The Long-term Health Implications of Depo-Provera

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Abstract

The reproductive health of adolescents and young adults is a major determinant of their future well-being. While Depo-Provera, or depot medroxyprogesterone acetate (DMPA), is highly effective at preventing pregnancy, mounting evidence suggests that its side effects may have a negative impact on long-term health. Together with mood changes, weight gain, menstrual irregularities, and delayed return to fertility, recent data indicate a correlation between DMPA use and an increased risk of fracture and HIV infection. These results have intensified concern about whether the benefits of DMPA outweigh the long-term risks. This paper reviews the health implications of DMPA and recommends alternative contraceptive methods that may have more favorable outcomes.

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Depo-Provera Use and Demographics

Currently, the combination (estrogen and progestin) oral contraceptive pill (OCP) and condom are the most common contraceptive methods used by teenagers.[1] In cases where women are at an increased risk of estrogen complications, however, progestin-only hormonal contraception is often prescribed as the method of choice. This practice applies to women who are breastfeeding or have an increased risk of forming blood clots as well as those who have experienced complications on estrogen-containing contraceptives.[2] One of the progestin-only methods, Depo-Provera (DMPA), was originally approved to alleviate endometriosis and certain cancers and is currently most commonly used as a contraceptive.[3] More than 2 million women in the United States, including approximately 400 000 adolescents, are using DMPA annually as of 2004.[4]

The benefit of DMPA relates to the fact that it is (1) 99% effective at preventing pregnancy when used properly; (2) requires only one injection every 3 months; and (3) offers extended protection due to the crystallized progestin that slowly dissolves into the bloodstream.[2,3,5] According to James Trussell in his chapter "Contraceptive Efficacy" in *Contraceptive Technology: Nineteenth Revised Edition*, "The typical failure rate of DMPA is 0.3 per 100 woman-years, which is comparable with that of implantable contraceptives, copper intrauterine devices (IUDs), and surgical sterilization."[6] Although the condom is the only method that offers protection from transmission of sexually transmitted infections (STIs) and is 98% effective when used properly, prescribers tend to rely on hormonal methods that are less dependent on users' compliance.[6]

Depo-Provera Adverse Effects

Compared to other progestin-only contraceptives, DMPA contains substantially higher levels of progestin.[5,7] A 90-day dosage of DMPA adds up to 150 mg,[5] significantly higher than the 90-day dosages of the progestin-only pill (POP) (31.50 mg), Mirena IUD (1.8 mg), and Implanon/Nexplanon (etonogestrel implant) (6.3 mg). Consequently, DMPA is associated with more side effects, including irregular menstruation, anxiety, headaches, weakness, fatigue, bloating, abdominal pain, and weight gain (almost 10 pounds in 2 years).[5,7] Additionally, many users experience delays in fertility (up to 18 months) following discontinuation. DMPA usage is also directly linked to amenorrhea in 70% of users after 2 years. Along with these common side effects, recent data revealed an increased risk of fracture caused by the DMPA-induced lack of estrogen over extended periods of time, particularly in women who have not yet attained peak bone mass.[8,9,10,11,12]

FDA Black Box Warning

In 2004, the Food and Drug Administration (FDA) responded to concerns regarding fracture risk and the potential of developing DMPA-induced osteoporosis by issuing the following black box warning[13]:

> Women who use Depo-Provera Contraceptive Injection may lose significant bone-mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. 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 for osteoporotic fracture in later life. Depo-Provera Contraceptive Injection should be used as a long-term birth-control method (eg, longer than 2 years) only if other birth-control methods are inadequate.

Reversal of Bone Density Does Not Guarantee Safety

Although the FDA's warning had an impact on prescription trends, some studies have offered reassurance, indicating that the DMPA-induced bone loss is at least partially reversible following the discontinuation of injections.[10,14,15,16] Consequently, DMPA remains a common prescription, often used as a contraceptive for sub-Saharan African women as well as young African American and Native American women who are in their formative years prior to reaching peak bone mass.[17] Building peak bone mass usually occurs from preadolescence until approximately age 30.[18] This prescription trend is socioeconomically driven and reflects a heightened concern for the personal and public health impact of unplanned pregnancies in these populations. Moreover, given the low socioeconomic status of women in these demographics, DMPA tends to be prescribed as a cheaper alternative compared to other contraceptives.

Until this point, using dual-energy, x-ray absorptiometry to determine bone-mineral density (BMD) has been the method of choice for assessing the influence of DMPA on bone health. A reversal of bone loss, however, does not guarantee safety from fracture and secondary osteoporosis. Although low BMD is associated with fracture risk, it is only one determinant,[19-25] and in reality, most fractures occur in individuals with a moderate BMD.[19,26] Evidence suggests that together with BMD, both bone quality and turnover contribute to bone strength and are important in determining the risk of fracture. As a result, the Fracture Risk Assessment Tool (FRAX) was developed and is currently used with BMD as a more comprehensive assessment of fracture risk in older populations. No such assessment is used to calculate fracture risk in younger hormonal contraceptive users. Similarly, studies designed to determine the influence of DMPA on bone health do not account for fracture risk variables other than BMD.

A 2010 systematic review by Unnanuntana et al confirmed that altered bone metabolism, whether induced by drugs or illness, contributes to the occurrence of fragility fractures. More specifically, Unnanuntana et al concluded that a balance between bone resorption and formation is critical to preventing microdamage and maintaining the structural integrity of bone.[27] Therefore, the rapid rate of bone formation following discontinuation of DMPA suggests the possibility of an increased risk of fracture regardless of the level of BMD attained. Consequently, the safety of DMPA can only be definitively determined by measuring the long-term incidence of fractures following use.

While the field lacks substantive information regarding the correlation of DMPA with fractures,[28] recent research has demonstrated that DMPA is associated with a slight, statistically significant risk of fracture in 20- to 44-year-olds. Meier et al "identified 17 527 incident fracture cases and 70 130 control patients (DMPA exposure: 11 and 8%, respectively). Compared with nonuse, current use of one to two, three to nine, or 10 or more DMPA prescriptions yielded adjusted OR for fractures of 1.18 (95% CI = 0.93-1.49), 1.36 (95% CI = 1.15-1.60), and 1.54 (95% CI = 1.33-1.78), respectively." Fracture risk was exacerbated by the length of use (>2-3 years) regardless of whether a user was under or over the age of 30.[9]

Evidence indicates that continued use of methods that combine estrogen and progestin following the discontinuation of DMPA interferes with the reversal of bone loss.[29] Therefore, it is possible that any interventions that affect normal hormone levels may negatively impact bone integrity, especially when used prior to attaining peak bone mass.[30] This recent research underscores the need to determine the lifetime risk of fracture following DMPA use, and it suggests that exploring contraceptive approaches that minimize the need for hormonal interventions in young people would be prudent.[9]

The Long-term Impact of Osteoporosis

Although studies indicate that DMPA reduces BMD and increases the likelihood of fractures during usage, the long-term influence of DMPA following discontinuation has not been established. Given that the drug was approved as a contraceptive in 1992[31] and osteoporosis is predominately a postmenopausal illness, determining a DMPA-associated influence on the development of osteoporosis has proven difficult. Prescribers, however, must consider all potential eventualities. DMPA may undermine the long-term health of individual users and exacerbate the health care burden associated with osteoporosis-related sequelae. Moreover, to assess the risk-to-benefit ratio of DMPA adequately, it is imperative to understand the long-term implications of osteoporosis fully.

The mortality and morbidity associated with osteoporosis is substantial. The lifetime risk of fractures is 40%, equal to the risk of cardiovascular disease.[19,32] After the age of 50, approximately 1 in 3 women will experience an osteoporosis-related fracture.[19,33,34] Following a hip fracture, as many as 20% will die in less than a year, and 50% will require assistance with walking.[19,35] The pain and deformity resulting from osteoporosis limit the range of functional activities required for independent living. This debilitation often leads to depression and anxiety about leaving home. Consequently, many individuals with osteoporosis become dependent on the help of others and often require nursing-home care.[19,36]

Together with the human cost, osteoporosis places an exorbitant financial strain on the health care system. Each year, $14 billion is spent on 1.5 million osteoporosis-related fractures.[19,35] Currently, complications associated with osteoporosis necessitate longer hospital stays than other diseases, including diabetes, myocardial infarctions, and breast cancer.[37] By 2050, the worldwide incidence of fractures in women is expected to increase by 240%.[38] This fact, combined with the disease's psychological and financial costs, makes the prevention of osteoporosis essential.[19]

While unintended pregnancies in young adults and low-income populations have serious consequences, the possible influence of DMPA on the development of osteoporosis cannot be ignored.

DMPA-induced HIV Risk

Together with the potential for increased fractures, new evidence has led to even greater concerns about health risks associated with DMPA use. A recent study published by *The Lancet,* examining contraceptive use in sub-Saharan African women, revealed that DMPA doubled the risk of both contracting and transmitting HIV.[39,40] The study investigated serodiscordant couples (ie, one partner is HIV positive, and the other is HIV negative) and found that "women using hormonal contraception became infected at a rate of 6.61 per 100 person-years, compared with 3.78 for those not using that method. Transmission of HIV to men occurred at a rate of 2.61 per 100 person-years for women using hormonal contraception compared with 1.51 for those who did not."[39,40] These findings are particularly concerning given that the majority of women who are prescribed DMPA are also at an increased risk of contracting HIV.[39,41]

While this *Lancet* publication exceeds other similar investigations in design, five of the most rigorous, prospective observational studies also indicated an increased risk of HIV infections associated with DMPA-induced physiological changes. The exact mechanism is unknown; however, theoretically the DMPA could influence the integrity of the vaginal-cervical epithelium, directly increase the virulence of the virus, and/or cause shifts in local immunology.[39] Irrespective of the cause, researchers were able to establish higher concentrations of HIV in genital fluid of those infected with HIV while using DMPA injections.[40] Studies on Macaques supported these findings by demonstrating that DMPA increased the risk of acquiring various strains of simian immunodeficiency virus.[39] The simian studies also demonstrated a DMPA-associated rise of virus in the blood and increased viral shedding in the genital tract.[39,41]

Although the recent human study was restricted to African subjects, the investigators stated that the findings can most likely be generalized to all populations. Considering that the majority of the 16 million women currently infected with HIV are living in sub-Saharan Africa, however, researchers are particularly concerned about these populations.[40] Promoting DMPA as a contraceptive for women who are underresourced, and/or who live in countries with a high prevalence of HIV infections, could contribute to the HIV epidemic. Isobel Coleman, director of the Women and Foreign Policy Program at the Council on Foreign Relations, expressed her concern, stating "if it is now proven that these contraceptives are helping spread the AIDS epidemic, we have a major health crisis on our hands."[40]

The World Health Organization (WHO) met in January 2012 to respond to the potential link between DMPA use and HIV transmission.[40] The WHO recommended that the guidelines be modified to emphasize the importance of using condoms concurrently while on hormonal contraceptives. The organization resisted amending prescription trends, however, stating that the hormonal link has not been proven.[42]

Yet current research in the area of vaginal immunology has confirmed the protective role of the hormonally regulated epithelial lining,[43] cervicovaginal secretions,[41,44] and vaginal microbiota.[41,43] Furthermore, the female reproductive tract's immune system provides both innate and adaptive immunity that is also tightly regulated by the cyclic shift in estrogen and progesterone levels.[41,45,46] Ample evidence indicates that hormonal contraceptives interfere with these natural defense mechanisms.[38,43,46] Given that the hormonal environment at the time of infection determines a female's susceptibility and predisposition to infection,[47,48] these disturbances to contraceptive users' immunophysiological systems come with inherent risks.

Accordingly, several plausible, evidence-based explanations for the increased risk of HIV infection in DMPA users exist. DMPA dramatically decreases estrogen, which causes a simultaneous reduction in both the vaginal lactobacilli levels as well as the thickness of the glycogen, vaginal epithelial layer. Lactobacilli are healthy bacteria that normally thrive in the vagina under ideal conditions and protect against infections by maintaining pH levels and producing H_2O_2. Researchers have suggested that the DMPA-induced microbiota disturbances, together with the thinning of the glycogen vaginal epithelial layer, may compromise the vaginal barrier and predispose users to infection.[43] These findings have added substantial weight to the concern about prescription practices for DMPA, given that a high proportion of HIV-exposed women are resistant to infection, and many researchers have argued that transmission most likely occurs in cases of vaginal epithelial atrophy or damage.[49] These findings also have supported the evidence that HIV infection is significantly higher in women lacking H_2O_2-producing lactobacilli, as is often the case in DMPA users.[41,50]

Furthermore, changes in the cervicovaginal fluid of DMPA users, including an increase in inflammatory cells[41,51] and a decrease of protective immunomodulatory factors, such as natural antibodies[41] and the secretory leukocyte protease inhibitor,[52] is also of fundamental importance. These protective factors might play a role in preventing the transmission of HIV infection.[41] Additionally, the increased accessibility of primary target cells, such as Langerhans cells,[41,49,53] in the vaginal epithelia and stroma of DMPA users could potentially elevate the risk of acquiring HIV.[54]

Although correlations between DMPA-induced immunophysiological changes and increased risk of HIV

infection have been established, a great deal of controversy exists surrounding this issue based on the fact that DMPA is highly effective at reducing unplanned pregnancies. Advocates argue that the number of women who are able to avoid HIV infection does not justify risking the much higher number of women facing unplanned pregnancies and the associated deaths that might result from limiting the prescription of DMPA. Still others believe the recent *Lancet* publication warrants switching DMPA users to lower-risk methods, such as the IUD or sterilization.[55]

Based on her 2003 review of the influence of hormonal contraceptives on the immune system, Brabin has cautioned that clinicians who prescribe contraceptives to patients at high risk of STIs, particularly HIV, require a more comprehensive understanding of the implications.[47] Consequently, although not yet definitive, the recent findings associating DMPA with a heightened risk of contracting and transmitting HIV must be explored further before discounting the influence of DMPA on the HIV epidemic. Furthermore, it would be prudent to reevaluate WHO's response to these findings. At a minimum, condoms should be distributed and probiotics and vaginal estrogen creams concurrently prescribed to help bolster the vaginal immunity of DMPA users and decrease their risk of infection. Additionally, vaginal phytoestrogen creams are a potential nonhormonal alternative to estrogen cream (Table 1).

Controversial Prescribing Practices

Potential racial and socioeconomic disparity in doctors' prescription practices regarding DMPA has also caused considerable controversy. Currently, the majority of users are from minority and low-income populations.[17,56-58] Approximately 6% (12 million) of sub-Saharan African women between the ages of 15 and 49 use DMPA injections as a contraceptive.[40] DMPA use is considerably lower in the United States. The Center for Disease Control's National 2006-2008 Survey of Family Growth indicated that 22.2% of women between the ages of 15 to 44 used DMPA at one time and 2% were currently using DMPA.[59] The drug, however, is disproportionately prescribed to minority and low-income women. According to the Committee on Women, Population, and the Environment (CWPE), "In a recent study of Depo users in the US, 33% were under the age of 19, 84% were black women, and 74% were low income."[17]

These trends reflect the fact that DMPA is prescribed as a means to address low compliance, which health care clinicians often associate with low-income populations, including young women in developing countries. Unfortunately, this population frequently lacks the sex education offered in more affluent schools and countries. Furthermore, while users may have a cursory understanding of the side effects, they are often unaware of the long-term implications of DMPA use, thus diminishing their ability to make well-informed choices.[17,56-58] The primary argument for promotion of DMPA in underserved populations and countries with a high prevalence of unplanned pregnancies is that the benefits outweigh the risks. McGouph and Bigrigg, however, validated the need to revisit these prescribing patterns by establishing that DMPA significantly decreased BMD in a group of underresourced, long-term users.[60] Moreover, the potential, far-reaching implications of promoting DMPA as a contraceptive in underresourced populations and developing countries is substantiated by the significant increases in HIV transmission and infection that may be associated with usage.[39,40]

Together with Stephen Lewis, former UN Special Envoy on AIDS in Africa, Paula Donovan—head of the international HIV advocacy organization, AIDS-Free World, and former East and Southern African advisor for UNICEF—expressed her concern for the WHO's response to the recent findings associating the potential link of DMPA to HIV transmission. She criticized WHO for their delay in responding to the results and publicly stated that their recommendations were not transparent and cautionary, thus reducing the public's ability to make well-informed decisions. She also cautioned that verbal statements recommending concurrent condom use will likely have little influence on behavioral change compared to providing a supply of condoms with DMPA and hormonal prescriptions.[61] These issues highlight the fact that social and racial disparities in prescribing practices may influence the quality of health care in developing countries and under-resourced communities.

In response to the DMPA-associated HIV findings, 40 women met in East Africa to clarify women's needs with respect to hormonal contraception and reproductive health care and prepared a summary for the UN's scheduled technical consultation. The women included researchers, medical professionals, women's rights advocates, HIV and reproductive-health counselors, and activist women living with HIV in Rwanda, Zimbabwe, Uganda, South Africa, Kenya, and the United States. After just half a day of discussion, they reached a consensus, including[62]:

> It is not sufficient to say that the data are mixed, and we need more research … Clear information must be provided now on the potential risks of both hormonal contraceptive use and pregnancy. Women need clear and balanced information on what is known and unknown. Women will not be divided by issues of various risks—the response cannot pit contraceptives versus maternal mortality. We don't accept an either/or approach. Both problems need to be addressed.

The following organizations oppose the use of Depo-Provera; the list is not exhaustive[17]: (1) Black Women's Health Imperative; (2) The National Latina Health Organization; (3) The Native American Women's Health Education Resource Center; (4) the National Women's Health Network; (5) the Women's Economic Agenda Project; (6) the Women's Health Education Project; (7) Committee on Women, Population, and the Environment;

Table 1. Integrative Medicine's Contraceptive Recommendations

Vaginal Health	Bone Health
Probiotic: oral capsules/powders and vaginal suppositories[a]	Calcium;[b] vitamin D[b] (or safe sun exposure); magnesium supplement; combined with diet, calcium daily dosage of 1000-1500 mg depending on age and type of contraceptive.
Phytoestrogen or estrogen cream[c]	Calcium-rich nutrients (organic): kelp; dulse; almonds; tofu; dark, leafy greens; yogurt; feta cheese; goat cheese; salmon and sardines with bones; blackstrap molasses; tahini and sesame seeds; etc.
	Other nutrients to be considered (ideally through dietary intake): zinc, manganese, boron, copper, B_6, vitamin C, vitamin K, CoQ10, and silicon.
Phytoestrogen-rich foods: unprocessed soy, fermented soy, and ground flaxseeds (theoretical benefit)[d]	Phytoestrogen-rich foods: unprocessed soy, fermented soy, and ground flaxseeds.[d]
Phytoestrogen herbs: *Pueraria mirifica*, *Saururus chinensis* (theoretical benefit)[e]	Phytoestrogen herbs: *Pueraria mirifica*, *Saururus chinensis*.[e]
Essential fatty acids (omega-3) (theoretical benefit)[f]	Essential fatty acids (omega-3).[f]
	Recommend avoidance of excess alcohol,[b] tobacco,[b] caffeine, carbonated sodas, red meat, salt, excess fluoride, and other substances that interfere with bone health.
	Weight-bearing exercise.
	Sauna/sweat therapy.[g]
	Healthy diet: minimize exposure to heavy metals, pesticides, and xenobiotics to avoid exacerbating compromised bone integrity.

Note: These treatments may be useful for current and recent users of hormonal and IUD contraceptives.

[a]Probiotics: A growing body of evidence supports the use of probiotics in the prevention and treatment of urogenital infections as well as in the enhancement of immunity. Li et al recently published an article, "The Importance of Vaginal Microbes in Reproductive Health," stating, "The use of probiotic lactobacilli vaginally and orally has shown great promise in helping to restore and maintain a healthy vagina, and studies have shown that certain strains have the capacity to interfere with…inflammatory pathway[s]…"[72]

[b]FDA-recommended.

[c]Phytoestrogen cream: While the research is limited, two clinical trials have supported the use of a gel containing hyaluronic acid, liposomes, phytoestrogens from *Humulus lupulus* extract, and vitamin E for the relief of atrophic vaginitis. These studies demonstrated improvement of vaginal atrophic symptoms without the side effects that are commonly attributed to hormonal creams.[73]

[d]Phytoestrogen foods (isoflavones and lignans): "Phytoestrogens have a similarity in structure with the human female hormone 17-β-estradiol, which can bind to both alpha and beta estrogen receptors and mimic the action of estrogens on target organs, thereby exerting many health benefits when used in some hormone-dependent diseases."[74] An animal study using ovariectomized ewes demonstrated an improved clearance rate of progesterone.[75] "Dietary intake of these so-called phytoestrogens has been associated with positive effects on menopausal complaints, hormone-related cancers, and osteoporosis."[76]

[e]*Pueraria mirifica* and *Saururus chinensis*: *P mirifica* was found to have an osteogenic effect on bone in ovariectomized rats, and a recent study confirmed these findings by demonstrating the herb's influence on estrogen-receptor-dependent osteoblast differentiation rather than proliferation.[77] "It was concluded that *S chinensis* treatment could prevent ovariectomized-induced loss of bone mass and deterioration in trabecular microarchitecture by suppressing bone turnover, thereby maintaining bone structural integrity. Furthermore, no stimulation or proliferation of uterine tissue was noted."[78] Given that *S Chunensis* interferes with bone turnover, future research might explore the intermittant use of the herb. This approach could theoretically support bone remodeling.

[f]Essential Fatty Acids: Omega-3 in a higher dose with respect to omega-6, helps to protect bone mass by preventing the formation of osteoblasts.[79] A recent study demonstrated that omega-3 in combination with aerobic exercise was synergistic in decreasing inflammation and increasing BMD.[80] Another study showed a positive correlation between omega-3 (DHA + EPA) and BMD in postmenopausal Korean women.[81]

[g]Sauna/sweat therapy: Bone and adipose tissue are storage sites of xenobiotics and xenoestrogens. Consequently, exposure may influence bone integrity. Sweating assists with decreasing the xenobiotic load. Additionally, unpublished data from the prospective 1999 Toronto Osteoporosis Prevention Study, which investigated the influence of lifestyle factors on BMD in 669 Caucasian women aged 18-35, revealed a slightly significant correlation between increased BMD and sweating as an independent variable.

(8) INCITE! Women of Color Against Violence (9) Communities Against Rape & Abuse (CARA); and (10) the Canadian Coalition on Depo-Provera. A number of scientists and women's associations in India are opposed to DMPA usage.[63] India removed DMPA from its Family Planning Protocol in 2002.

Comprehensive Approaches

To adequately address reproductive health issues in adolescents and young adults, many factors must be taken into consideration and a combination of approaches explored.[64-71] Within the context of adolescent wellness, lifestyle, together with the high rate of pregnancies and newly acquired STIs, must be weighed against the short and long-term risks of hormonal interventions. Therefore, it is imperative to find alternative options to DMPA while improving the proper and consistent use of condoms. Furthermore, racial and socioeconomic disparities in prescribing practices must be addressed by ensuring that all young people have equal access to information. To accomplish these goals, school-aged youth must be better educated and the obstacles to compliance and healthy sexuality addressed. Such an approach holds considerable promise given that a large number of educational programs with common characteristics were demonstrated to be effective in influencing the sexual health and contraceptive practices of young people in various cultures and regions.[71]

Integrative Medicine's Clinical Recommendations

Primary care clinicians can support well-informed choices by providing patients with a concise picture of the risks and benefits of each contraceptive method. Additionally, by encouraging partners to attend these educational sessions, clinicians can facilitate responsibility and healthy communication between both parties. In compliant patients, the condom alone, or simultaneous use of the condom and diaphragm (without the irritant spermicide), deserves consideration as a potential option. All users need to be aware of the availability of the emergency contraception pill should any issue arise. In noncompliant patients, lower-risk contraceptive options warrant consideration as a safer alternative to DMPA.

Contraceptive prescribers may have a greater influence on reducing the incidence of STIs and unplanned pregnancies by distributing condoms and ensuring access to education and/or links to videos with comprehensive instructions (eg, www.sexualityandu.ca). Although intended for postmenopausal women and older populations, a modified FRAX assessment for younger populations might be a useful evaluation tool to more accurately assess fracture risk in current and potential DMPA/hormonal contraceptive users. Together with other variables that have an impact on bone health, this score should reflect nutritional status and take the prevalence of eating disorders and disordered eating in younger populations into consideration.

Furthermore, any contraceptive method that causes disruptions to normal physiology requires a means to address its side effects. Accordingly, complementary and alternative medicine (CAM) is strongly indicated to alleviate potentially compromised bone as well as vaginal health (Table 1). The FDA states, "Although no studies address whether calcium and vitamin D may lessen BMD loss in women using Depo-Provera contraceptive injection, all patients should have adequate calcium and vitamin D intake"[13] Future studies are required to identify the efficacy of supplementation as well as other CAM treatments in mitigating the side effects associated with DMPA, other hormonal contraceptives, and the copper IUD.

Conclusion

DMPA is used primarily as an effective contraceptive for young adults who are considered to be less compliant.[16] Although DMPA helps to address the high prevalence of unintended teen and young adult pregnancies, the side effects and long-term health risks are cause for concern. Given the possible impact of DMPA on future wellness, the fact that the vast majority of DMPA users are minority, low-income women has raised ethical concerns. While cultural differences play a role in lifestyle and associated risk factors, reforming inequalities in sex education and reproductive health care may help to alleviate the serious health issues relevant to all racial and socioeconomic demographics.[71]

Among several DMPA-induced adverse effects, concerns exist about increased fracture risk over time. To date, studies have used BMD levels as the primary measure and indication of fracture risk. Osteoporosis research, however, indicates that bone quality is equally relevant.[19,35] Therefore, safety can only be definitively established based on longitudinal studies of lifetime-fracture incidence in women with a history of DMPA use.

Together with the potential influence of DMPA on fracture risk, associated increases in the incidence of HIV transmission warrant reevaluating the current practices for prescribing DMPA. The WHO failed to amend its prescription guidelines based on their position that the hormonal link has not been proven; however, correlations between DMPA-induced immunophysiological changes and increased risk of HIV infection have been established. These DMPA-induced changes are associated with susceptibility to HIV and other STIs. Additionally, DMPA may accelerate HIV progression.

While it is essential to prevent unplanned pregnancies and their sequelae, these epidemiological links between DMPA and HIV infections cannot be ignored. This need is underscored by the fact that DMPA is predominantly prescribed to underserved populations who are living in HIV-endemic areas. Moreover, the black box warning on DMPA strongly advises that the contraceptive's use be limited to a period of 2 years. This warning suggests that DMPA is a short-term solution at best. Unfortunately,

relying on DMPA as a means to address unplanned pregnancies in under-resourced areas, often results in prescriptions that exceed the cautionary 2-year limit.

Given that disease prevention is influenced by health during the formative years,[70] it is crucial that health care solutions weigh the long-term risks of hormonal interventions instituted at an early age. Some researchers suggest replacing prescription recommendations for DMPA with lower-risk contraceptives, such as the IUD or sterilization. A clinician might also discuss the possibility of using the condom and diaphragm simultaneously. At a minimum, condoms should be distributed, probiotics and estrogen/phytoestrogen creams concurrently prescribed, and bone health actively addressed with all hormonal contraceptives. Furthermore, beyond unwanted pregnancies, true prevention should address the high rate of newly acquired STIs, the emotional aspects of sexuality, and obstacles to information and resources that support reproductive health in adolescents and young people of all demographics.

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