Evaluating use of Depo-Provera: a closer look at association with skeletal, cardiovascular and metabolic systems

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Evaluating use of Depo-Provera: A Closer Look at Association with Skeletal, Cardiovascular and Metabolic Systems

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The University of Toledo
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Dedication

Half of my degree belongs to my family and friends who have been patient with me and supportive of me throughout the past 27 months of this program.
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Introduction

In June 1992 the Food and Drug Administration (A. s. o. P. C. Pharmacia & Upjohn Company, 2004) advisory committee approved the use and marketing of Depot-medroxyprogesterone acetate (DMPA), brand name Depo-Provera® (Stone, 1992), for contraception. In the 1970’s the FDA attempted to gain approval for contraceptive marketing of this drug, but the attempt was unsuccessful as a result of inadequate information about how this drug would influence females and their risk for breast cancer, cervical cancer and osteoporosis (Stone, 1992). Pfizer U.S. Pharmaceuticals issued a black box warning in 2004, only 12 years after the initial contraceptive marketing of Depo-Provera®, advising healthcare professionals of the significant loss in bone mineral density (BMD) that may occur with the use Depo-Provera® (Urbanski, 2004). The black box warning also stated:

It is unknown if use of Depo-Provera Contraceptive Injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture later in life. Depo-Provera Contraceptive injection should be used as a long-term birth control method (e.g., longer than 2 years) only if other birth control methods are inadequate (see WARNINGS). (Urbanski, 2004)

Pfizer’s label for prescribing information, which can be accessed via the FDA webpage, gives a brief description of the drug’s mechanism of action. Essentially, Depo-Provera® Contraceptive Injection (CI), contains 150 mg of medroxyprogesterone acetate (MPA; a progesterone derivative) which is administered as an intramuscular

Another formulation of Depo-Provera® comes in a subcutaneous (SubQ) formulation, 104mg/0.65 mL. The SubQ, unlike the IM formulation, is indicated for endometriosis as well as contraception. In clinical studies, the SubQ formulation of Depo-Provera® is associated with less loss of BMD than leuprolide, which is the current therapy for endometriosis (D. o. P. I. Pharmacia & Upjohn Company, 2005).

Depo-Provera’s® lowest expected and typical failure rates of women experiencing an accidental pregnancy are 0.3% and 0.3% respectively (A. s. o. P. C. Pharmacia & Upjohn Company, 2004). However while very efficacious as a contraceptive, Depo-Provera has several side effects and 6 contraindications to its use (A. s. o. P. C. Pharmacia & Upjohn Company, 2004). The 6 contraindications to the use of Depo-Provera®:

1. Known or suspected pregnancy or as a diagnostic test for pregnancy.
2. Undiagnosed vaginal bleeding
3. Known or suspected malignancy of breast
4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.
5. Significant liver disease

6. Known hypersensitivity to Depo-Provera CI (medroxyprogesterone acetate or any of its other ingredients)."

In order to grasp the powerful contraceptive efficacy of Depo-Provera ®, an understanding of the female menstrual cycle is essential. The menstrual cycle can be divided into three phases: follicular phase, luteal phase, and menstrual phase (Welt, 2009). The follicular phase is a time during which the ovaries contain a group of follicles that are maturing, with only one eventually gaining full maturation and becoming the egg that is released at ovulation (Welt, 2009). At the end of the follicular phase, just before the luteal phase, there is a surge of follicle stimulation hormone (FSH) and luteinizing hormone (LH), both of which are anterior pituitary hormones, and estradiol, an ovarian hormone (Welt, 2009). Ovulation occurs during the surge of LH and FSH (Welt, 2009). Estradiol levels then decline, and progesterone remains elevated throughout the rest of the luteal phase (Welt, 2009). When estradiol and progesterone levels are low, such as during the very early follicular phase, this signals the hypothalamus to release gonadotropin releasing hormone (GnRH) which signals the anterior pituitary to release FSH and LH (Welt, 2009). When progesterone is elevated, such as during the luteal phase, pregnancy, or with the use of Depo-Provera ®, the signal to the hypothalamus to produce more GnRH is “turned off” and the female does not ovulate (Welt, 2009). Without an ovulated mature egg, fertilization and pregnancy cannot occur.
Through progesterone-induced suppression of GnRH (Depo-Provera induced), the body mimics pregnancy and is in the luteal phase for an extended period of time. This results in a decrease of estradiol, essentially forcing the body into a hypoestrogen state. Pfizer acknowledges in their warning that Depo-Provera is associated with reduced serum estrogen levels (Urbanski, 2004). In summary, Depo-Provera, works in 3 ways: inhibiting GnRH secretion, which in turn inhibits ovulation, and then ultimately causing the endometrial lining to thin (Depo-SubQ Provera 104)

Estrogen is essential to bone development and linked to protection against cardiovascular disease. Pfizer, on the WARNING label of Depo-Provera states:

Use of Depo-Provera Contraceptive Injection reduces serum estrogen levels and is associated with significant loss of BMD as bone metabolism accommodates to a lower estrogen level.

Mendelsohn and Karas, in their review "The Protective Effects of Estrogen on the Cardiovascular System" collected data that supports the hypothesis that estrogen is largely responsible for vasodilatation in blood vessels (Mendelsohn & Karas, 1999). Menopause, a natural hypoestrogen state, is associated with a higher risk for cardiovascular disease. Mendelsohn and Karas's review also collected data to support the protective role of estrogen in lipid metabolism. 17β-estradiol has antioxidant properties which could be protective against the development of oxidized low density lipo proteins (LDL) (Mendelsohn & Karas, 1999). Development of oxidized LDL can lead to atherosclerotic plaques (Mendelsohn & Karas, 1999). One of the contraindications to Depo-Provera use is: “Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease” (A. s. o. P. C. Pharmacia &
Upjohn Company, 2004). The use of Depo-Provera®, could potentially negate the suppression of oxidized LDL's, placing someone at higher risk of developing a thromboembolic disorder through development of atherosclerotic plaques.

In summary, the menstrual cycle is a complex system of several hormones working together. Since the hormones of the menstrual cycle may have roles in the body that have not been fully researched or are yet to be discovered (e.g., role of estrogen in metabolism), it is reasonable to speculate that the forced hypoestrogen state induced by Depo Provera may be harmful to certain aspects of a female's health.

The manufacturers state in their black box warning that Depo-Provera should “…be used as a long term birth control method (e.g., longer than 2 years) only if other birth control methods are inadequate.” (A. s. o. P. C. Pharmacia & Upjohn Company, 2004). However, given the efficacy of this drug as a contraceptive and the relative convenience of administration every 3 months, this may be a popular choice among many reproductive aged females. The black box warning also states that it is currently not known whether or not Depo-Provera places females at a higher risk for osteoporosis and fractures (A. s. o. P. C. Pharmacia & Upjohn Company, 2004).

The Centers for Disease Control and Prevention released a report in 2005 in which they surveyed women aged 15-44 nationwide. Their data show that as of 2002 42% of all women surveyed had used Depo-Provera ® (Chandra, Martinez, Mosher, Abma, & Jones, 2005) and that 72.3% of the women they surveyed stopped using this contraception as a result of side effects (Chandra, et al., 2005). With the hypoestrogenic effects that Depo-Provera imposes on the body (A. s. o. P. C. Pharmacia & Upjohn Company, 2004), research is focused on the physiological outcomes associated
with its use. With the number of people using Depo-Provera®, healthcare providers need to be empowered with knowledge on Depo-Provera and the research that supports or negates not only the black box warnings, but the use of this contraceptive among a diverse patient population.
Bone Mineral Density

“...osteoporosis is a pediatric disease with geriatric consequences” (Nelson, 2010) So one can imagine the importance of bone health during adolescence and young adulthood. Osteoporosis, which is related to low baseline bone mass (Raisz, 2008) is associated with increased risk of fractures. Excessive bone resorption is a contributing factor in the pathophysiology leading to osteoporosis (Raisz, 2008). During a female’s reproductive years, estrogen (estradiol), provides a protective role against excessive bone resorption (i.e., helps to maintain balance between osteoclasts and osteoblasts and therefore helps to keep osteoporosis risk at a minimum (Raisz, 2008). The start of menopause is associated with a drop in BMD, as a consequence of loss of estrogen. Without estrogen, osteoclast activity increases without a subsequent increase in osteoblast activity. This imbalance leads to more bone resorption than bone deposition. BMD can be measured via dual energy x-ray absorptiometry, DXA scan, the results of which are presented as a T-score or Z-score (Goldman, 2008).

The T-score is the number of SD’s below or above which the patient’s BMD differs from peak bone density of an individual of the same gender and ethnicity.
The Z-score is the number of SD’s by which the patient’s bone density differs from that of an individual matched for age, gender and ethnicity.(Goldman, 2008).

Depo-Provera, by inducing a hypoestrogen state, could be hypothesized to essentially deny the body those protective osseous effects. Several researchers have been concerned with the hypoestrogenic effect of Depo-Provera with regard to bone
mass accrual and subsequent osteoporosis. Luckily for pre-menopausal females, regular menstrual cycles are indicators that their endocrine system is functioning properly, and that endogenous estrogen is present. (Nelson, 2010). With regards to bone health, data supports estrogen’s beneficial role. Health care practitioners should always ask about a female’s menstrual cycle, and to regard it as a vital sign. Signs of irregular menstrual cycles, particularly ammenorhea, could be signs of estrogen deficiency, and in turn could be signs of risk to bone health. “Women who had the onset of menstrual irregularity before the age of 20 years were nearly 3 times as likely to have BMD below normal for their age compared to women who had onset after 20” (Nelson, 2010). This excerpt from Nelson’s paper stresses that adolescence is a crucial time for bone formation, and that a hypoestrogen state in adolescence is a serious concern. A study by Sabatier focused on trying to find a time at which peak bone mass is achieved in women. In this longitudinal study, Sabatier et al., provide data to support that bone mineral density (BMD) peaked six months before the first menstrual period and that bone mineral content (BMC) peaked seven months before the first menstrual period. This is not to say a female has reached her maximum BMD and/or BMC, because in this longitudinal study, the data shows that 46.7% of BMC is reached 5 years after the first menstrual period, and with the greatest accumulation being within the first 2.5 years after menarche (Sabatier, Guaydier-Souquieres, Benmalek, & Marcelli, 1999).

While Sabetier et al, did not conduct research directly related to Depo-Provera®, these findings are informative to health care providers. The Sabetier study was able to follow 646 females ages 10-24 as well as 407 females ages 27-47. This allowed for a spectrum of physiological/ menstrual ages, essentially helping to build a timeline of
bone accrual relative to menstruation. This knowledge can assist health care providers in determining regimens, whether contraceptive, nutritional, or related to physical activity, to essentially augment periods of greatest bone accrual. At the same time, studies that show times of greatest bone loss would be essential too, so health care providers can take extra precautions not to expedite the bone loss process any further during those years (Sabatier, et al., 1999). With respect to Depo-Provera, this knowledge could lead to different prescribing methods for different post-menarchal years.

Given Depo-Provera’s black box warning regarding bone health, several studies are focused on bone loss and Depo-Provera. In the package insert, Pfizer cites studies that show adolescents using Depo-Provera had BMD loss while on Depo-Provera® and two years after discontinuing use (Urbanski, 2004). During a similar time period, adolescents not using Depo-Provera® continued to show gains in BMD.

Similar to the United states black box warning, the regulating organization of the United Kingdom advises patients not to use Depo-Provera® for more than two years (Beksinska, Kleinschmidt, Smit, Farley, & Rees, 2009). Interestingly, Bekinska and colleagues cite literature showing the discontinuation rate among DMPA users is very high. They cite data that states that “…continuation rates as low as 27% at 1 year have been found in the United States”(Beksinska, et al., 2009). Many studies on Depo-Provera® unfortunately have this problem of high rate of discontinuation due to adverse side effects, and as a result they are left with a small sample size. Bekinska and colleagues collected data from a cross sectional study focusing on 100 females of an average age of twenty-two (range of ages 19-24). The 100 females were selected from
a larger, 5 year longitudinal study in South Africa. The cross sectional study collected data between October 2005 and February 2006 (the original study collected data between July 2000- April 2006) (Beksinska, et al., 2009). Bekinska et al., divided the subjects into those who only used an injectable contraceptive (Norethisterone enanthante [NET-EN] or Depo-Provera® [DMPA]), those who used a combined oral contraceptive (COC) and an injectable, and those who did not use hormonal contraception. The data shows that measurements taken at the spine, hip and femoral neck among these three groups were significantly different between the injectable contraceptive group and the group that did not use hormonal contraception(Beksinska, et al., 2009). Between the mixed users (i.e., injectable contraceptive and combined oral contraception) there was no significant difference at any of the three sites, although in general, BMD was lower in the mixed users (Beksinska, et al., 2009).

Bekinska’s findings, while certainly supportive of several studies reporting BMD loss with Depo-Provera, are not without weakness, because of the small sample size. With regard to the subjects that were grouped in the combined oral and injectable contraceptive group, the paper did not address the length of time the patient spent on either contraception, and it was not clear why they were on a combination of both. The comparisons also did not seem very balanced. The injectable users had a sample size of 40, 14 of whom were using NET-EN, 19 of whom were using DMPA, and 17 of whom were using NET-EN and DMPA. In the mixed contraceptive group COC and NET-EN use consisted of 7, COC and DMPA use consisted of 3 and COC & NET-EN and DMPA use consisted of 3. This is a major limitation to the paper because there was no real way of identifying the role of any one method of contraception. Since the data collected
and analyzed was reported as averages, how is one to know whether the NET-EN and DMPA which consisted of 17 users, was enough to make the data statistically different for BMD loss (Beksinska, et al., 2009)?

In a Pfizer supported study 535 subjects, ages 18-35, were followed. 267 were randomly assigned to the DMPA-subQ group and 268 to the DMPA-IM group. Subcutaneous injection of Depo-Provera is administered at a lower dose, 104 mg, compared to its intramuscular counterpart, which is administered at 150 mg (Kaunitz, Darney, Ross, Wolter, & Speroff, 2009) Also, the subcutaneous form is absorbed more slowly than the intramuscular form (Kaunitz, et al., 2009)

When subcutaneous Depo-Provera® is compared with intramuscular Depo-Provera® the data shows that both formulations result in decreased BMD. However, within year one and two, greater bone loss was seen with the intramuscular formulation, though none of the differences were statistically different between the two formulations (Kaunitz, et al., 2009). At the end of year one, there was a significant difference between BMD loss at the lumbar spine, with the intramuscular formulation having significantly more loss than the subcutaneous formulation (Kaunitz, et al., 2009). At the end of the Pfizer study, 8.1% of the subQ group at some point had T-scores that fell below -1.0 at the hip and 5.6% of the IM group had T-scores that fell below -1.0 at the hip at some point during the study. 14.5% of SubQ patients had T-scores that fell below -1.0 at the spine 2% of the IM subjects had T-Scores that fell below -1.0 at the spine (Kaunitz, et al., 2009). A T-score less than -1.0 is considered osteopenia and <-2.5 is clinically considered osteoporosis (Johnson, et al., 2008).
As far as comparing efficacy, during the study none of the SubQ participants became pregnant, while one of the IM subjects became pregnant (Kaunitz, et al., 2009). As far as adverse side effects, increased weight gain was the complaint most commonly given for discontinuation of both formulations. However, while more IM subjects discontinued the study as a result of adverse side effects, statistically there was no significant difference among the groups in weight gain or irregular bleeding patterns (Kaunitz, et al., 2009). An adverse effect that is of great concern with BMD loss is fracture, and three DMPA-SubQ subjects and one IM subject had a fracture, but none of these subjects were classified as having osteoporosis (Kaunitz, et al., 2009). The researchers fail to acknowledge the events leading to the fracture (Kaunitz, et al., 2009).

The data from this study is beneficial to health care providers because it shows that majority of BMD loss is during the first two years in both SubQ and IM, but that SubQ has a slower onset of loss and slower decline of BMD in the first two years. This could help determine how health care providers prescribe Depo-Provera. For instance, if prescribing to young adolescents, it may be wise to administer SubQ because it has lower bone loss associated with it in the first 2 years, and could therefore preserve baseline bone mass and protect against future osteoporosis (Kaunitz, et al., 2009).

Depo-Provera® is only one form of a progesterone contraceptive. There are several others and there are combination oral contraceptives that contain estrogen and progesterone. Studies are showing that exogenous progesterone maybe harmful to the skeletal system regardless of what form they are given. Cromer and colleagues examine the use of low dose estrogen in combination oral contraceptive pills. Their concern is that clinicians are placing females on low dose combination oral
contraceptives in an effort to avoid side effects typically associated with estrogen, such as thrombosis. In adolescents, the risk of thrombosis is minimal (Cromer, et al., 2008). Cromer and colleagues are more concerned that while attempting to avoid thrombosis, low dose combination contraceptive pills are continuing to place females at risk for bone loss (Cromer, et al., 2008). The risk that Cromer and colleagues find concerning is whether the low dose estrogen in this combination pill is enough estrogen to counteract the negative effects that levonorgestrel, a derivative of progesterone, has on osseous accrual (Cromer, et al., 2008). In their study they compared BMD in females ages twelve to eighteen who selected either Depo-Provera, combined oral contraceptive, or a non-hormonal contraceptive as a contraceptive method. Baseline measurements for the following categories were taken: chronological age, gynecologic age, body weight, spine BMD, femoral neck BMD, regular menses, smokers, and physical activity (Cromer et al., 2008). Within these categories the control group/ non-hormonal contraceptive group had 188 subject and had a statistically significant percentage of subjects with the highest physical activity, and significantly the lowest number of participants who were smokers. Whereas Depo-Provera® group, with 58 subjects, had a significant percentage of smokers. Oral contraceptive users with 187 subjects, had the oldest chronological aged participants and gynecological aged participants, as well as the highest weight participants (Cromer et al., 2008). The demographics of subjects with in each group are important to view, since certain lifestyles may lend themselves to choosing different forms of contraception, and to different risks thereof.

The Cromer study gave the subjects that voluntarily chose combined oral contraceptive the lowest dose of estrogen in a combination pill (i.e., 20 micro gram of
ethinyl estradiol E2 and 100 micrograms of levonorgestrel. The Depo-Provera users were given the standard 150 mg IM dose. In this study, there was a high compliance rate among Depo-Provera® users, reflecting Depo-Provera’s® ease of use. Higher compliance is potentially another contributing reason behind its powerful contraceptive efficacy. Bone mineral density measurements were taken prior to starting the study, and at 6 month intervals during the study (Cromer, et al., 2008). At the end of year one, all the participants except the Depo-Provera participants showed mean percent increases at the spine and femoral neck, with the Depo-Provera participants showing mean percent decreases at both sites that were significant. At the end of the study (twenty-four months) there was a mean of loss of 5.2% BMD at the femoral neck and a mean loss of 1.5 % at the lumbar spine among the Depo-Provera participants. In order to determine when the greatest amount of BMD loss occurs, measurements were taken at the end of year one, and they showed that at the spine, Depo-Provera users had lost 1.4% BMD, and at the femoral neck they had lost 2.2% (Cromer, et al., 2008). The study then measured the total BMD loss from baseline at the end of the 24 months, and showed that 1.5% BMD loss was seen at the spine, and 5.2% at the femoral neck among Depo-Provera users (Cromer, et al., 2008). This data shows that spine had the greatest BMD loss at the end of year one, where as the femoral neck continued to have significant losses (Cromer, et al., 2008).

Cromer and colleagues hypothesis was not supported in this study as participants in both groups, combined oral contraceptive as well as non-hormonal contraceptives, continued to have significant BMD gains at the femoral neck and spine (Cromer, et al., 2008).
Cromer and colleagues provide compelling data for any clinician prescribing Depo-Provera® to an adolescent. Their data shows that between age twelve and age eighteen there is continued bone mineral density accrual. One variable that should be accounted for in the Cromer study is that the participants in the non-hormonal contraceptive group and the combined oral contraceptive, were significantly young in chronological and gynecological age (Cromer, et al., 2008). This variable, age, is of importance because, studies have supported that there is little increase in BMD around the 7th to 8th post-menarche years (Sabatier, et al., 1999). Depo-Provera® may have had significant losses associated with participants due to their being older in age.

In a prospective seven and a half year study (five years of treatment and two and a half year follow-up) published in 2008, Johnson and colleagues sought to examine BMD, and urine and serum markers indicative of increased bone resorption among females 11-18 years old who were using Depo-Provera® or non hormonal contraception. Serum and urine markers were collected at 6 months, 15 months, 21 months, 36 months, 45 months, 51 months, and 60 months, as well as at 75 months and 90 months.

Unlike the majority of study findings on BMD and Depo-Provera® use, the study by Johnson et al found that subjects using Depo-Provera® had higher BMD than subjects in the non-hormonal contraceptive group upon completion of the study (Johnson, et al., 2008). The non-hormonal contraceptive group also had higher serum and urine markers indicating increased bone resorption (Johnson, et al., 2008). This study had a total of 389 participants all of whom selected their own method of contraception. 169 selected Depo-Provera® and 220 selected non-hormonal
contraceptive (Johnson, et al., 2008). DMPA users tended to have higher baseline BMD and were also older in age, both chronological and gynecological (Johnson, et al., 2008). While the findings in this study are not supportive of the Depo-Provera black box warning issued with respect to bone health, the findings were noteworthy supporting that perhaps different body types may fare well using Depo-Provera and not suffer from BMD loss.

The majority of participants who chose Depo-Provera® in Johnson’s study were African Americans, and were older. Baseline measurements were different among the non-hormonal contraceptive group and the Depo-Provera® group. Johnson and colleagues cite studies with data supporting that African Americans accrue their bone mass earlier than non-African American population (Johnson, et al., 2008). A total of 9 participants had had baseline T-scores, as measured at the lumbar spine, less than -2.5, which is considered osteoporosis. Of these 9, 8 were participants in the non-hormonal contraceptive group and one was a participant in the Depo-Provera® group (Johnson, et al., 2008). The participants in the Depo-Provera® group had significantly higher number of smokers (current or past), alcohol users, and number of participants who had one or more pregnancies (Johnson, et al., 2008). This study does not necessarily provide the best data, as they had participants with osteoporosis participate, but it can provide clinicians with comfort knowing that African-Americans accrue bone mass earlier and maybe at lower risk for losing significant BMD through Depo Provera use.

In another study, Rosenberg and colleagues specifically looked at calcaneus bone mineral density in females after discontinuation of Depo-Provera® or
norethisterone enanthate, grouping these together as injectable progestin contraceptive IPC (Rosenberg, et al., 2007). However, in their study the results are specifically divided to represent the effects of Depo-Provera ® singly, and norethisterone enathate separately as well (Rosenberg, et al., 2007). 3,544 women were included in this study, of which 1,592 subjects were black and the remainder were of “mixed race” (Rosenberg, et al., 2007). The females using IPC in this study were younger in age and had more years of education compared to non IPC users, they also had higher BMI’s (body mass index) and were more likely to smoke (Rosenberg, et al., 2007). Physiologically, these females also tended to have started their periods later (Rosenberg, et al., 2007).

The study investigators not only looked at current users and non-users of injectable progesterone contraceptives, but they also looked at subjects who had ever used injectable progesterone contraceptives. The calcaneus was measured via broadband ultrasound, speed of sound and quantitative ultrasound index. All of the measurements for current injectable progesterone contraceptive users were lower than those of non-users and those who had discontinued injectable progesterone contraceptive use for two years or more (Rosenberg, et al., 2007). Those who had discontinued use of an injectable progesterone contraceptive for two years or more had calcaneus measurements comparable to those who had never used an injectable progesterone contraceptive (Rosenberg, et al., 2007). However while calcaneus measurements after 2 or more years of discontinuing injectable progesterone contraceptive are comparable to those who had never used an injectable progesterone contraceptive, Rosenberg et al cite a study done in 2005 where females who
discontinued using Depo-Provera® never re-achieved baseline measures for bone mineral density at the hip. Among injectable progesterone contraceptive users it did not make a difference if they were Depo-Provera® users or NET users, or how long they have been using the injectable progesterone contraceptive (Rosenberg, et al., 2007). There were also no significant findings for increased bone loss if person had begun using an injectable progesterone contraceptive at a younger age (Rosenberg, et al., 2007).

These findings from Rosenberg et al., are compelling data for clinicians who want to continuing prescribing Depo-Provera®. The calcaneus, while it may be a good prognostic indicator of overall bone health, is probably less important to look at than bone mineral density at the lumbar spine and femoral head. According to the CDC, the spine and hip fractures are among the most common injuries associated with falls (CDC).

In a seven year study, five years of treatment and two years follow up, women aged twenty five to thirty five were followed to make comparisons among Depo-Provera® users versus non users (Kaunitz, Miller, Rice, Ross, & McClung, 2006). The measurements made in this study of bone mineral density were using dual energy x-ray absorptiometry (DEXA). Kaunitz and colleagues collected data on 608 subjects, the majority of whom were white. When the study began, 248 participants were Depo-Provera® users. Only seventeen percent of those 248 completed the full length of treatment. Several subjects in both the non-hormonal treatment and the Depo-Provera® group were lost to follow up. Of the participants that remained in the study, significant changes in bone mineral density from baseline were found at the hip and lumbar spine.
for the Depo-Provera® users. Minimal deviations from baseline were observed among nonusers. BMD change at the lumbar spine in the Depo-Provera ® users was -5.16% at the hip and -5.38% at the lumbar spine, with the greatest loss seen within the first year of use. At the end of six months, Depo-Provera users were showing a -0.7% change from baseline, with nonusers showing +0.6% change from baseline. At the end of two years Depo-Provera users had continued to lose BMD with a -3.1% change from baseline, where non-users had a +0.6% change from baseline. At the end of the follow up period, Depo-Provera users still had not achieved baseline values at total hip measures. They continued to have -0.2% change from baseline (Kaunitz, et al., 2006).

Lumbar spine findings also showed significant deviations from baseline among Depo-Provera® users. At the end of six months, Depo-Provera® users showed -1.4% deviation from baseline. In the two years of follow up after cessation of treatment, the Depo-Provera users did not regain baseline measures at the lumbar spine, with a BMD measure -1.2% from baseline. The percent changes at the femoral neck at the end of the treatment were -6.1% among Depo-Provera users and -0.3% among non-hormonal contraceptive users. At the end of the two year follow up after discontinuing Depo Provera, the Depo-Provera users continued to have greater loss from baseline, -3.1%, and the non-users had a -0.4% change from baseline. The Depo-Provera users had the greatest deviation from baseline at the end of treatment for the femoral trochanter BMD, with a deviation of -6.3%, while non-users had + 0.3% from baseline at the trochanter (Kaunitz, et al., 2006).

Some other important findings in the Kaunitz’s study are the measurement of estradiol levels. There was a decrease in estradiol levels among Depo-Provera® users
from baseline which then returned to baseline in the two year follow up time. Also important in the study was that none of the Depo-Provera subjects became pregnant (Kaunitz, et al., 2006). This study was funded by Pfizer and they conclude in their discussion that while Depo-Provera does have side effects, you should weigh the side effects against the risk of becoming pregnant (Kaunitz, et al., 2006).

A study done in 2010 by Rahman and colleagues supports continued use of Depo-Provera®. The researchers in this study evaluated risk factors that may place Depo-Provera® users at higher risk for BMD loss (Rahman & Berenson). In their study they found that risk factors such as smoking, low calcium intake and nulliparity were all associated with greater loss of BMD (Rahman & Berenson). They also found that those who had lost the most BMD tended to be younger and were more likely to have recently started using DMPA (Rahman & Berenson). This study doesn’t offer much in regards to factors contributing to BMD while using DMPA, it is however a helpful reminder that the use of Depo-Provera® should be taken seriously and that a good social history should be obtained, to better assess a patient’s overall risk for BMD loss.
Metabolic

The effects of bone mineral density are not the only adverse effects associated with the use of Depo-Provera®. Many of the studies cited in this paper have large dropout rates due to the metabolic effects of Depo-Provera®. The Depo-Provera® drug label shows that women who were on Depo-Provera® for 2 years had an average weight gain of 8.1 lbs. The drug label also cautions using this product in diabetics because of insulin resistance associated with use (D. o. P. I. Pharmacia & Upjohn Company, 2005). In 2010 Bekinska and colleagues evaluated weight change in adolescents using DMPA, NET-EN, COC’s and those who were not using any contraceptive. They followed 15-19 year old females for 4-5 years (depending on what year they were recruited the follow up schedule differed) (Beksinska, Smit, Kleinschmidt, Milford, & Farley, 2010). In their study, they classified weight gain or weight loss as any increase or decrease of 2kg respectively (Beksinska, et al., 2010). The study included 490 females. Baseline measurements as well as demographic information were collected and then followed up on every 6 months (Beksinska, et al., 2010). At the 6 month follow up subjects were asked about matters concerning contraceptive use, (i.e., have they switched their choice of contraception and why), as well any changes in diet and nutrition, as well being weighed in at each visit (Beksinska, et al., 2010). Subjects also had BMD data collected as part of a study assessing the effects of injectable contraceptives on BMD (Beksinska, et al., 2010). Only 42% of subjects completed the 4-5 year follow up, and of those 42% the number that used Depo-Provera® was much too small to be analyzed alone. Thus subjects using Depo-Provera or NET-EN were grouped as one group, that being injectable contraceptive
group (Beksinska, et al., 2010). The other subjects were divided into combined oral contraceptive users, non users and discontinuers (Beksinska, et al., 2010). In this study, 50 subjects withdrew from the study, 45 of whom had used an injectable contraceptive (Beksinska, et al., 2010).

The only significant difference in characteristic of subjects was the degree of education, with combined users having the highest level of education (Beksinska, et al., 2010). Study results found that the subjects using injectable contraceptives had significantly greater weight gain (6.2 kg=12.4 lbs), and within the IC group those using Depo-Provera®, had the greatest amount of weight gain (7.2 kg= 14.4 lbs) (Beksinska, et al., 2010). A limitation to this study would certainly be sample size, as the researchers themselves admit.

Obesity, particularly central body fat, is associated with adverse health. Persons with abdominal fat are at higher risk for developing metabolic syndrome (Meigs, 2010) & Berenson 2009). Metabolic syndrome can lead to cardiovascular health complications, as well as endocrine complications (i.e., type II diabetes mellitus) (Meigs, 2010 & Berenson & Rahman, 2009). Berenson and colleagues found that subjects taking DMPA gained significantly more weight, body fat, percent body fat and central-to peripheral ratio of body fat when compared to oral contraceptive users and non-hormonal contraceptive users (Berenson & Rahman, 2009). The study conducted by Berenson and colleagues looked at a total of 703 females, with a roughly equal distribution of black, white and Hispanic females (Berenson & Rahman, 2009). The study, which was conducted for 3 years, found that DMPA users gained on average 5.1 kg, with the most weight gain occurring in the first 18 months (Berenson & Rahman,
One of the major reasons for discontinuation of DMPA was the weight gain. In this study several subjects that discontinued DMPA and switched to an oral contraceptive continued to gain an average of 0.43 kg every 6 months, while those who opted for non-hormonal contraceptive lost approximately 0.42 kg every 6 months (Berenson & Rahman, 2009). Clinicians should be made aware of this finding as it could be a crucial determinant to what hormonal contraception to prescribe. Based on findings by Bereson and colleagues, subjects who switched from DMPA to an oral contraception continued to gain weight while those who used non-hormonal contraception lost weight. A patient who presents with a complaint of weight gain, and desires to discontinue Depo-Provera®, should be made aware that they may have continued weight gain with oral contraceptives, based on Berson’s study. In the United Kingdom patients are advised to use DMPA no longer than 2 years. If the United States follows this example, clinicians in the U.S. will have to be creative in implementing effective contraceptive regimens without the unwanted weight gain. Another concern is compliance. Berenson and colleagues found that adherence/compliance decreased among those who gained >5% total body fat within 6 months (Berenson & Rahman, 2009). This also presents another complication, especially for patients who do not wish to become pregnant.

Body fat increased by 4.1 kg, a 3.4% in percent body fat in the 3 year study (Berenson & Rahman, 2009). The analyses conducted by these researchers leads them to believe that “…women who were not obese at the start of the study were twice as likely to become obese over the next 3 years” (Berenson & Rahman, 2009). Many of the metabolic changes that occur when a female is taking Depo-Provera are not
substantially different than the physical changes that take place during menopause. Another interesting finding in Berenson’s study was that of the three groups of contraceptive use, DMPA, COC, and NHC, only the DMPA users were at increased risk of having a BMI level that would be defined as obesity (i.e., >30) (Berenson & Rahman, 2009). Another variable that complicates this scenario is that within the Depo-Provera group, being white, black, or Hispanic affected weight gain, as did baseline measurements of obesity. Overall, obese women gained significantly less weight than non-obese among white females (Berenson & Rahman, 2009). This trend was seen among Hispanics as well, although the findings were not significant. Black females however did not exhibit such a trend (Berenson & Rahman, 2009). While the data presented in this paper is not comforting for patients who want an effective contraceptive without the weight gain, during follow up visits patients were asked about diet, and those who consumed the most protein were less likely to have increased weight gain (Berenson & Rahman, 2009).

Contrary to Berenson’s findings, Bonny and colleagues cite a study showing increase in fat among black adolescents using DMPA compared to white adolescents. They admit that a limitation to this study is not having a control group to measure and see whether there are differences between non-Depo-Provera ® users in these two racial groups (Bonny, Secic, & Cromer, 2009). Bonny and colleagues wanted to examine the changes in body fat among adolescents receiving hormonal contraception. A difficult aspect in the study of adolescents is determining how much weight gain is attributable to normal growth. This study offered a novel twist, aside from solely comparing DMPA vs COC vs NHC. The researchers went one step further and
administered DMPA plus 5mg of estrogen or DMPA plus 5mg of a placebo (Bonny, et al., 2009). Much like Berenson’s findings the DMPA subjects had increased weight and increased body fat. However, the novel twist of combining estrogen resulted in the DMPA plus estrogen subjects having a decreased amount of weight gain as well as a decreased amount of increased total body fat (Bonny, et al., 2009). Another variable that Bonny and colleagues failed to address was the issue of contraception. While the effects of Depo-Provera® on weight and metabolism are certainly not favorable in a society that admires slender females, it maybe the best choice of contraception in a female who desires potent hormonal contraception.

Mangan and colleagues created a study aimed to see if being overweight was associated with increased weight gain while on DMPA. Their results showed that the participants using DMPA gained significantly more weight than those using an oral contraceptive pill (Mangan, Larsen, & Hudson, 2002). A BMI greater than the 85th percentile was classified as overweight, and those participants who were overweight and on DMPA showed significant weight gain compared to those using DMPA that were not overweight (Mangan, et al., 2002).

The issue of weight gain and factors that predispose to increased weight gain is somewhat controversial. A literature review of nine articles, done by Curtis and colleagues, found that among adult females there is no difference in weight gain when using a progesterone only contraceptive (Curtis, Ravi, & Gaffield, 2009). However, in reviewing the 3 studies conducted on adolescents, they concluded that obesity is a predisposing factor for increased weight gain when on a progesterone only contraceptive (Curtis, et al., 2009). This correlates with the findings of Bonny and
colleagues as well as Mangan et al., but contradicts the findings of Berenson and colleagues.
Cardiovascular

Generally, males are at a higher risk for cardiovascular disease compared to pre-menopausal females. After menopause a female's risk for cardiovascular disease increases. The increased risk for cardiovascular disease has been attributed to decreased estrogen, as the risk of cardiovascular disease decreases in women using estrogen replacement therapy at the start of menopause (Mendelsohn & Karas, 1999). Estrogen offers a protective effect to the cardiovascular system (Mendelsohn & Karas, 1999) The role of estrogen in cardiovascular health is dynamic. Estrogen has protective roles with respect to cholesterol, it has been shown to decrease low density lipoprotein and increase high density lipoprotein (Mendelsohn & Karas, 1999). Estrogen has been shown to have vasodilatory effects on blood vessels (Mendelsohn & Karas, 1999). The theory behind estrogen’s vascular protection is believed to be due to receptors directly on blood vessels, and these receptors are present in males and females (the receptors are found in the endothelial and smooth muscle cells of blood vessels) (Mendelsohn & Karas, 1999). People who lack these receptors, or have fewer receptors were shown to develop atherosclerosis at a younger age (Mendelsohn & Karas, 1999). When estrogen binds to one of these receptors it causes vasodilatation and release of nitric oxide immediately (Mendelsohn & Karas, 1999). Estrogen can only prevent the damage from occurring, not repair damage already present. However, estrogens effects are not all beneficial to the cardiovascular system. Estrogen has been shown to decrease factors crucial to preventing coagulation (Mendelsohn & Karas, 1999).

Selecting a contraceptive with a focus on cardiovascular health can be challenging, as estrogen has both protective and harmful effects on cardiovascular
health, i.e., vasodilatory effects and increased tendency to coagulation, respectively (Mendelsohn & Karas, 1999). Patients with history positive for deep vein thrombosis or any blood clot are encouraged to avoid contraceptives containing estrogen, and are generally started on a progesterone only contraceptive (Lizarelli, et al., 2009). Interestingly, a contraindication to the use of Depo-Provera® is a prior history of DVT’s. Progesterone only contraceptives such as DMPA create a hypoestrogenic effect. Given estrogen’s protective role on blood vessels it would be prudent for clinicians to ask themselves if they are forgetting about a crucial component to developing thrombosis; Virchow’s triad. Virchow’s triad are three risk factors that contribute to thrombosis: stasis, damage, and coagulability of blood (Lizarelli, et al., 2009). Estrogen may contribute to decreased vessel damage, thereby potentially eliminating one of the risk factors of Virchow’s triad. DVT patients however are urged to avoid estrogen-containing contraceptives. Given the mechanism of action of DMPA i.e., creating a hypoestrogenic effect in the body, research regarding DMPA’s affect on the cardiovascular system is crucial, especially if the medication is going to be used as an alternative for a patient at risk for cardiovascular disease. Lizarelli and colleagues evaluated DMPA’s damage to blood vessels via flow-mediated dilation (FMD). FMD measures endothelial function (Lizarelli, et al., 2009). The endothelial cells as well as the smooth muscles are believed to have the alpha receptors which bind to estrogen and cause vasodilatation (Mendelsohn & Karas, 1999). Their study looked at 100 females with demographics that were very similar due to their stringent inclusion and exclusion criteria. The female subjects all had a BMI <30, as obesity was included among the exclusion criteria (Lizarelli, et al., 2009). Patients could not be taking anti-inflammatory medications or
over the counter medications of any kind during data collection, as the researchers feared any exogenous substance could potentially skew results (Lizarelli, et al., 2009). Data was always collected after an overnight fast, and, depending on the contraceptive used, data was collected at specified times to correlate with the follicular phase (i.e., when estrogen is highest) of the menstrual cycle (Lizarelli, et al., 2009). Data was collected on days 14-21, the point at which COC’s had reached a peak concentration within the body (Lizarelli, et al., 2009). For DMPA users, data was collected a week to two weeks after administration of the contraceptive (Lizarelli, et al., 2009). The procedure for data collection was systematic, starting with blood pressure measurements, followed by ultrasound measurements, and finally serum blood measurements (Lizarelli, et al., 2009). Comparisons were made among non hormonal contraceptive users, combined oral contraceptive users and DMPA users (Lizarelli 2009). The data showed significant differences in FMD among DMPA users and non-hormonal contraceptive users as well as COC users and non-hormonal contraceptive users. Between the two hormonal contraceptive groups there was no significant difference in FMD (Lizarelli 2009). DMPA users also had lower total cholesterol as well as lower low density lipoprotein, where as non-hormonal contraceptive users had a higher high density lipoprotein (Lizarelli, et al., 2009).

The data collected regarding FMD show that both DMPA users and COC’s users had significantly lower FMD values compared to non-hormonal contraceptive users. This data supports the use of progesterone only contraceptive in patients at risk for thrombosis, as progesterone contraceptive only induced one of Virchow’s triad risk factor for thrombosis, damage to endothelial cells, with respect to Lizarelli and
colleagues study. Combined oral contraceptives however, with respect to this study, damaged the vessel wall, and produced a hypercoagulable state, fulfilling 2/3 of Virchow’s triad.

Meendering and colleagues investigated the cardiovascular effects of oral medroxy-progesterone acetate (MPA) along with exogenous estrogen (Meendering, Torgrimson, Miller, Kaplan, & Minson, 2008). Their hypothesis was that the androgenic properties of progesterone negate the beneficial properties of estrogen with regard to cardiovascular risk (Meendering, et al., 2008). In their study they evaluated several markers for cardiovascular disease. These included measures of lipids, c-reactive protein, endothelin-1, homocysteine and endothelium-dependent vasodilatation (Meendering, et al., 2008). This well organized research design involved 14 females, all of whom were started with gonadotropin releasing hormone (GnRH), to suppress their body’s natural production of hormones (Meendering, et al., 2008). After 4 days of GnRH treatment, data was collected to measure lipids, cardiovascular markers, as well as hormone levels, then 12 females began an estradiol patch of 0.1mg plus GnRH. Two females were used as a control and continued with only GnRH for the remainder of the study (Meendering, et al., 2008). After 7 days, subjects had the same labs performed again, and now 10 patients began 5mg a day of oral MPA plus the estradiol patch plus GnRH, 2 continued with 0.1mg estradiol patch plus GnRH (Meendering, et al., 2008). Figure 1 will illustrate the study’s division of subjects much more concisely.

The results from Meendering and colleagues support previous literature that suggests that oral progesterone (which may be considered to have properties similar to DMPA) has androgenic effects that are harmful to the cardiovascular system. Their
results showed significantly lower levels of endothelin-1, a potent endogenous vasoconstrictor, in the 10 female subjects during GnRH plus 0.1mg estradiol treatment, compared to GnRH alone and GnRH plus estradiol and MPA (Meendering 2008). Monitoring the change in endothelin-1, (i.e., the response to estradiol), indicates that MPA could perhaps negate the benefits of estradiol. It is important to note that the addition of MPA brought endothelin-1 levels close to the level they were when GnRH was administered alone (no significant difference between endothelin-1 GnRH and endothelin-1 GnRH plus estradiol and MPA) (Meendering, et al., 2008). Dependent vasodilatation was significantly higher during the GnRH plus estradiol phase compared to the GnRH phase and the GnRH plus estradiol and MPA phase (Meendering, et al., 2008). Among the 2 female subjects that had two hormonal phases, GnRH phase and estradiol phase, dependent vasodilatation was higher during the GnRH plus estradiol phase (Meendering, et al., 2008). The control group showed no differences, There were no differences in vasodilatation when NO was administered, demonstrating that arterial health was the same among subjects, and changes in vasodilatation could be attributed to changes in hormonal levels (Meendering, et al., 2008).

The same group of researchers that investigated the effects of MPA + estrogen on cardiovascular markers hypothesized that progesterone’s androgenic effects are so strong that they can be seen in combination oral contraceptives (Meendering, Torgrimson, Miller, Kaplan, & Minson, 2009). Meendering and colleagues believe this to be true, due to continued reports of cardiovascular incidents, despite implementing progesterone along with estrogen (Meendering, et al., 2009). The researchers behind this study speculate that as hormonal contraceptives started decreasing the amount of
estrogen in an effort to decrease rates/risk of venous thrombosis, progesterone began to have an antagonistic effect on the estrogen therapy (Meendering, et al., 2009).

In the study by Meendering and colleagues, 22 females were divided equally, with 11 taking a low dose combined oral contraceptive, and 11 taking a very low dose combined contraceptive. The low dose contraceptive contained 30μg ethinyl estradiol (i.e., estrogen), and 150μg of progesterone. The very low dose contraceptive contained 20μg of estrogen and 150μg of progesterone (Meendering, et al., 2009). The group taking the low dose contraceptive took the 30/150 combination for 3 weeks and then nothing for the 4th week. The group taking very low dose contraceptive combination took the 20/150 combination for 3 weeks and then 10μg of estrogen alone for the 4th week (Meendering, et al., 2009).

Data collection in the Meendering study included measurements of lipids, blood pressure, heart rate, brachial artery images, and most importantly dependent and independent FMD (2009). The dependent FMD values were based on the vessels ability to vasodilate after being put under stress, i.e., a blood pressure cuff, held at 300mmHg for 5 minutes (Meendering, et al., 2009). Whereas, independent vasodilation was based on administration of exogenous nitric oxide. Previous studies have shown that nitric oxide, a potent arterial and venous vasodilator, is released endogenously when estrogen binds to receptors on endothelial cells of blood vessel wall ((Meendering, et al., 2009)&(Mendelsohn & Karas, 1999). If vasodilation is impaired due to already damaged endothelial cells, there will be no vasodilation with exogenous administration of nitric oxide, thus exogenous administration of nitric oxide is the control/independent variable. The results of the Meendering study support their hypothesis, showing that
FMD was highest during the estrogen only phase of the contraceptive among those using the very low dose (Meendering, et al., 2009). In the low dose group, FMD was greatest during the active phase and lower during the pill free-phase (Meendering, et al., 2009). While this study isn’t directly about Depo-Provera it continues to support cardiovascular health concerns with the use of a progesterone contraceptive. This study indicates that if the estrogen is too low it will not be able to overcome the effects of progesterone. Their findings also support estrogen’s role in cholesterol health, as it was shown in the data that LDL levels were greater during the pill free phase, i.e., no estrogen, among low dose users, and HDL levels were lower in during the same phase, in comparison to the estrogen only phase (Meendering, et al., 2009).
Conclusion

The use of hormonal contraception has become ubiquitous. In much the same way that the population at large takes Advil®, Tylenol® and Aspirin without questioning adverse effects, providers and patients use hormonal contraception. The studies in this paper support that hormonal contraception is a medical decision with long term consequences that should be taken seriously.

The data presented in the above chapters should guide clinicians to conversations they should be having with their patients before initiating Depo-Provera®, and while continuing the prescription. The advantage of using Depo-Provera®, in addition to its potent contraceptive benefit, is that it lends itself to continued patient care, since the patient must visit the provider every 3 months for continued injections. The downside to Depo-Provera® is that this routine visit can easily be managed by a medical assistant or nurse working in the clinic and thus the patient may not be in medical dialogue with their primary health care provider. A suggestion to clinicians is to optimize each of these visits to evaluate the patient’s mood, appetite change, activity level, weight gain, diet, and overall satisfaction with the contraception.

A clinician’s autonomy is directed by a patient’s autonomy, and a patient cannot make an informed decision regarding their health without knowledge. Clinicians should not initiate a therapy unless the patient fully understands the risks and benefits of a treatment and is able to assess the risk to benefit ratio. The data in this paper also guides clinicians to evaluate patient behaviors that may place a patient at higher risk for bone mineral density loss. For example, in the study by Rahman and colleagues, smoking, low calcium intake and nulliparity were all associated with greater loss of BMD
(Rahman & Berenson). Upon initiating Depo-Provera® clinicians should advise all of their patients to begin taking a calcium supplement to counteract potential negative effects on bone strength.

The studies cited in this paper suggest that Depo-Provera is manipulating a woman’s hormone levels in a negative manner. The data provided support significant differences between Depo-Provera® users and non-users in the areas of bone, metabolic and cardiovascular health. However, Depo-Provera continues to be an effective form of contraception and if avoiding pregnancy is a patient’s priority then that decision should be respected. Proper education on the risks associated with this medication should be part of all patient encounters related to prescription of Depo Provera®. Depo-Provera’s ® high discontinuation rate might also be avoided if patients are educated appropriately on what they should expect upon initiating this medication.

Ultimately Depo-Provera® is a potent contraceptive with consequences. The research is ongoing to assess the long term risks associated with this contraceptive. In the meantime, healthcare providers should follow the black box warning and not use this contraception for longer than 2 years, working with the patient to choose an acceptable alternative once the 2 years are up.
References


Fig 1: Illustration of the division of subjects in the Meendering 2008 study
Abstract

**Objective:** The objective of this literature review is to examine the risks associated with Depo-Provera®, depo-medroxy progesterone acetate. This potent, progesterone only contraceptive, produces a hypoestrogenic effect in the body, and the effects of which are still being examined. This paper focuses on the role of estrogen as a protective factor with respect to osseous health, metabolic health, and cardiovascular health. The paper will examine health consequences associated with manipulating levels of estrogen in the body, via a progesterone contraceptive i.e., Depo-Provera®.

**Method:** Databases used: Pubmed, CINAHL, Ohio Link

**Results:** Depo-Provera®, produces a hypoestrogenic effect in the body, and is associated with negative osseous, metabolic and cardiovascular consequences.

**Conclusion:** Continuing research is necessary to establish long term effects of Depo-Provera®. As of present, clinicians should be made aware of the short term risks associated with this contraception, and should inform patients.