Reasons to limit the use of depot medroxyprogesterone acetate in adolescents

Rachelle Drouin

November 15, 2007
Abstract

In recent years, depot medroxyprogesterone acetate, more commonly known as DMPA or Depo-Provera®, has been mired in controversy: a number of clinical studies have shown that long-term use of DMPA, a progesterone-only contraceptive, is known to have deleterious effects on bone mineral density (BMD). Consequently, the United States Food and Drug Administration, on November 17, 2004, issued a black box warning regarding DMPA and its potential impact on bone health, particularly with respect to the adolescent population.

Some may argue that, because adolescent girls tend to use DMPA for short periods of time, bones' exposure to the drug's potentially harmful effects is minimized. However, the findings of studies into long-term use of DMPA are nevertheless relevant: some of these studies even suggest that the effect of DMPA on BMD may be reversed upon both adult women’s and adolescent girls’ discontinuation of the drug. While this may be true, one question remains: did adolescent girls using DMPA achieve the same peak bone mass they would have in the absence of DMPA? Until more is known and because young adolescent girls between 12 and 15 years of age are experiencing the highest levels of bone mass accrual (Cromer et al., 2006, p. 298), use of DMPA by this sub-set of the adolescent population should be limited.

Pharmacologic action of DMPA

Administered as a 150 mg dose every three months, DMPA inhibits the secretion of gonadotropins by the pituitary gland. This, in turn, suppresses follicle-stimulating hormone (FSH), the hormone that stimulates both the development of ovarian follicles and the release of estrogen; and luteinizing hormone (LH), which stimulates ovulation and controls length and
sequence of the menstrual cycle. In the absence of FSH and LH, ovarian production of estrogen is halted, ovulation ceases, and menstrual periods stop (Kass-Wolff, 2001, p. 22).

The appeal of DMPA

Unlike other contraceptive methods that require daily or weekly attention, DMPA is injected intramuscularly every 12 weeks. This convenience appeals to adolescents for whom compliance is an issue. In addition, DMPA is discreet: no one but her doctor need know a woman is using it. There is no evidence of pills, implants, or patches (Cromer et al., 2006, p. 296). Furthermore, DMPA also offers non-contraceptive benefits: because it suppresses the pituitary-ovarian-uterine axis and results in amenorrhea, it is often prescribed to patients with bleeding disorders (e.g., menorrhagia) and to developmentally delayed patients. Amenorrhea offers relief from the difficulties associated with premenstrual symptoms and menstrual hygiene (Kass-Wolff, 2001, p. 26). Furthermore, DMPA has been used to manage dysmenorrhea and endometriosis, and it has also been shown to provide protection against endometrial cancer (Cromer et al., 2006, p. 296).

The relevance of the FDA's black box warning and of clinical studies

The FDA’s black box warning “highlights that prolonged use of [DMPA] may result in significant loss of bone density, and that the loss is greater the longer the drug is administered” (United States Department of Health and Human Services, 2004). Some may argue, of course, that adolescents tend to use DMPA for brief periods of time: over 50 percent of teens using DMPA decide to discontinue it within one year. Bones' exposure to DMPA’s effects, therefore, is brief, and it has been suggested that recovery of normal bone metabolism may occur more quickly than in girls using DMPA for extended periods (Cromer et al., 2006, p. 298).
Reasons to limit the use of

Yet there are adolescents who use DMPA both for contraceptive and non-contraceptive purposes who may choose to use it for longer periods of time. Given this, studies into the effects of long-term DMPA use are particularly relevant. Up to 60% (Greydanus, Patel & Rimsza, 2001, p. 570) of bone mass is accumulated up to age 18, with 37% deposited during the adolescent growth spurt\(^1\,^2\) (Kass-Wolff, 2001, p. 21). Furthermore, given that teen use of DMPA has increased from 4% in 1994 to 17% in 1997 (Bunsen, 2004, p. 57), any contraceptive that reduces bone mineralization is cause for concern.

Analysis

A number of studies have investigated the relationship between decreased estrogen production resulting from DMPA use and loss of BMD. Of four prospective, observational studies including adolescents receiving DMPA injections and untreated adolescents, BMD at the lumbar spine decreased an average of 3.1 percent (range 1.5 to 6.0 percent) compared with an average increase of 7.2 percent (range 5.9 to 9.5 percent) in untreated adolescents. This means, therefore, that the total average discrepancy in BMD between DMPA users and untreated teen girls was 10.3 percent. In addition, bone metabolism in DMPA users resembles that of a perimenopausal woman; that is to say that in DMPA users, a one to three percent loss of bone mineral density is expected each year (Cromer et al., 2006, p. 297).

Uses and limitations of dual energy x-ray absorptiometry (DEXA technique)

Common to the majority of these DMPA studies is the use of dual energy x-ray absorptiometry (DEXA technique). The most common means of measuring bone density, a DEXA scan is more accurate than other measurements currently available and reveals bone density as grams per centimetre of bone; the T score, or the comparison of an individual's bone
density with that of persons in their peak bone mass years; and the Z score, or the comparison of an individual’s bone density with persons in his or her own age group (Lindemann, 2005).

It should be noted, however, that some of these studies may be criticized for a number of reasons, not the least of which is the use of the DEXA technique. Because the T score is a measure of bone density loss since early adulthood, Binkovitz and Henwood (2007) caution against the inclusion of the T score in pediatric DEXA reports. Use of the T score in children whose BMD has yet to peak will always yield a low result.

A further limitation of DEXA scans is that they do not provide information about changes in bone geometry as a result of hormone or other treatments. Bones' geometric shape is an important factor in determining bone strength. To assess bone geometry, one must use either peripheral quantitative computed tomography or indirect formulae for special DEXA views. Because such measurements are new to the field of bone research and have not been applied to young women with hypoestrogenism (e.g., DMPA users), the effects of estrogen deficiency on bone strength and geometry in the adolescent population is not yet known (Cromer et al., 2006, p. 298).

Clinical studies of long-term DMPA use: criticisms and limitations

The prospective studies investigating DMPA and loss of BMD in adolescent women may be further criticized for their small size (Bachrach, Cundy & Ott, 2000, p. 1137). The 1996 study by Cromer et al., the first of these two studies, involved just 15 participants, only eight of whom remained in the study by the end of its second year. Furthermore, in the 2003 study by Busen et al., only six of the cohort of 22 females (aged 15 to 19 years) remained in the study after
Reasons to limit the use of 12 months. Moreover, of those six, only four continued through the second year of the study. Thus, participants’ attrition is clearly a limitation of these studies (Bunsen, 2004, pp. 59-60).

**High-risk behaviors and BMD**

Critics will also point to these studies' failure to control other risk factors, both intrinsic and extrinsic (Bachrach, Cundy & Ott, 2000, p. 1137). Bone mineral density may also be affected by high-risk behaviors such as early initiation of sexual activity, smoking, and alcohol consumption. According to Middleman, Robertson, DuRant, Chiou, and Emans (1997), able-bodied teens using DMPA are more likely to demonstrate clustering of these high-risk behaviors (cited in Kass-Wolff, 2001, p. 25).

Criticism of the 1994 study by Cundy et al., for instance, points to a considerable difference in the percentage of smokers (22% versus 6%) between the women who stopped using DMPA and those who had never used it (Sharma, Newman & Smith, 1994, p. 717). Similarly, Kristinsson et al. (1998) found a significant negative correlation between smoking and BMD, particularly in the hip and total body (cited in Kass-Wolff, 2001, p. 25). This would imply that smoking has a negative effect on BMD.

The fact is that the effects of smoking on BMD are mixed. Lottborn, Bratteby, Samuelson, Ljunghall, and Sjöstrom (1999), for instance, determined that smoking had no significant effect on bone density. Moreover, the same researchers found that alcohol had no significant influence on BMD in adolescents, likely due to bones’ short exposure to these toxins (cited in Kass-Wolff, 2001, p. 25).
Other factors affecting BMD

As mentioned already, while contraceptives (including DMPA) may affect bone mineral density, many other factors influence BMD. Foremost among these is a low body weight and a body mass index of less than 16. Other risk factors include ethnicity, race, physical immobility, renal disease, cystic fibrosis, hyperthyroidism, previous hypoestrogenism, malabsorption, and chronic use of corticosteroids and other immunosuppressive drugs (Cromer et al., 2006, p. 299). For instance, lower BMD in premenopausal women may be linked to estrogen deficiency from such causes as anorexia, athletic amenorrhea, or conditions associated with ovarian failure. Peak bone mass may also be influenced by genetics and by such modifiable factors as nutrition, physical activity, and calcium intake (Bunsen, 2004, p. 59; Kass-Wolff, 2001, pp. 23-25).

This long list of risk factors raises an interesting question: given that bone mineral density among some adolescent girls may already be affected by poor nutrition, low calcium intake, eating disorders, and athletic amenorrhea, does it not stand to reason that prescription of DMPA should be limited in this sub-set? After all, adolescents and young women with amenorrhea and oligomenorrhea (e.g., athletes, ballet dancers, and those with eating disorders) have low serum estrogen levels (Hergenroeder et al., 1997; cited in Kass-Wolff, 2001, p. 24). The pharmacologic action of DMPA further reduces serum estrogen levels.

Counteracting DMPA’s effect on BMD: estrogen supplementation

To counteract this, estrogen supplements may be recommended to osteopenic girls using DMPA and to those who have not undergone a DEXA scan but who are at high risk for osteopenia (reduction of bone mass). This is, of course, provided they do not have a
contraindication for estrogen. Estrogen supplements have been shown to increase BMD among women taking DMPA (Cromer et al., 2006, p. 300).

This would seem a straightforward solution; however, one distinct clinical advantage of DMPA is that it appeals to women for whom daily or weekly compliance is an issue. Therefore, adding estrogen supplements detracts from this (Cromer et al., 2006, p. 300). More significantly, one must note that, while menopausal doses of oral estrogenic analogues such as micronized estradiol or oral equine estrogen—estrogen pills, in other words—or transdermal patches containing estradiol have all been used concurrently with DMPA, optimal dose, route of administration, and point of maximum benefit are unknown. Similarly, there are insufficient clinical trials to recommend a particular protocol to any one patient. For this reason, and because DMPA is often prescribed due to contraindications for estrogen use, estrogen supplementation may, in some circumstances, be ill advised (Cromer et al., 2006, pp. 299-300).

*BMD upon discontinuation of DMPA*

Those in favor of continued use of DMPA in adolescents will also point to the studies suggesting that loss of BMD can be recovered upon discontinuation of the drug. For instance, a 2006 study by Harel, Stager, Gold, Coupey, Burman, et al. of adolescents (mean age 15.4 years) found that BMD, measured in the spine 48 months after discontinuation of DMPA, increased 4.9 percent (cited in Cromer et al., 2006, p. 298). In studies by Scholes, LaCroix, and Ichikawa, BMD, measured 12 months after discontinuation of DMPA, was at least as high as those of non-users (cited in Cromer et al, 2006, p. 297). In addition, a 1994 study by Cundy et al. demonstrated that bone density returned to near normal levels with discontinuation of DMPA (cited in Kass-Wolff, 2001, p. 23).
Conclusions

While the results of the aforementioned studies are encouraging and suggest that loss of BMD is reversible upon cessation of DMPA, it should be noted that no comparison group was included in the study by Harel et al. Furthermore, despite these results, one question still remains: did adolescent girls using DMPA achieve the same peak bone mass they would have in the absence of DMPA? It is not known whether full recovery of bone density after discontinuation of DMPA occurs. Similarly, it is also unclear whether full recovery occurs in young adolescents (between 12 and 15 years) who are normally experiencing the highest levels of bone mass accrual (Cromer et al., 2006, p. 298).

It is apparent, however, that despite the contradictory data, a relationship does exist between DMPA and BMD. The Food and Drug Administration's black box warning, moreover, would support this: “It is unknown if use of Depo-Provera® Contraceptive Injection during adolescence or early adulthood, a critical period for bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture later in life” (cited in Cromer et al., 2006, p. 296).

Additional study is needed to resolve the issue of bone loss in adolescents using DMPA. Greydanus, Patel and Rimza (2001, p. 570) state that some experts recommend not using DMPA for those younger than 15 years old or within 3 years of menarche. They further suggest that, until more research is done, DMPA should be avoided in teens at risk for osteoporosis and osteopenia, including those who have chronic renal disease, are wheelchair-bound, have eating disorders, and/or have chronic amenorrhea.

One's preferred method of contraception may differ from that of other women; over time, it may even vary in that same person. DMPA may seem well suited to adolescents for whom the active, daily regimens of birth control pills or barrier contraceptive methods (e.g., condoms,
Reasons to limit the use of diaphragms, contraceptive sponges) are difficult. Yet, given the findings of studies into the negative effects of long-term DMPA use on BMD, one ought to re-evaluate her lifestyle, risk factors, contraindications, and any high-risk behaviors to determine whether DMPA is the most viable contraceptive method. It may not be. However, the wide array of birth control options available today stand to improve not only the likelihood of user satisfaction, but also the effectiveness of the chosen method. Until additional study is done to determine conclusively whether reduced or lost BMD may be recovered upon discontinuation of DMPA, the drug ought not be used by adolescent girls who have yet to reach their peak bone mass.
Footnotes

1 Whiting, Vatanparast, Baxter-Jones, Faulkner, Mirwald and Bailey (2004) determined the times of maximal peak bone accrual to be 14.0 ± 1.0 years in boys and 12.5 ± 0.9 years in girls.

2 While Kass-Wolff (2001, p. 21) indicates that 37% of adult bone is deposited during the adolescent growth spurt, calculations by Whiting et al. (2004) indicate that in the two-year period of peak skeletal growth, adolescents accumulate 25% of adult bone. It is unclear whether this discrepancy is statistically significant.
Glossary

amenorrhea: absence or cessation of menstruation

anovulation: the absence or cessation of ovulation

athletic amenorrhea: absence of menstrual periods in female athletes who exercise strenuously and/or who engage in activities such as rowing, long-distance running, cycling, or gymnastics; this condition is usually linked to poor nutrition, low body fat, weight loss, and excessive training

body mass index: a key index used to relate a person's weight to his or her height in order to determine whether that individual is at a normal weight, overweight, or obese; the body mass index, or BMI, measures an individual's weight in kilograms divided by his or her height in metres squared. Anyone with a BMI lower than 18.5 is considered underweight. Anyone whose BMI falls between 18.5 and 24.9 is considered to be at his or her ideal weight while anyone whose BMI falls between 25 and 29.9 is considered overweight. Obesity is defined as a BMI of 30 or more.

corticosteroids: any of the steroid hormones made by the cortex (outer layer) of the pituitary gland; may also refer to synthetic hormones used as anti-inflammatory agents, as agents to control salt and water balance through action on the kidneys, to treat of leukemia, or to suppress rejection following bone marrow transplantation

dysmenorrhea: difficult and painful menstruation

endometriosis: growth of cells similar to those forming the inside of the uterus, but in a location outside the uterus (i.e., the endometrium); such growths are usually benign

endometrium: glandular mucous membrane that lines the uterus; this tissue is shed monthly in response to hormonal changes in the menstrual cycle. Following menstruation, the endometrial cells grow back until they are once again sloughed off during the next menstrual period.

estradiol: a form of the hormone estrogen; the most potent, naturally occurring estrogen in mammals

estrogen: female hormone produced by the ovaries

follicle stimulating hormone (FSH): a protein secreted by the pituitary gland, FSH stimulates both the development of ovarian follicles (eggs) and the release of estrogen
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>gonad:</td>
<td>reproductive gland (ovary or testis)</td>
</tr>
<tr>
<td>gonadotropin:</td>
<td>hormone secreted by the pituitary gland, gonadotropin affects the function of the male or female gonads (i.e., testis or ovary)</td>
</tr>
<tr>
<td>hyperthyroidism:</td>
<td>overproduction of thyroid hormones by an overactive thyroid gland</td>
</tr>
<tr>
<td>hypoestrogenism:</td>
<td>diminished production of estrogen by the ovaries, such as that which occurs during menopause</td>
</tr>
<tr>
<td>luteinizing hormone (LH):</td>
<td>a hormone released by the pituitary gland, LH controls the sex hormones in men and women. In women, LH stimulates ovulation and controls length and sequence of the menstrual cycle, including ovulation; preparation of the uterus for implantation of a fertilized egg; and ovarian production of both estrogen and progesterone</td>
</tr>
<tr>
<td>malabsorption:</td>
<td>alteration in the intestines' ability to absorb the nutrients in food</td>
</tr>
<tr>
<td>menarche:</td>
<td>the time in a girl's life when menstruation first begins; puberty</td>
</tr>
<tr>
<td>menopause:</td>
<td>the time in a woman's life when menstrual periods permanently cease</td>
</tr>
<tr>
<td>menorrhagia:</td>
<td>excessive uterine bleeding occurring during menstrual periods; these start on schedule, but the bleeding is heavier than usual and may last longer than usual. Menorrhagia may be indicative of an underlying disorder such as endometriosis, uterine fibroids, or uterine cancer.</td>
</tr>
<tr>
<td>oligomenorrhea:</td>
<td>infrequent or very light menstruation</td>
</tr>
<tr>
<td>osteopenia:</td>
<td>mild thinning or reduction of bone mass that is less severe than that which occurs with osteoporosis</td>
</tr>
<tr>
<td>osteoporosis:</td>
<td>reduction or loss of bone mass or of bone mineral density that occurs when bones begin to lose some of their essential elements (e.g., calcium)</td>
</tr>
<tr>
<td>ovarian follicle:</td>
<td>egg</td>
</tr>
<tr>
<td>perimenopause:</td>
<td>the transition in a woman's life that occurs before natural menopause. Usually occurring within approximately six years of natural menopause, this is a time when the levels of hormones produced by the aging ovaries fluctuate, resulting in such symptoms as hot flashes, irregular menstrual patterns, night sweats, mood swings, fluctuations in sexual desire, vaginal dryness, sleep disturbances, forgetfulness, and fatigue.</td>
</tr>
<tr>
<td>premenopause:</td>
<td>the entire time prior to menopause</td>
</tr>
</tbody>
</table>
Reasons to limit the use of

References


Cromer, Barbara; Scholes, Delia; Berenson, Abbey; Cundy, Tim; Clark, M. Kathleen, & Kaunitz, Andrew M. (2006). Depot Medroxyprogesterone Acetate and Bone Mineral Density in Adolescents—The Black Box Warning: A Position Paper of the Society for Adolescent Medicine. *Journal of Adolescent Health*(39), 296-301.


