO EM: 06/06/12 (O formulário encontra-se no *site* acima).

II – OBJETIVOS.

Comparar a aceitabilidade e alguns eventos clínicos entre Implanon, DIU TCu380A e o SIU-LNG até um ano após a inserção.

Comparar a aceitabilidade entre Implanon, DIU TCu380A e o SIU-LNG, quando oferecidos como livre escolha;

Comparar a taxa de continuação até um ano entre o Implanon, DIU TCu380A e o SIU-LNG, quando oferecidos como livre escolha;

Avaliar a aceitação das alterações menstruais induzidas pelo Implanon, DIU TCu380A e o SIU-LNG após as sessões de orientação intensiva;

Avaliar a opinião de usuárias de Implanon, DIU TCu380A e o SIU-LNG sobre a amenorréia induzida por dois dos métodos (Implanon e SIU-LNG).

III – SUMÁRIO.

O Objetivo geral deste estudo é comparar a aceitabilidade e alguns eventos clínicos entre Implanon, DIU TCu380A e o SIU-LNG até um ano após a inserção. Um total de 300 mulheres participarão do estudo, sendo 100 mulheres em cada grupo. As mulheres do estudo serão recrutadas entre aquelas que procuram métodos contraceptivos no Ambulatório de Planejamento Familiar do CAISM-UNICAMP. Todas as mulheres receberão orientações e informações sobre as mudanças do sangramento menstrual que possam ocorrer durante o uso dos métodos. Todas as mulheres que escolherem o Implanon, DIU TCu380A e o SIU-LNG serão instruídas a manter um contato com o ambulatório em caso de qualquer queixa de inserção relacionadas aos três métodos. Serão programados retornos ao ambulatório em 30 ± 7 dias após a inserção para consulta e outra sessão de orientação, dedicada às mudanças do sangramento comum e esperada com estes métodos. Para evitar eventuais distorções, a sessão de aconselhamento será exatamente igual para todas as mulheres. As mulheres incluídas no estudo serão convidadas a

retornar ao ambulatório em seis e dozes meses após a inserção, para a sessão de orientação similar ao fornecido anteriormente. Todas as mulheres serão instruídas a marcar em um calendário menstrual os dias com manchas ou sangramento. As razões de interrupção do método serão obtidas de todas as mulheres que apresentaram interrupção precoce. A comparação de aceitação entre os três métodos serão avaliados pelo teste $\chi 2$. A avaliação da aceitabilidade da irregularidade do sangramento do Implanon e a amenorréia induzida pelos métodos contraceptivos, será realizada através de regressão logística.

IV - COMENTÁRIOS DOS RELATORES

Após respostas às pendências, o projeto encontra-se adequadamente redigido e de acordo com a Resolução CNS/MS 196/96 e suas complementares, bem como o Termo de Consentimento Livre e Esclarecido.

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

7.4 Publicação: Exploratory study of the effect of lifestyle counselling on bone mineral density and body composition in users of the contraceptive depot-medroxyprogesterone acetate

FACULDADE DE CIÊNCIAS MÉDICAS
COMITÊ DE ÉTICA EM PESQUISA

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

CEP, 23/11/09.
(Grupo III)

PARECER CEP: N° 903/2009 (Este n° deve ser citado nas correspondências referente a este projeto)
CAAE: 0698.0.146.000-09

I - IDENTIFICAÇÃO:

PROJETO: **"ESTUDO PROSPECTIVO DE AVALIAÇÃO DA RESISTÊNCIA INSULÍNICA, METABOLISMO DE LÍPEDES E REPERCUSSÃO SUBCLÍNICA DE DOENÇA CARDIOVASCULAR EM MULHERES QUE INICIAM O USO DO CONTRACEPTIVO INJETÁVEL TRIMESTRAL DE ACETATO DE MEDROXIPROGESTERONA DE DEPÓSITO EM SEGUIMENTO DE DOIS ANOS".**
PESQUISADOR RESPONSÁVEL: Luis Bahamondes.
INSTITUIÇÃO: CAISM/UNICAMP
APRESENTAÇÃO AO CEP: 02/10/2009
APRESENTAR RELATÓRIO EM: 23/11/10 (O formulário encontra-se no *site* acima)

II - OBJETIVOS

Avaliar os possíveis mecanismos para o ganho de peso de mulheres que iniciam o contraceptivo injetável trimestral com acetato de medroxiprogesterona de depósito na dose de 150mg, (Depoprovera), durante o período de dois anos.

III - SUMÁRIO

Será um estudo prospectivo com 100 usuárias iniciais de AMPD, acompanhadas pelo período de dois anos. Cada usuária terá como controle uma usuária de dispositivo de cobre (DIU TCu380A), de igual idade (±1) e índice de massa corpórea (IMC±1), que cumprirá os mesmos procedimentos diagnósticos e tempo de seguimento. As mulheres com idade de 18 a 40 anos e IMC<30kg/m2, que consultarem no ambulatório de Planejamento Familiar do Caism/UNICAMP, e optarem pelo AMPD como contraceptivo e seus controles, serão convidadas a participar do estudo. Serão aceitas aquelas que cumprirem os critérios de inclusão e assinarem o TCLE. Todas as mulheres retornarão ao serviço trimestralmente para injeção da AMPD. As 200 mulheres responderão a questionário sobre hábito alimentar, atividade física, tabagismo e etilismo, e terão aferidos a pressão arterial, peso, medidas antropométricas e de bioimpedância para avaliação da gordura corporal, e dosados em amostra de sangue o perfil lipídico, tiroídeo, função hepática, parâmetros glicêmicos (glicemia e insulina de jejum e HOMA) nos meses 0, 6, 12, 18 e 24. Uma amostra secundária e randomizada de 30 mulheres usuárias e seus controles, após concordarem e assinarem um novo TCLE, nos meses 0, 12 e 24 terão avaliadas a resistência e secreção pancreática de insulina através de clamp hiperglicêmico, dosadas as adiponectinas e apolipoproteínas A/B e serão submetidas à medida da íntima-média (IMT) da artéria carótida e diâmetro da artéria braquial por ultrassom e medidas a deposição de gordura na parede abdominal e visceral intra-abdominal, ambas através de ultrassom.

IV - COMENTÁRIOS DOS RELATORES

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Após respostas às pendências, o projeto encontra-se adequadamente redigido e de acordo com a Resolução CNS/MS 196/96 e suas complementares, bem como o Termo de Consentimento Livre e Esclarecido.

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 27 de outubro de 2009.

Profa. Dra. Carmen Silvia Bertuzzo
VICE-PRESIDENTE DO COMITÊ DE ÉTICA EM PESQUISA
FCM/UNICAMP

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7.4.4 Publicação: Body composition and bone mineral density in etonogestrel users.

FACULDADE DE CIENCIAS MEDICAS - UNICAMP (CAMPUS CAMPINAS)

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Composição corporal e densidade mineral óssea de usuárias de implante contraceptivo liberador de etonogestrel (Implanon) comparadas a usuárias de dispositivo intrauterino (DIU) TCu380A

Pesquisador: Luis Guillermo Bahamondes

Área Temática:

Versão: 1

CAAE: 07405112.9.0000.5404

Instituição Proponente: Hospital da Mulher Prof. Dr. José Aristodemo Pinotti - CAISM

DADOS DO PARECER

Número do Parecer: 130.288

Data da Relatoria: 25/09/2012

Apresentação do Projeto:

A Densidade mineral óssea (DMO) e a Composição corporal em mulheres depende de numerosos fatores que ocorrem durante a vida reprodutiva e/ou na pós-menopausa, como pico de massa óssea, peso corporal, fatores genéticos e hábitos de vida. Além dos fatores que apresentam relação bem estabelecida com o desenvolvimento de osteopenia/osteoporose e aumento de peso, permanece controverso na literatura se a utilização e o tempo de uso de métodos anticoncepcionais (MACs) hormonais durante a idade reprodutiva influenciariam a DMO no momento ou, anos depois, na pós-menopausa. Os estudos sobre os efeitos na DMO de alguns MACs contendo apenas progestogenio, como os implantes subdérmicos ainda são inconclusivos como causador da diminuição da DMO e aumento de peso. O estudo será uma coorte prospectiva, com 40 usuárias de Implante subdérmico e 40 usuárias de DIU TCu 380A, que escolheram voluntariamente usar tais métodos na rotina do serviço, tendo sido previamente informadas dos possíveis riscos de cada método.Os critérios de exclusão são: Mulheres usuárias de DIU TCu380A com ciclos menstruais irregulares. Doenças osteometabólicas que interfiram na massa óssea:hipoparatireoidismo, síndrome de Cushing, diabetes, alterações hipofisárias, doenças hepáticas, doenças renais, obesidade (IMC 30 kg/m2),câncer.Mulheres que estejam amamentando. Uso de medicamentos que influenciam na constituição mineral óssea: anticonvulsivantes, benzodiazepínicos, corticoesteróides, diuréticos e hormônios tireoidianos, hormônio de crescimento, ingestão de vitamina D, ingestão de suplemento de cálcio, uso de terapia hormonal.

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Uso de dieta exclusivamente vegetariana. Distúrbios alimentares: bulimia, anorexia.Para participar deste estudo, serão selecionadas mulheres que farão início do uso do Implanon e mulheres que farão início do uso de DIU TCu380A, mantidos por um período de tempo de um ano. Estas são acompanhadas no Ambulatório de Planejamento Familiar do CAISM/UNICAMP. A escolha do método contraceptivo é feito exclusivamente pela usuária, salvo indicações médicas, todas as mulheres no momento da escolha do método serão informadas quanto suas vantagens e desvantagens por uma enfermeira treinada e capacitada para responder todos os questionamentos que possam surgir. Após preencherem a lista de verificação, que contém os critérios de inclusão e exclusão, as mulheres que cumprirem os critérios deinclusão serão convidadas, pela pesquisadora, a participar do estudo. Será então, explicado às mulheres sobre o exame de DMO de corpo total, que será realizado no próprio Ambulatório de Planejamento familiar do CAISM/UNICAMP uma vez antes de se iniciar o uso do MAC escolhido e outra vez um ano após o início do uso do método. Se aceitarem participar do estudo, o Termo de Consentimento Livre e Esclarecido deverá ser lido e assinado. Será também preenchida a ficha de dados onde contém informações relacionadas a tabagismo, consumo de bebida alcoólica e café e atividade física prévia ao uso do método contraceptivo. Um ano após, estas mesmas informações serão obtidas novamente. Cada mulher que entrar na pesquisa será pareada com outra mulher do outro grupo por idade e peso inicial. A evolução e a diferença entre os grupos serão avaliadas através do Wilcoxon para as amostras pareadas e test t para análise das demais variáveis.O nível de significância assumido será de 5% e o software utilizado para análise será o SAS versão 8.2.

Objetivo da Pesquisa:

Objetivo Primário: Avaliar a DMO e a composição corporal de dois grupos de mulheres: usuárias de implante contraceptivo liberador de etonogestrel(Implanon) e usuárias de dispositivo intra-uterino (DIU) TCu 380A.

Objetivos específicos - Determinar a variação de gordura corporal e a massa magra de usuárias de Implanon e DIU TCu 380A.- Determinar a variação de DMO em ambos os grupos.- Comparar a composição corporal e DMO de usuárias de Implanon com as usuárias de DIU TCu 380A.

Avaliação dos Riscos e Benefícios:

Os pesquisadores apresentam na sua hipótese que pode haver riscos para os sujeitos que foram informados previamente no momento da escolha voluntária do método contraceptivo, na rotina do Ambulátorio de Planejamento Familiar. Apenas não ficou claro se pesquisadores e enfermeiros que participam da rotina pertencem a grupos distintos. Os critérios de exclusão estão bem explicitados e são amplos, assim como os critérios de inclusão. Os pesquisadores apresentam como benefício para os sujeitos o acompanhamento da DMO pelo período de ano. Aparentemente os riscos estão

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bem controlados pelos pesquisadores, pois o uso é relativamente curto.

Comentários e Considerações sobre a Pesquisa:

Projeto de pesquisa apresenta-se adequadamente desenhado, com objetivos claros, critérios de inclusão e exclusão precisos. Houve cálculo do tamanho da amostral. O desfecho está definido e existem facilidades para acompanhamento local desta variável.

Considerações sobre os Termos de apresentação obrigatória:

TCLE adequado.

Recomendações:

Sugerir ao pesquisador que as equipes participantes do projeto e da pesquisa sejam distintas para evitar possíveis conflitos de interesse.

Conclusões ou Pendências e Lista de Inadequações:

Aprovado.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

CAMPINAS, 24 de Outubro de 2012

Assinador por:
Carlos Eduardo Steiner
(Coordenador)

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7.5 Artigo Publicado

ORIGINAL ARTICLES: CONTRACEPTION

Effect of hormonal contraceptives during breastfeeding on infant's milk ingestion and growth

Luis Bahamondes, M.D., Ph.D.,[a] M. Valeria Bahamondes, M.D., Ph.D.,[a] Waleska Modesto, M.Sc.,[a] Ian B. Tilley, M.D.,[c] Alviclér Magalhães, Ph.D.,[b] João Luiz Pinto e Silva, M.D., Ph.D.,[a] Eliana Amaral, M.D., Ph.D.,[a] and Daniel R. Mishell Jr., M.D.[c]

[a] Department of Obstetrics and Gynecology, Faculty of Medical Sciences, and [b] Chemistry Institute, University of Campinas, Campinas, Brazil; and [c] Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, California

Objective: To measure infants' breast milk intake and infant growth when their mothers initiated either combined oral contraceptive (COC), levonorgestrel-releasing intrauterine system, or etonogestrel-releasing implant, or copper intrauterine device (IUD) as a reference group.
Design: Prospective trial.
Setting: University-based hospital.
Patient(s): On postpartum day 42, 40 women initiated a contraceptive method according to their choice.
Intervention(s): Deuterium (D_2O; 0.5 g/kg mother's weight) was ingested by mothers on postpartum days 42, 52, and 63 as a marker of total body fluid.
Main Outcome Measure(s): Infants' milk intake from 42 to 63 postpartum days was assessed by measurement of D_2O levels in infants' saliva and infant growth by measuring their body weight, height, and tibia length. Women recorded all infant feed and changes of diapers wet with urine. Breastfeeding continuation was assessed at 6 months postpartum.
Result(s): Infant mean milk intake, mean growth increase, mean number of breastfeeding episodes, daily wet diaper changes, and mean duration of exclusively breastfeeding (~5 months) were similar in the four groups.
Conclusion(s): Use of a COC, the two progestin-only contraceptives, or copper IUD did not affect the amount of infant milk intake and growth up to 9 weeks of age. The incidence of full breastfeeding and breastfeeding continuation was similar with contraceptive hormonal use and no use.
Clinical Trials Registration Number: NCT01388582. (Fertil Steril® 2013;100:445–50. ©2013 by American Society for Reproductive Medicine.)
Key Words: Breastfeeding, combined oral contraceptives, contraceptive implant, hormonal contraceptives, levonorgestrel-releasing intrauterine system, deuterium

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/bahamondesl-oral-contraceptives-breastfeeding/

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The World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use (1) states that the use of combined oral contraceptives (COCs) by breastfeeding women >6 weeks and ≤6 months postpartum is classified as category 3: a condition where the theoretical or proven risks usually outweigh the advantages of using the method. However, use of the progestin-only contraceptives, including the etonogestrel (ENG)–releasing implant and the levonorgestrel-releasing intrauterine system (LNG-IUS) is category 1 (no restriction) (1), although information during breastfeeding is limited (2–4).

The main reason for the WHO restriction of breastfeeding and COC use is concern about exogenous estrogens' effects on possible decrease in milk production (1). Another reason for this restriction was the increased risk of venous thromboembolism (VTE) associated with exogenous estrogens use (1). The Centers for Disease Control and Prevention (CDC) reviewed the WHO recommendations (5) and

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classified COCs as category 4 (unacceptable health risk) for use during the first 21 days postpartum independently from breastfeeding status because of the increased risk of VTE. However, beyond 1 month postpartum, use of COCs is classified as category 2 by the CDC in both breastfeeding and nonbreastfeeding women: advantages generally outweigh the risks if there are no other risk factors for VTE (5).

Evidence demonstrating the negative effect of COC upon milk production in breastfeeding was obtained many years ago and was based mainly on decreases of infant growth or milk production by pump expression with maternal COC use (6–9). One study (10) compared the ingestion of COC with a progestin-only pill (POP), administered daily at 2 weeks postpartum by evaluating breastfeeding and infant growth up to 6 months. At 8 weeks, breastfeeding was maintained by 64.1% and 63.5% of the women in the COC and POP groups, respectively, without an effect on infant growth by either agent. At 8 weeks postpartum, only 28.3% of the women were exclusively breastfeeding, a common incidence in the U.S. (10–12).

Earlier publications (2–4, 6–9) evaluating breastfeeding milk intake by infants relied mainly on measurement of infant growth based on the assumption that the infants ingest only their mothers' milk. For this reason, many studies are now using markers such as deuterium (D_2O) to determine infant breast milk intake, because D_2O is dissolved and disseminated throughout the total fluid in the body, allowing the detection of fluid intake other than the mother's milk by the infant. These studies addressed the effect of nutrition on total body fluid volume or breast milk intake by infants (13–17) and established the validity and safety of D_2O for quantifying breast milk production. However, there are no reports that have used maternal D_2O intake to assess the effect of maternal contraceptive use on breast milk intake and infant growth.

The objective of the present study was to assess whether there is any difference in breast milk intake and infant growth among infants whose mothers were fully breastfeeding and on postpartum day 42 started use of a low-estrogen COC, an LNG-IUS or an ENG-releasing implant compared with mother-infant pairs in which the mother started use of a copper IUD. Measurements of these parameters were continued to postpartum week 9, and the incidence of full breastfeeding continuation was assessed until 6 months postpartum.

MATERIALS AND METHODS

This was a prospective study conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Campinas, Campinas, Brazil. The Institutional Review Board approved the study and each of the women signed an informed consent form. The trial was registered at ClinicalTrials.gov: NCT01388582.

Subjects

Parous women aged ≥18 and <45 years of age who delivered infants from February to October 2011 at our hospital were invited shortly after the birth of the infant to participate in the study. The inclusion criteria were: healthy noncomplicated pregnancy, term vaginal delivery (>37 weeks), previous experience of postpartum breastfeeding, willingness to breastfeed on infant demand during the study period, and planning to use one of the four contraceptive methods of the study. Exclusion criteria included: delivery of a small-for-gestational-age newborn and a newborn with a major congenital anomaly. Additional exclusions were conditions established as exclusion by WHO for use of each of the four contraceptives evaluated (1). Eligible women were instructed to return to the clinic on postpartum day 42 to initiate the study and to receive the contraceptive method of their choice. Mothers were also instructed to give no food, liquid or solid, to the babies from birth until the end of the study while breastfeeding.

Procedures

On day 42, each woman initiated use of her desired contraceptive. The COC contained 150 μg levonorgestrel (LNG) and 30 μg ethinyl-estradiol (EE) (Microvlar; Bayer). The COC was given daily for 21 days followed by 7 days of no medication. The LNG-IUS releases 20 μ/d LNG (Mirena; Bayer), and the ENG implant releases 40 μ/d ENG (Implanon; Merck). The copper IUD used was the TCu380A (Optima; Injeflex). The women were weighed before starting the contraceptive methods.

Milk intake was measured orally by determining the amount of D_2O in the saliva of the infants. Deuterium (99.9% pure, 0.5 g/kg mother's weight; Cambridge Isotope Laboratories) (13, 14) was administered orally with a single ingestion by the mothers on day 42 1 hour before contraceptive initiation. Before and 30 minutes after the D_2O administration, a saliva sample from the mother was self-collected and a sample from the infant was collected by the mother. Additionally, saliva samples from both mothers and infants were collected in plastic sterile vials (5 mL) by the mothers 30 minutes after a breastfeeding episode in the middle of the morning on postpartum days 43, 44, 45, 52, 53, 54, 56, 58, 60, and 63 at home. The mothers were instructed to collect ~2 mL of the infants' saliva with a disposable syringe when they observed more intense saliva production following deposit of two drops of lemon juice on the infants' lips. Each saliva sample was brought to the clinic within 2 hours for analyses, were centrifuged (5 minutes at 1,200 rpm), and the supernate frozen at −80°C until the assays were performed.

The infants' weights and heights were measured on postpartum day 42 (baseline) with the use of dedicated calibrated scales, and a caliper rule was used to measure the length of the left tibia. All measurements were performed in duplicate by two professionals, and a third measurement was undertaken if the first two were not in agreement (within 0.1 kg for weight, within 1.0 cm for height, and within 1.0 cm for tibia length). On days 52 and 63 after delivery, the mother-infant pairs returned to the clinic and additional D_2O ingestion by the mothers and measurement of growth parameters of the infants were done. At enrollment the women were instructed to maintain a diary to record each feeding episode and change of wet diapers with urine from the infant. These analyses were done to decide whether the

study should be stopped if users of COC caused any deleterious effect on breastfeeding frequency. At 6 months postpartum, the women were contacted by telephone to determine the duration of exclusive breastfeeding.

Deuterium Evaluation

Deuterium concentration in the mother and infant was calculated from the integral of D_2O nuclear magnetic resonance (NMR) spectra of deuterated water (4.75 ppm) against the acetonitrile signal (1.98 ppm) used as a standard reference (1 μL/tube) (17, 18). D_2O spectrum was obtained in a sample containing 500 μL saliva and 1μL acetonitrile in a Bruker Avance III spectrometer at 76.73 MHz, with the use of 90-degree pulse experiment with 64 scans and 1 second as a repetition delay. The final spectrum was processed with the use of exponential apodization with line broadening of 1 Hz. The personnel who evaluated the amount of D_2O in saliva were blinded to treatment assignment and if the sample come from the mother or the infant.

Sample Size and Statistical Analysis

The goal of the study was to determine whether there was a 10% difference in breast milk intake between each hormonal contraceptive and a copper IUD. The sample size was estimated to detect that 10% difference in breast milk intake. A two-sided statistical test with a significance level of .05 was used, which corresponds to a z value of 1.96. The acceptance error was 0.20, giving a power of 80%, which corresponds to a z value of 1.28, with a sample estimated to be 9.4 per group. The tests used were Student t test or Mann-Whitney test for quantitative variables and Fisher exact test for qualitative variables. Significance was established at $P<.05$.

RESULTS

Forty women were enrolled, ten in each group. There were no early discontinuations or protocol violations. The main demographic characteristics of the women in the four groups are presented in Table 1. All variables showed no significant differences between copper IUD users and the other three groups. All of the women were in amenorrhea at the initiation of the study; however, those who choose COC presented a bleeding episode during the first free-pill interval. The mean duration of exclusively breastfeeding before entering the study was 5.2 months, and at the 6-month evaluation it ranged from 5.0 to 5.6 months in the four groups. Male infants represented 55% of the sample.

The mean increase of infants' growth variables between postpartum day 42 and 63 for weight ranged from 0.5 to 0.8 kg with no significant differences among the groups; infant height increases ranged from 2.0 to 2.6 cm with no significant differences between the groups. Increase of length of the left tibia ranged from 0.6 to 1.3 cm with a significantly lower increase observed only when the implant but not the COC or LNG-IUS group was compared with the IUD group ($P=.030$; Table 2).

Mean D_2O measurement in mothers' saliva 30 minutes after ingestion increased from 2.6 ng/mL at basal time to 5.6 ng/mL. The mean amount of D_2O in the mothers' saliva at each point of evaluation was similar among the four groups of contraceptive users (Fig. 1A). The mean D_2O amount in the infants' saliva was significantly higher in the LNG-IUS versus IUD group on day 45 ($P=.020$) and significantly lower in the COC versus IUD group on day 56 ($P=.015$; Fig. 1B). All other mean D_2O levels were not significantly different among the 4 groups at any time.

The mean number of breastfeeding episodes (Fig. 2A) was significantly higher with COC versus IUD use on 7 out of 21 days (days 48, 49, 50, 51, 52, 54, and 55; $P<.05$) and significantly higher with implant versus IUD use on days 48, 49, 51, and 61 ($P<.05$). The mean number of diapers with urine changed each day (Fig. 2B) was significantly higher with COC versus IUD use only on days 42 and 46 ($P<.05$) and significantly higher with implant versus IUD use on days 43, 44, 45, 46, and 49 ($P<.05$). There were no other significant differences of the parameters on the four groups.

TABLE 1

Demographic characteristics of the participating women and infants according to the contraceptive method used.

Variable	COC (n = 10)	Implant (n = 10)	LNG-IUS (n = 10)	Copper IUD (n = 10)
Age (y)	24.8 ± 2.1	27.9 ± 1.4	27.0 ± 2.1	28.5 ± 1.8
P value[a]	.206	.797	.594	
No. of pregnancies	2.2 ± 0.3	2.7 ± 0.4	2.0 ± 0.3	2.4 ± 0.5
P value[b]	.969	.475	.605	
BMI (kg/m^2)	24.2 ± 1.0	24.7 ± 1.0	25.9 ± 1.2	25.9 ± 1.5
P value[a]	.356	.528	.981	
Months of exclusive breastfeeding	5.0 ± 0.4	5.1 ± 0.4	5.6 ± 0.3	5.4 ± 0.3
P value[b]	.317	.544	.745	
Infants' weight at birth (g)	3,317.5 ± 108.4	3,443.0 ± 142.9	3,287.0 ± 97.0	3,453.5 ± 127.8
P value[a]	.443	.957	.313	
White ethnicity (n)	4	2	2	5
P value[c]	>.999	.315	.315	
Male infants (n)	5	6	4	7
P value[c]	.650	>.999	.370	

Note: Values are presented as mean ± SEM or n. COC = combined oral contraceptive; implant = etonogestrel-releasing implant; IUD = intrauterine device; LNG-IUS = levonorgestrel-releasing intrauterine system.
[a,b,c] Comparison of each method with IUD: [a] t test; [b] Mann-Whitney test; [c] Fisher exact test.

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TABLE 2

Weight, height, and length of the tibia of the infants according to the contraceptive method in use by the mother by exclusively breastfeeding mothers from days 42–63 postpartum.

	Days after delivery				
	42	52	63	Δ[a]	*P* value
Weight (kg)					
COC	4.6 ± 0.1	5.2 ± 0.1	5.3 ± 0.2	0.7 ± 0.1	.613[b]
Implant	4.9 ± 0.2	5.3 ± 0.2	5.6 ± 0.2	0.8 ± 0.1	.678[b]
LNG-IUS	4.9 ± 0.3	5.2 ± 0.2	5.4 ± 0.3	0.5 ± 0.2	.241[c]
IUD	4.9 ± 0.2	5.5 ± 0.3	5.7 ± 0.3	0.8 ± 0.1	
Height (cm)					
COC	55.6 ± 0.5	56.9 ± 0.6	58.2 ± 0.7	2.6 ± 0.3	.583[b]
Implant	57.2 ± 0.5	58.3 ± 0.7	59.2 ± 0.7	2.0 ± 0.3	.824[b]
LNG-IUS	56.6 ± 0.5	57.3 ± 0.6	58.7 ± 0.8	2.0 ± 0.6	.891[b]
IUD	57.1 ± 0.8	58.1 ± 0.6	59.3 ± 0.6	2.2 ± 0.7	
Length of tibia (cm)					
COC	14.6 ± 0.2	14.9 ± 0.2	15.3 ± 0.2	0.8 ± 0.2	.097[b]
Implant	14.9 ± 0.2	15.2 ± 0.2	15.5 ± 0.1	0.6 ± 0.2	.030[c]
LNG-IUS	14.4 ± 0.3	15.1 ± 0.2	15.3 ± 0.2	0.8 ± 0.3	.110[c]
IUD	14.1 ± 0.3	15.1 ± 0.3	15.4 ± 0.2	1.3 ± 0.2	

Note: Values presented as mean ± SEM. Abbreviations as in Table 1.
[a] Measure at day 63 – measure at day 42.
[b,c] Comparison of each method with copper IUD: [b] Student *t* test; [c] Mann-Whitney test.

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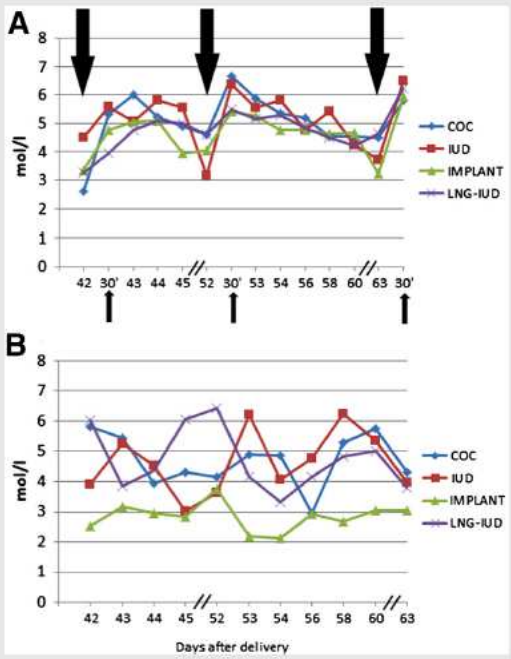
FIGURE 1



Mean D_2O amount (mol/L) in the saliva of (A) the mothers and (B) the infants from postpartum day 42 to 63 according to each contraceptive method. The *large arrows* indicate D_2O intake by the mothers, and the *small arrows* indicate D_2O measurement in saliva of the mothers 30 minutes after intake. COC = combined oral contraceptive; implant = etonogestrel-releasing implant; IUD = intrauterine device; LNG-IUS = levonorgestrel-releasing intrauterine system. (A) No analysis performed; (B) LNG-IUS versus IUD (day 45): *P*=.020; COC versus IUD (day 56): *P*=.015.

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DISCUSSION

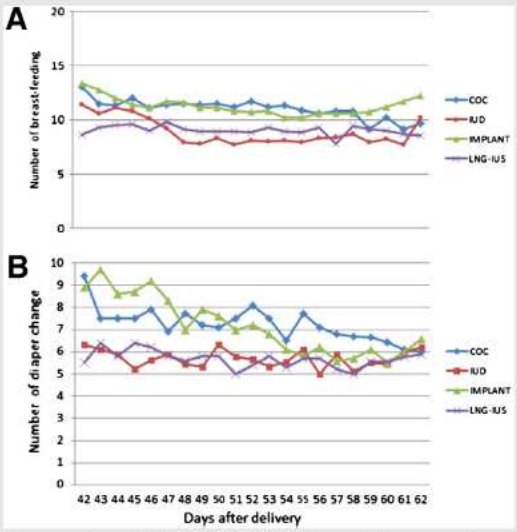
Our results show that fully breastfed infants whose mothers received a 30 μg-EE/150 μg-LNG COC pill or an LNG-IUS or ENG-releasing implant had breast milk intake (according to the values of D_2O in infants' saliva) and infant growth (delta variation of body weight, height and length of left tibia between baseline and the end of the study) similar to infants breastfed by mothers with a copper IUD during postpartum days 42–63. These findings indicate there is no effect of contraceptive steroids either combined with estrogen or progestin alone on infant growth or milk intake by fully breastfeeding infants. The most relevant finding was that the use of a low-EE COC administered from postpartum day 42 to day 63 did not alter the amount of milk ingested by the fully breastfeeding infants from their mothers.

Our results of exclusive breastfeeding duration are different from the Brazilian rates. The prevalence of exclusive breastfeeding in Brazil in children aged up to 6 months averaged 41.0% in the country overall (ranging from 27.1% to 56.1% in different regions). The median duration of exclusive breastfeeding was 1.8 months, and the median non-exclusive breastfeeding was 11.2 months (19). The duration of breastfeeding at the 6-month evaluation was similar among the four groups in the present study. However, we have to take into account that the participants had a previous successful experience of breastfeeding.

Our results had good validation because calculation of infant milk ingestion was performed by D_2O enrichment and quantified by NMR compared with earlier studies in which milk intake was evaluated indirectly by measuring infant growth (2–4, 6–9). Maternal D_2O intake has been used in other studies mainly to assess infant breast milk intake (13–17), but many of those studies on breastfeeding did not use NMR to quantify D_2O (17, 18). Since 1979 (20) D_2O has been used as a noninvasive test for tracking milk transfer from breastfeeding mothers to infants and the common method for assessment was Fourier-transform infrared spectroscopy (21, 22). Nevertheless, this method requires sample preparation with specialized analytical manipulations, in contrast to NMR which is a more workable approach (18). The advantage of NMR is that it is a noninvasive and nondestructive technique and can make the determination without degrading the sample.

The results obtained in this study are not in agreement with the most important two studies (9, 23), conducted by WHO, which compared the same COC used here and POP intake on milk production by breastfeeding women. Maternal milk volume was measured by breast pump expression and was analyzed by documenting breastfeeding frequency, time to introduction of supplemental feed, and infant growth. The infants were followed to 24 weeks postpartum. The investigators observed a reduction of volume of milk in the COC group although infant growth and breastfeeding continuation were not affected. The explanation by the investigators for this discrepancy was

FIGURE 2



Mean number of (A) breastfeeding episodes and (B) mean number of diaper change wet with urine from postpartum day 42 to 63 according to each contraceptive method. Abbreviations as in Figure 1. (A) COC versus IUD: $P<.05$ on days 48, 49, 50, 51, 52, 54, and 55; implant versus IUD: $P<.05$ on days 48, 49, 51, and 61. (B) COC versus IUD: $P<.05$ on days 42 and 46; implant versus IUD: $P<.05$ on days 43, 44, 45, 46, and 49.

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that the mothers could have compensated for decreased milk production by supplementary feeding the infants or by intense and prolonged suckling episodes (9, 23).

Other authors compared the intake of the same COC used in our study with a nonhormonal contraceptive beginning on postpartum day 30 (24, 25). The COC users had a lower proportion of women who maintained full and exclusive breastfeeding at the third and sixth postpartum months than those using nonhormonal contraceptive. Lower infant mean weight increase occurred in the COC group than the nonhormonal group at the second, third, and fourth months of age; nevertheless, the infant mean weight at 1 year was similar in both groups. The results of these studies (9, 23–25) are often used as justification for preventing COC use by breastfeeding women.

Our results are in agreement with a recent study (10) in which no deleterious effect was observed on breastfeeding and infant growth among mothers who initiated use of a COC during the second week after delivery. The principal criticism of that study is that at 14 days after delivery the intake of COC poses a high risk of VTE. For this reason COC use is not begin at this time. We begin COC use at 42 days postpartum because this is the time recommended to initiate use of a progestin-only contraceptive or the copper IUD (1).

In addition, to avoid the possibility that a reduction in milk intake occurred before the D_2O measurement was performed, we measured the number of breastfeeding episodes and the diaper change frequency. Decreased breast milk production of each feeding episode could be masked by an increase in the breastfeeding frequency to maintain total volume of milk. Our results showed no significant differences in the amount of breast milk ingestion by infants on several days among the four groups evaluated. The results of this study showed that infants in the COC and implant groups had significantly more breastfeeding episodes than the IUD group only 7 and 4 days after study initiation, respectively.

Wet diaper change frequency can also reflect breastfeeding adequacy. If the infant feeds more frequently but fails to make wet diapers, then it suggests that the breast milk volume was inadequate. However, if the infant was fed frequently and makes many wet diapers, the findings suggest that the infant is simply a good feeder. The number of changes of wet diapers was significantly higher in the COC and implant groups only on 2 and 5 days after study initiation, respectively. These findings reinforce the conclusion that there is no influence of hormonal contraceptives with or without estrogens on breastfeeding amount or infant growth between 6 and 9 weeks of age.

Regarding the two groups of women who received LNG-IUS and ENG-releasing implants, the results of breastfeeding were as expected because there are no restrictions by WHO or CDC to initiate progestin-only contraceptives immediately after delivery (1, 26). A systematic review (27) on the effect of progestin-only contraceptives on breastfeeding and milk production, mainly with mothers who were using injectable contraceptives or a progestin-only pill, showed that most studies did not show a deleterious effect on breastfeeding, growth, or development from 6 months to 6 years of age with use of these steroids.

Regarding the use of LNG-IUS, we were able to identify one study (4) in which fully breastfeeding mothers inserted the device at 6–8 weeks postpartum and breastfeeding parameters were compared with mothers who received a copper IUD. There were no significantly differences in mean breastfeeding duration (149 vs. 160 days) for the mothers using LNG-IUS versus copper IUD, respectively. Additionally, no significant differences were observed between the groups regarding infant growth and development. Regarding the ENG implant, three studies (2, 28, 29) evaluated frequency and duration of breastfeeding and milk composition when the implant was inserted at 28–56 days postpartum, and no differences were observed compared with copper IUD users (2, 24). Others (3, 29) inserted an ENG-releasing implant 24–48 hours after delivery and did not observe differences in milk production or infant weight compared with nonusers.

The main strength of the present study was the technique used to assess milk intake and the fact that we compared three hormonal contraceptive methods, including one COC, with a nonhormonal method. The main limitations are that we were unable to allocate the women at random owing to ethical limitations and that we can not extrapolate the results to other COCs because we tested only one formulation, albeit one that is widely used worldwide. Nevertheless, the findings of no

effect on breastfeeding with this COC could be applied to COC formulations with lower amounts of EE. Many women may wish to use a COC despite the fact that they are fully breastfeeding due to fear of insertion of an IUD or implants or lack of supplies of other contraceptive methods. Consequently, the possibility to offer COC at postpartum day 42 could improve contraceptive access and reduce unintended pregnancies. In conclusion, the use of a COC containing 150 μg LNG and 30 μg of EE did not affect fully breastfeeding infants' milk intake compared with two progestin-only contraceptives or the copper IUD from 6 to 9 weeks postpartum.

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