Abstract

Introduction

Up to 30% of women will have heavy menstrual bleeding (HMB), leading to 20% of gynecology visits. HMB impairs women’s quality of life. As 80% of HMB cases have normal anatomy, generally, surgery is clinically excessive, cost-ineffective treatment. Both intramuscular medroxyprogesterone acetate (DMPA) and the 5-year, 52 mg, levonorgestrel intrauterine device (5yr-IUD) are known for potential amenorrhea. Weight gain is a known adverse effect of DMPA. Astute patients also question the 5yr-IUD’s weight gain potential. Therefore, the comparative efficacy of DMPA and 5yr-IUD for menstrual control and the associated weight gain need clarification.

Methods

An evidence-based mini-review was performed. PubMed searches for the terms “depo provera weight gain,” “mirena weight gain,” “depo provera effectiveness treatment heavy menstrual bleeding,” and “mirena effectiveness treatment heavy menstrual bleeding” yielded 17 included articles.

Results

Up to 2-years post-insertion the 5yr-IUD is the most efficacious hormonal means of HMB control. For 31% of DMPA users, DMPA is as efficacious as the 5yr-IUD. Obese adolescents have up to 9.4 kg in 18 months DMPA associated weight gain, whereas obese endometrial and pre-endometrial cancer 5yr-IUD users can lose 5.4 kg in 12 months.

Discussion

While retrospective and prospective studies’ outcomes differ in magnitude, DMPA is consistently associated with greater weight gain than underlying population-based weight gain trends, whereas the 5yr-IUD is associated with maintenance of underlying population-based weight gain trends.

Conclusion

The 5yr-IUD is weight-neutral in comparison to the DMPA. The 5yr-IUD is most likely to normalize menstruation or result in amenorrhea within 6-months of initiation, but at 5-year surveillance all HMB hormonal control methods have similar efficacy.
Hyperreactio luteinalis (HL) is a rare condition of bilateral cystic ovarian enlargement usually found in twin and molar pregnancies.

Heavy menstrual bleeding (HMB) affects 8% - 30% of women [1,2]. HMB has been defined as greater than 80 mL menstrual blood loss per menstrual cycle, more than 7 days of menstruation per cycle, or sufficient blood loss to negatively affect a patient’s perceived emotional, material, physical, or social quality of life [3-6]. In both the United States of America (USA) and the United Kingdom (UK), about 20% of gynecology visits are for HMB [4]. HMB Normal body mass index (BMI), reproductive age, non-adolescent women may experience distressing, idiopathic, irregular, HMB. Undetermined causation in most HMB cases precludes directed treatment [3]. Despite pathologically normal anatomy in 80% of women with HMB, 60% of women with HMB undergo surgical treatment [5,6]. Consistent with the above and an overall 18% hysterectomy rate unsupported by pathologic findings, more than 33% of women undergoing hysterectomy for HMB have pathologically normal uteri [5,7]. Therefore, medical management is the recommended initial treatment of HMB [5-7].

Non-contraceptive benefits of hormonal contraceptives include HMB control [6]. In 2007, the 5-year, 52 mg, levonorgestrel intrauterine device (5yr-IUD) was recommended by the United Kingdom National Institute for Health and Clinical Excellence for first-line treatment of HMB. [2,3] Subsequently 114 nations, including the United States followed suit. [2,8] Within four months of insertion, the 5yr-IUD results in an 80% reduction in menstrual blood loss (MBL), increasing to a 100% reduction in MBL via amenorrhea at 2 years. [9] Menstrual pattern at 6-months after 5-yr IUD insertion reflects that at 24-months post-insertion. [10] There is sufficient clinical data to support clinical efficacy and cost-effectiveness of the 5yr-IUD for control of HMB in comparison to oral hormonal and non-hormonal treatments. [11,12] But, cost-effectiveness of HMB treatment varies with the quality of life and cost-benefit analysis measure used. [13,14] Thus, other means for selecting HMB treatment are appropriate.

Weight gain is not commonly listed as an adverse effect of the 5yr-IUD, but patients directly ask about potential weight gain. [3] Off-label, quarterly intramuscular or subcutaneous medroxyprogesterone acetate (DMPA) may result in amenorrhea or irregular menstruation, with, or without weight gain. [15,16] However, direct comparison of the 5yr-IUD and DMPA associated weight gain is not obviously available. Women with idiopathic, irregular, HMB may prefer forgettable or almost forgettable contraception, to daily, weekly, or monthly methods. [17] The 5-yrIUD and DMPA have an efficacy boosting convenience factor.

Diabetic and non-diabetic adult American women born after 1950 tend to gain weight with age, which is consistent with global literature. [18] Weight gain can comprise 55.1% of contraceptive adverse effects, leading to method cessation in 40.9% of cases when an adverse effect drives method cessation. [19] Women prefer contraceptives associated with weight loss, not weight gain. [20,21] Intrauterine device insertion can be sufficiently technically challenging in obese women to require performance in an operating room, whereas DMPA is easily administered. [22] Weight gain associated with 5yr-IUD use by obese women could favor Q-DMPA selection. Therefore, contraceptive weight-neutrality is important. Thus, the comparative efficacy of DMPA and the 5yr-IUD for menstrual control and the associated weight gain need clarification. Thus, the evidence-based medicine population, intervention, comparison, outcome, and time interval (PICOT) question is: For normal BMI adult females with idiopathic, irregular HMB, will the 5yr-IUD compared to DMPA be weight-neutral and more likely to either normalize menstruation or result in amenorrhea within 6-months of initiation and effectively control HMB for 5 years?

PubMed searches were performed on December 27, 2016 with the inclusion criteria filters clinical trial or review, full text English language, publication from 2014 onwards, female human subjects, aged 13 to 64 years old, for the terms “depo provera weight gain,” “mirena weight gain,” and “depo provera effectiveness treatment heavy menstrual bleeding,” yielding 13, 8, and 4 articles respectively. For the term “mirena effectiveness treatment heavy menstrual bleeding” the filter free full text replaced full text, yielding 4 articles, as shown in Figure 1. Unfortunately, the systematic review of progestin-only contraception during lactation evaluated infant weight gain, not maternal postpartum weight changes. [23] Exclusion of 15 articles (4 duplicate, 6 extraneous, and 5 redundant articles) left 17 studies from the PubMed literature search. To this, 22 hand search articles supplemented milieu formation, and added content to the weight gain and bleeding control
Weight Gain Potential: Intramuscular medroxyprogesterone acetate

The progestin, megestrol acetate, a United States Food and Drug Administration (FDA) approved treatment for cachexia and anorexia, lending biologic plausibility to progestin-associated weight gain. [16] Reportedly, 25% of adolescent females receiving DMPA gain more than 10% of their baseline weight, [15] that was confirmed by a pilot study of 40 DMPA initiators of whom 27.5% gained 10% or more of their baseline BMI at 11 months of use. [24] A retrospective study on injectable progestin contraceptive users, found that 14.2% of DMPA users gain weight. [25] A cohort of 22 women showed that DMPA received in the progestin-dominant luteal phase increases resting metabolic rate, in-turn causing hyperphagia and insufficient non-shivering thermogenesis to convert all the additional consumed...
calories into heat, resulting in weight gain. [16] A prospective cohort of 38 adolescent females found that DMPA associated weight gain was linked to low pre-initiation serum adiponectin concentration. [15] Therefore, DMPA given in the follicular phase, which is the FDA approved protocol, may be weight-neutral in some patient populations.

The largest prospective trial studying weight gain in 240 DMPA users, found a mean 5.1 kg weight gain at 36 months, comprised of 4.1 kg fat, and 1.16 kg lean body mass. [26] Obese, adolescent American DMPA users can gain 9.4 kg within 18 months. [26] However, in a retrospective cohort of Brazilian public family planning clinic users, those initially of normal weight gained more than twice as much weight as the obese, 4.5 kg to 1.9 kg. [27] In stark contrast, in a retrospective cohort of 172 Navajo, inter-pregnancy (interval) DMPA users gained an average of 4.20 kg at 12-months, and 7.14 kg at 24-months, while postpartum DMPA users gained an average of 3.16 kg and 6.42 kg respectively. [28]

The literature on DMPA associated weight gain is of low quality due to the lack of randomization and short-term follow-up. [21] Nonetheless, DMPA is associated with 1.3 ± 0.15 kg weight gain at 12 months and 6.6 ± .61 kg weight gain at 10 years. [21] At 12-month follow-up a cohort of 20 DMPA users had a mean 1.4 kg weight gain, 2% body fat increase, and a 2% lean mass decrease. [29]

A prospective study with 31 DMPA users showed mean increased BMI by .7 kg/m², waist circumference by 1.1 cm, fasting insulin by 20.8 µmol/l, and homeostasis model assessment of insulin resistance (HOMA-IR) by .6 at 12 months. [30] A prospective study of 45 DMPA users showed mean increased BMI by 1.6 kg/m², percent body fat by 4.3 percentage points, and percent lean mass decreased 5.6 percentage points by 12 months. [31] Increased BMI was inversely associated with ample dietary fiber, linoleic acid, and magnesium, p<.05. [31]

<table>
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<tr>
<th>Weight gain incidence</th>
<th>DMPA 12 months</th>
<th>DMPA 18 months</th>
<th>DMPA 24 months</th>
<th>DMPA 36 months</th>
<th>DMPA overall</th>
<th>5yr-IUD 3 months</th>
<th>5yr-IUD 12 months</th>
<th>5yr-IUD 36 months</th>
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<tr>
<td>Quantified weight change (kg)</td>
<td>+1.4 ± 0.7 [29]</td>
<td>+1.3 ± 0.15 [21]</td>
<td>Navajo, interval + 4.20 ± 4.97 Postpartum + 5.16 ± 4.3 [28]</td>
<td>+ 5.1 [26]</td>
<td>14.2% of users [25]</td>
<td>25% gain &gt; 10% baseline weight [15]</td>
<td>0 to + 5.1 [26,36]</td>
<td>+ .05 [33]</td>
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<td>BMI &lt;25 kg/m²</td>
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<td>21% gain 1.5 [32]</td>
<td>28.7% gain more than 2 [34]</td>
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<td>BMI 25-29.9 kg/m²</td>
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<td>BMI &gt; 30 kg/m²</td>
<td>Adolescents +8.4 [26]</td>
<td>+4.5 ± 4.5 [27]</td>
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<td>+3.4 ± 5.5 [27]</td>
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<td>Mean BMI (kg/m²)</td>
<td>.7 [30]</td>
<td>1.6 [31]</td>
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<td>+ .4 ± 8.8 [36]</td>
<td>+ .6 ± 6.6 [36]</td>
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<td>Total body fat (kg)</td>
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<td>Body fat (%)</td>
<td>+2 ± 9 [29]</td>
<td>+4.3 percentage points [31]</td>
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<td>Central-to-Peripheral fat ratio</td>
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<td>Total body lean mass</td>
<td>-2% ± 9 [29]</td>
<td>-5.6 percentage points [31]</td>
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Table 1. Contraception-based weight change and weight related outcome changes from pre-method initiation weight.

Weight Gain Potential: Five-year levonorgestrel intrauterine device

The 5yr-IUD is not weight-neutral. Over 12 months, 21% of users in a retrospective study gained 1.5 kg. [32] Amongst 5yr-IUD users with endometrial pathology, weight gain was .05 kg over 11.7 months. [33] However, obese patients whose BMI was ≥ 35 lost 5.40 kg with a median 11.7 months of 5yr-IUD treatment. [33] A prospective study of 5yr-IUD treatment of dysmenorrhea associated with adenomyosis found that 28.7% of 94 participants gained more than 2 kg by 36-months post-insertion. [34] When the above is placed in the context of the trend of 39 to 48 year olds gaining .3 to .4 kg annually. [35] 5yr-IUD associated weight gain is consistent with population-based weight gain. Although not designed for weight gain as an outcome measure, a randomized controlled trial (RCT) of 571 participants with HMB experienced 2 standard medical care and 4 5yr-IUD discontinuations for weight gain. [4] Nonetheless, the mean BMI of 26.5 kg/m² for a prospective cohort of 120 HMB patients treated with the 5yr-IUD was not significantly changed after 1-year. [36] Table 1 depicts DMPA associated weight gain.
Heavy Menstrual Bleeding Control

A retrospective cohort of 741 women attending an academic center family planning clinic, who choose DMPA for contraception showed 14.2% of participants gained weight, 3.4% had HMB, 22.5% had intermenstrual bleeding, and 47.7% had secondary amenorrhea. [25] Unfortunately, discontinuation rates for DMPA and norethisterone enanthate were combined. Therefore, bleeding disorder and weight gain associated discontinuation rates for DMPA are unavailable from this study. [25]

At 3 and 6 months, in a prospective cohort of 29 Q-DMPA users and 37 5yr-IUD recipients, unacceptable irregular menstruation or unacceptable HMB occurred at one-quarter to half the rate in 5yr-IUD users, in comparison to DMPA recipients ($p = .05$ for unacceptable irregular menstruation at 6 months). [37] Clinically significant, by 12 months, 57.1% of DMPA recipients had discontinued use introducing high risk of bias into this study, whereas only 23.3% of 5yr-IUD users had discontinued use. [37] In this light, that none of the remaining nine DMPA recipients had unacceptable irregular menstruation or unacceptable HMB at 12 months (31% of initial DMPA recipients), whereas 26 of remaining 28 (93.75%) 5yr-IUD users did not have unacceptable irregular menstruation or unacceptable HMB at 12 months, does not clinically favor DMPA use instead of 5yr-IUD use.

A systematic review and meta-analysis included two RCT of 5yr-IUD with DMPA as a comparator. [2] Pictorial bleeding assessment chart (PBAC) favored the 5yr-IUD, mean difference, inverse variance method, 72.00 and 95% confidence interval (CI) 52.22 to 91.78. [2] Patient satisfaction also favored the 5yr-IUD, Mantel-Hansel odds ratio 4.81, 95% CI 1.69 to 13.72. A RCT with 99 5yr-IUD users incurred 1.3% discontinuation for weight gain and 2.7% discontinuation for bleeding by 12 months. [38]

Another systematic review included 14 studies on HMB control by hormonal contraception in women desiring future fertility. [6] The 5yr-IUD was the subject of 10 studies, including eight RCT. One prospective cohort included DMPA and the 5yr-IUD. As shown in Table 2, the 5yr-IUD consistently achieved HMB control via decreased menstrual blood loss, measured directly by alkaline hematin and indirectly by ferritin or hemoglobin level or PBAC. [6]

A prospective cohort of 120 women who accepted the 5yr-IUD for HMB control had a 95.8% 1-year continuation rate, a 60.9% amenorrhea rate, a 33% hypomenorrhea rate, and a 6.1% eumenorrhea rate. [36] Discontinuation was for inter-menstrual spotting and unchanged menstruation (2.5% and 1.7% of total participants respectively). HMB was ascertained via PBAC. Serial hemoglobin and ferritin levels as shown in Table 2, indicated significant improvement, supporting the participants’ PBAC description of menstruation.

A RCT of the 5yr-IUD versus standard medical care for 571 participants with HMB found Menorrhagia Multi-Attribute Scale (MMAS) total score improvement for 5yr-IUS use at 24- but not 60-months, mean difference 13.4 points, 95% confidence interval (CI) 9.9 to 16.9 points ($p < .001$) and mean difference 3.9 points, 95% CI -.6 to 8.3 points ($p = .09$), respectively. [4] Nevertheless, the 5yr-IUD had a 47% 60-month continuation rate, whereas standard medical care had a 15% 60-month-continuation rate. [4] The MMAS has variable moderate correlation with the Short Form-questionaire-36 item (SF-36), weaker correlation with the European Quality of Life-5 Dimensions (EQ-5D), and lacks correlation with age or BMI. [4] Both 5yr-IUD and standard medical care participants had similar surgery-free rates at all recorded time points. [4]

A manufacturer funded, Asian-Pacific, international, prospective cohort of 572 patients already under treatment for HMB, also used the MMAS. [11] The 5yr-IUD achieved an 83.5% “satisfied” or “very satisfied” rating from 437 participants. Obese participants had the greatest improvement in MMAS satisfaction rating from baseline (27.9) to 12-months surveillance (95.5). [12]

A retrospective, non-comparative study of 48 adenomyosis patients, 10 of whom had HMB, and 30 of whom had both HMB and dysmenorrhea, had an HMB subjective symptom score of 69.4 ± 26.1 prior to 5yr-IUD insertion. [39] By 6-months post-insertion the HMB subjective symptom score was more than halved to 25.3 ± 17.7 ($p < .001$), which was stable at 12-months with 31 patients reporting, and further reduced to 8.9 ± 12.7 ($p < .001$) at 36-months, with 9 patients reporting. [39] However, 64.3% of patients did experience vaginal spotting in the first 3-months of 5yr-IUD use. [39] Reported IUD expulsion rates are 0-8.5%, increasing to 16% in an adenomyosis patient population with a mean initial uterine volume of 113.8 mL. [34,39] However, this cohort, with a mean initial uterine volume of 253.5 mL (larger than a 12-week size uteri) had a 37.5% 5yr-IUD expulsion rate. [39]
Up to 30% of women will experience HMB. [1,2] While numerous studies have demonstrated the clinical efficacy and cost-effectiveness of the 5yr-IUD for the treatment of HMB in comparison to oral hormonal and non-hormonal treatments, limited RCT of the 5yr-IUD compared to DMPA exist. To recap, the PICOT question was: For normal BMI adult women with idiopathic, irregular HMB, will the 5yr-IUD compared to the DMPA be weight-neutral and more likely to either normalize menstruation or result in amenorrhea within 6-months of initiation and effectively control HMB for 5 years?

As evidenced in Tables 1 and 2, historically studies have used an array of outcome measures. Outcome measure standardization will facilitate outcomes comparison for systematic review and meta-analysis. Direct comparator RCT of the 5yr-IUD to DMPA for control of HMB are lacking. Direct measures of menstrual blood loss reduction associated with DMPA seem lacking in comparison to the 5yr-IUD. Nevertheless, in response to the above PICOT question, the literature shows that at 3-months through 2-years from treatment initiation the 5yr-IUD is the most efficacious hormonal, non-surgical means of HMB control. [4,6,36] Nevertheless, in 31% DMPA users, DMPA may be equally efficacious. [37] Neither off-label contraceptive and endometrial protection 5yr-IUD use for 7 years, nor HMB control for up to 10 years or menopause onset (whichever is later) are reflected in the PubMed searches performed above. [40] Consistent with this, although studies with 3- to 10-year follow-up for DMPA compared to the 10-year copper IUD exist, such studies comparing DMPA to the 5yr-IUD are lacking. [21]
While a single retrospective cohort found that 14.2% of DMPA users gained weight, a single prospective cohort found that 25% of DMPA users had greater than 10% weight gain. With a prospective cohort demonstrating 5.1 kg weight gain over 3 years of DMPA use, versus another showing 28.7% of 5yr-IUD users gaining 2 kg over 3 years of use. Therefore, the 5yr-IUD does not worsen underlying population trends for weight gain with time [35]. Clearly, DMPA use has shown greater weight gain propensity than has the 5yr-IUD [26,34]. While DMPA is associated with even greater weight gain in certain populations, including obese adolescents and the Navajo, the 5yr-IUD is associated with weight loss in obese endometrial and pre-endometrial cancers patients [26,28,33]. Weight gain associated with DMPA use may be limited by restricting use to follicular phase administration in persons with high serum adiponectin concentration, and ensuring patients’ consumption of ample fiber, healthy fats including linoleic acid, and magnesium. [15,31] Given conflicting reports of ethnic and body mass index (BMI)-based DMPA associated weight gain, prospective RCT are required to clarify medical determinants of DMPA use associated weight gain.

Conclusion

Systematic reviews, a meta-analysis, and a prospective trial not included in the systematic reviews, found the 5yr-IUD consistently reduced menstrual blood loss during 3-month to 2-year post-insertion surveillance. [4,6,36] DMPA is associated with weight gain potential, whereas the 5yr-IUD is associated with the underlying population weight gain rate, and in certain cases, with weight loss. Therefore, the response to the normal BMI adult woman with idiopathic, irregular HMB, should be that the 5yr-IUD is weight-neutral in comparison to the DMPA, that the 5yr-IUD is more likely to normalize menstruation or result in amenorrhea within 6-months of initiation, but that at 5-year surveillance all HMB hormonal control methods result in similar menstrual patterns.

However, neither the 5yr-IUD nor DMPA have sufficient long-term outcomes data (for 10 years of use or longer, or to menopause onset), which are needed to adequately assess clinical-effectiveness, cost-effectiveness, and potential for exogenous progesterone negative effects on carbohydrate metabolism. [4,29,30] Moreover, as interval 5yr-IUD replacement is necessary to acquire long-term outcomes data, which is not necessary for the 10-year copper IUD, such RCTs may not be performed.

Acknowledgement

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Cite This Article