

Mini-Review

Menstrual Suppression for Adolescents with Developmental Disabilities

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Abstract. The approach to menstrual suppression for adolescents with developmental disabilities has evolved considerably over the years due to changing philosophies and evolving treatment options. We review the medical management options available for menstrual suppression with a focus on the needs and treatment of adolescents with developmental disabilities.

Key Words. Developmental disabilities—Mental retardation—Adolescent—Menstrual cycles—Menstrual suppression—Combined oral contraceptive pill—Medroxyprogesterone 17-acetate—Transdermal contraceptive patch—Levonorgestrel intrauterine system

Introduction

A variety of medical options are available to address the various concerns that caregivers have regarding adolescent girls with developmental disabilities. These options must meet the needs of women affected by a wide spectrum of developmental disabilities: a group ranging from highly functioning adolescents with mild cognitive impairment, who are actively involved in school and extracurricular activities, to severely handicapped adolescents who require complete care for all activities of daily living. A recent retrospective review of clinical characteristics and management of young women with developmental delay referred to a pediatric gynecology clinic revealed that while the primary purpose for consultation was menstrual related in 90% of cases, nearly half of the patients seen were still premenarchal.¹ These early consultations highlight caregiver anxiety about coping with menstruation and the need for counseling and education about what to expect and about available options.

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The following paper will review the different medical management options available for menstrual suppression, with a focus on the needs and treatment of the developmentally disabled population. While surgical approaches such as endometrial ablation, tubal ligation, and hysterectomy, remain options for some patients, the following treatment choices are more appropriate initial management options and will be sufficient for most patients.

Depo-medroxyprogesterone acetate

Depo-medroxyprogesterone acetate (DMPA), an injectable progesterone, was approved for use as a contraceptive agent by the U.S. Food and Drug Administration (FDA) in 1992, and in Canada in 1997.² A 1992 survey of prescription practices of adolescent health care providers found that the strongest potential indication for DMPA administration was for adolescents with developmental disabilities.³ A more recent review still supports DMPA as a common treatment choice for this population.¹ A retrospective review of the experiences and attitudes of a group of cognitively impaired female adolescents and their primary caretakers found an average satisfaction rating for DMPA of 4/5.⁴ DMPA is a well-suited method of menstrual control for this population because it is an effective contraceptive which requires an injection only four times per year and has a high potential for inducing amenorrhea.⁵

The contraceptive efficacy of DMPA exceeds 99% and is not affected by patient weight or the concomitant use of other medications.² This is particularly important in women taking anticonvulsants and antibiotics, common to this population. Furthermore, DMPA has been found to be useful in management of women with seizure disorders.⁶ A small study of DMPA use in 14 women with uncontrolled seizures showed a 30% reduction in seizure frequency in the 11 women who became amenorrheic.⁷ DMPA is also an ideal

treatment choice for women who are at risk of thromboembolic events for whom estrogen-containing contraceptive agents are contraindicated.⁸

The effectiveness of medical management in reducing cyclical behavioral changes in women with developmental disabilities has been examined by only one small study.⁹ This study compared the effectiveness of non-steroidal anti-inflammatory agents (NSAIDs), oral contraceptive pills, and DMPA. Sixty-six percent of patients treated with DMPA showed improvement, not statistically different from the other modalities.⁹

Common complaints with DMPA use include weight gain and breakthrough bleeding. Controversy regarding the effect of DMPA on weight remains^{10–17}; however the product monograph suggests an average gain of 2.5 kg in the first year of use, 3.7 kg in two years, and 6.3 kg after four years of use.^{18,19} Baseline body weight and ethnic background have been suggested to be associated with weight gain with DMPA.^{16,17} A study examining the risk factors for weight gain among adolescent women using DMPA found that black subjects had a significantly higher weight gain than white subjects, and that baseline weight was predictive of weight gain in both groups.¹⁷ Weight gain attributable to DMPA is thought to be due to appetite stimulation.²⁰ Irregular spotting and bleeding occur commonly during the first few months of use; however, approximately 50% or more of women using DMPA for one year will become amenorrheic.² Anticipatory pre-treatment counseling and guidance of patients and their families regarding these two common side effects may help to significantly reduce discontinuation rates.

A more recent concern with DMPA is associated loss in bone mineral density.² The FDA issued a black box warning regarding DMPA and its potential negative impact on bone mineral density, particularly as it relates to the adolescent, in November of 2004.²¹ The warning was based on four prospective observational studies comparing bone mineral density in women aged 11–21 years who received either DMPA or no treatment for up to two years.^{22–25} The bone mineral density at the lumbar spine decreased by an average of 3.1% in the DMPA group compared with an average increase of 7.2% in untreated women. Similar results were also found in a more recent study in adolescents aged 14–18, wherein a mean reduction of 5.0% was found at the spine and 6.1% at the hip in DMPA users after two years, compared to a change of +2.3% and –0.9% at each site respectively in untreated adolescents.²⁶ It remains unclear, however, whether this association will translate into a reduced peak bone mineral density, and whether these changes are completely reversible after discontinuation of DMPA.²¹ Although bone mineral density has been used as a surrogate marker for bone strength, it does not necessarily translate into an increased risk of

future bone fractures.²¹ In adolescents with developmental disabilities, for whom DMPA use is proposed on a long-term basis and who may already be at increased risk of osteoporosis due to immobility, this dilemma may become even more pronounced. It is therefore strongly urged that the risk-to-benefit ratio of DMPA be carefully considered before recommending its use.

Combined Oral Contraceptives: Extended Regimen

The use of oral contraceptive pills (OCP) in women with developmental disabilities has not been well studied. One study did examine the experience of a group of cognitively impaired female adolescents taking OCP with traditional cyclical use.⁴ Compared to other contraceptive methods, it found that OCP received the lowest average satisfaction rating, 2.7/5, compared to 4/5 for DMPA, and 5/5 for the copper intrauterine device (IUD).⁴ It is unknown if an extended or continuous regimen of the OCP would receive a higher or lower satisfaction rating for menstrual suppression use in adolescents with developmental disabilities.

Oral contraceptive pills have been used in an extended fashion in the general population to reduce the symptoms of endometriosis, the incidence of hormone withdrawal related symptoms, and menorrhagia. Extended regimens of OCP have been used to treat adolescent females with developmental disabilities who have cyclical behavioral problems such as self-mutilation and aggression; however, there are no studies examining this use directly. We must therefore extrapolate from the results of studies of continuous OCP use in the general population.

Sulak et al encouraged 50 consecutive patients referred for menstrual related complaints to extend their active pill schedule by increments of 3 weeks, up to a maximum of 12 weeks.²⁷ Thirteen of these women returned to the traditional regimen or discontinued oral contraceptives altogether due to breakthrough bleeding (n = 8) or headaches (n = 6). All 37 women who stabilized on an extended regimen reported delayed onset and decreased severity of their reported complaints. Despite a convincing rationale for an expected reduction in menstrual related complaints with extended regimen of oral contraceptives, only three randomized trials have reported on this, only as secondary outcomes, and with variable results.^{28–30}

Families are concerned with avoiding menstrual bleeding for ease of hygiene and often desire amenorrhea. Comparisons of bleeding patterns between the traditional and extended regimens are difficult to make due to inconsistencies in the literature. A randomized multicenter study comparing a 91-day extended cycle (12 weeks of hormone followed by 7 days of placebo)

to traditional cycling found no difference in the severity or duration of the withdrawal bleeds experienced during the pill free intervals.³¹ Unscheduled bleeding or spotting during the active pill phase of the extended regimen is initially greater than that with the traditional scheduling, but becomes comparable within one year.^{32,33} When the bleeding patterns in 41 women on an extended regimen of oral contraceptive pills consisting of six months of continuous use without a hormone-free interval, it was found that the occurrence of any type of bleeding was greatest during the third month of continuous use.³² The most frequent bleeding pattern recorded was spotting, increasing from 12.5% during the first month to 43.7% by the end of the third month, and then progressively declining to only 12.5%.³² The rate of amenorrhea increased considerably after the third month, reaching 81.2% during the last month of continuous use.³² The unpredictability of bleeding patterns during the first three months of continuous oral contraceptive use is similar to that experienced during the first months of treatment with DMPA, and is often a cause for treatment discontinuation.³⁴ However, with adequate counseling in motivated patients and families, this hurdle may be surpassed and high rates of amenorrhea will be achieved.

Contraceptive efficacy is important to patients and families in addition to avoiding withdrawal bleeding. The contraceptive efficacy of the extended regimen has been found to be comparable, or superior, to that of the traditional OCP regimen. The transition period from one pack to the next has been shown to be the highest-risk time for contraceptive failure.^{35,36} The extended regimen, which offers fewer transition intervals, may lead to less risk of contraceptive failure with the quoted Pearl Index for extended cycle contraceptive use being 0.60, compared to that of conventional use being 1.78.³¹

Despite concerns that the extended cycle regimen exposes one to higher cumulative levels of estrogen and a potential association with increased adverse events, this has not been substantiated in the literature.³² Concerns have been raised about potential for development of endometrial hyperplasia with extended cycles. However, the continuous exposure to low-dose progestin inhibits the proliferative estrogenic influence and leads to endometrial atrophy. This has been shown in several small studies examining endometrial thickness with ultrasound or endometrial histology by biopsy.^{33,37}

Issues that require further study include potential effects on breast cancer risk, cardiovascular disease, time to return to normal reproductive and ovulatory cycles after discontinuation, and bone mineral density, especially with proposed use in adolescent girls. Due to the small absolute number of these events, many thousand women-years of treatment will be necessary

to further elucidate any differences in risks between traditional and extended cycle contraceptive regimen.

Transdermal Contraceptive Patch

The recent development of novel delivery systems that eliminate the need for compliance with daily pill taking present alternative methods for families and patients to achieve menstrual suppression. The transdermal contraceptive patch marketed in the U.S. contains 6.0 mg norelgestromine (NGMN) and 0.75 mg ethinyl estradiol (EE). A bioequivalent formulation marketed in Canada contains 6.0 mg NGMN and 0.60 mg EE. Both products are designed to deliver 20 mcg of EE and 150 mcg of NGMN to the systemic circulation daily.³⁸ The patch is applied weekly for three consecutive weeks, followed by one patch-free week, mimicking the traditional dosing schedule of oral contraceptives. However, extended use of the patch, like that of the oral contraceptive pill, is also under investigation.

The acceptance and satisfaction of the patch among Canadian women was proven by an open-label, multicenter, descriptive cohort study which found that 60% of participants preferred the patch to their previous birth control method.³⁹ The use of the transdermal contraceptive patch in adolescent populations has been evaluated by two studies, both of which found an overall positive impression with the patch and comparable side effects to those found in adults.^{40,41} However, only 62% (31/50) of participants completed all three months of one study, with most complaints about the patch being about the adhesive. A higher rate of partial and complete patch detachment was found among the adolescent participants in one of these trials compared to previously reported adult data.⁴⁰ Use of the transdermal contraceptive patch in the developmentally disabled population specifically has not yet been studied.

With cyclical administration of the transdermal contraceptive patch, the incidence of breakthrough bleeding has been found to be similar to that with OCP, with the patch showing slightly higher rates during the first two cycles.⁴² Significant differences in adverse reactions with patch use compared to oral contraceptives include the occurrence of minor application site reactions and a higher incidence of mild to moderate breast discomfort with the patch during the first two cycles of use.⁴²

A single randomized controlled trial has evaluated the extended use of the transdermal contraceptive patch in 239 healthy women for 12 consecutive weeks compared to a cyclic regimen.⁴³ The primary endpoint of the trial was total bleeding days. Extended use of the patch resulted in a delayed median time to first bleeding from 25 to 54 days. Extended patch use over 8 and 12 weeks lead to 28% and 12%

amenorrhea rates, respectively, compared to only 1% with cyclic use at both time intervals. There was no significant difference in median spotting days between the two regimens, but bleeding days were reduced. These preliminary findings parallel the results found with continuous oral contraceptive use and support its use for menstrual suppression.

The overall Pearl Index of the patch was found to be 0.88, superior to that quoted for traditional OCP use.^{44,45} Although DMPA and intrauterine devices provide improved contraceptive efficacy over oral and transdermal hormonal contraceptives, the latter do not require administration by a health care provider and are readily reversible. Pooled analysis of the clinical trial data for patch use found that there were a greater proportion of pregnancies occurring in women weighing 90 kg or more, suggesting a reduced efficacy in obese patients.⁴⁴

Recently, concern was raised regarding the potentially increased risk of thromboembolic events with the transdermal contraceptive patch. In November 2005, the U.S. FDA updated labeling for the patch. The advisory was based on the results of an unpublished post-marketing study comparing the pharmacokinetic profile of EE following administration of an oral contraceptive compared to that of transdermal contraceptive patch. This found that systemic absorption of EE, as measured by the steady state concentration and the area under the curve, is approximately 60% higher with patch compared to that with the oral contraceptive.⁴⁶ Peak concentrations for EE are, however, approximately 25% lower in women using the patch.⁴⁶ Unpublished pharmacokinetic studies comparing the Canadian transdermal contraceptive patch to oral contraceptives found the overall exposure to be comparable, and peak concentrations to be approximately 50% lower in women using the patch.³⁸ Two epidemiological studies were conducted to evaluate the risk of developing a venous thromboembolism (VTE) in women aged 15 to 44 years.^{47–49} The FDA subsequently made another update to the label in September 2006. The first study found that the risk of non-fatal VTE events associated with the use of the patch was similar to that with oral contraceptive pills containing 35 mcg EE (OR 0.9; 95% CI 0.5–1.6).^{47,48} In contrast, the second study found a more than two-fold increase in the rate of VTE (odds ratio 2.4, 95% CI 1.1–5.5) compared to oral contraceptive pill users.⁴⁹ There are no studies examining the risk of VTE events in patients using the Canadian transdermal contraceptive patch, nor the risk of such events with continuous or extended use of either patch. As with OCP use, physicians are advised to carefully assess a patient's baseline and cumulative risk of VTE before prescribing the transdermal contraceptive patch, particularly in adolescents with developmental disabilities with limited mobility.

Levonorgestrel Intrauterine System

The U.S. FDA approved the levonorgestrel intrauterine system (LNG-IUS) as a 5-year contraceptive agent in 2000. This intrauterine device is also being investigated for a variety of other uses, including idiopathic menorrhagia, endometriosis associated pelvic pain, hyperplasia and endometrial adenocarcinoma.

Once inserted into the uterine cavity, the LNG IUS releases 20 mcg/d progestin locally. Plasma levels of levonorgestrel reach a steady state of 100–200 pg/ml within the first few weeks after insertion, one tenth of the levels found with daily oral contraceptive use containing 150 mg levonorgestrel.⁵⁰ These low plasma levels of levonorgestrel have minimal effects on ovarian function and, although the LNG IUS has been shown to suppress ovulation in some women,⁵¹ its main contraceptive mechanism is through its inhibition of endometrial proliferation and sperm motility, and thickening of cervical mucus.⁵⁰ The histological changes in the endometrium induced by the LNG IUS have been observed for up to 7 years.⁵²

The LNG IUS causes a decrease in both the number of days of bleeding and the amount of menstrual blood loss due to its local endometrial effects.⁵³ Similar to continuous oral contraceptive use, a common complaint and the most common reason for discontinuation of the LNG IUS is irregular bleeding during the first 3–4 months of use. In a 2-year follow-up study of 256 women using the LNG IUS, 44% reported amenorrhea at 6 months and this rate was stable at 50% at 12 and 24 months after insertion.⁵⁴ The percentage of women with spotting was 25% at 6 months, and decreased to 8% and 11% at 18 and 24 months, respectively.

The efficacy of the LNG IUS as a contraceptive is comparable to that of tubal ligation, with a Pearl Index of 0.14.⁵⁵ Ectopic pregnancies remain a possibility and occur at an estimated rate of 0.2 per 1000 women-years. This is, however, significantly lower than a quoted ectopic pregnancy rate of 3.25–4.50 in those not using any form of contraception.⁵⁰

Traditionally, intrauterine devices were not recommended for patients with cognitive impairment because they may not be able to report discomfort or pain that could accompany a medical complication, such as uterine perforation at the time of insertion, pelvic inflammatory disease, or ectopic pregnancy.⁵⁶ Twenty-one cases of uterine perforation in predominantly parous unimpaired patients during LNG IUS insertion were reviewed, and in only 4 of the cases did the patients complain about the insertion being particularly painful.⁵⁷ It was estimated that the incidence of perforation was 2.6/1000.⁵⁷ Another randomized study comparing the safety and acceptability of a LNG IUS and oral contraceptives in young

nulliparous women reported no cases of uterine perforation in 94 attempted LNG IUS insertions.⁵⁸ There are no studies examining the use of the LNG IUS in the developmentally disabled population; however, the above findings would suggest that insertion in the nulliparous population is clearly possible and that one cannot rely on the report of pain for the detection of uterine perforation even in the communicative patient. It has been suggested that performing a transvaginal ultrasound after insertion may be helpful in detecting uterine perforation.⁵⁷ A preinsertion ultrasound exam to confirm normal uterine anatomy in the developmentally disabled population, where pelvic examination may be challenging, can be considered. A general anesthetic or conscious sedation would be recommended for insertion in this patient population.

A possible association between IUD use and pelvic inflammatory disease (PID) was initially suggested by case-control studies which lead to a significant decrease in IUD use, especially in higher risk populations, such as adolescent women.⁵⁹ A large meta-analysis found that women receiving an IUD have a higher risk of PID during the first 20 days after insertion compared with longer use.⁵⁹ Subsequent studies have shown that the LNG IUS is associated with a lower incidence of PID compared with the copper IUD, although others have found the rates to be comparable.⁶⁰ The patient must be screened for risk factors associated with PID prior to insertion and one should consider performing cervical swabs on all patients amenable to examination prior to IUD insertion. The risks and benefits must be explained to, and accepted, by the patient and/or caregiver.

The LNG IUS presents a viable option for menstrual suppression in the developmentally disabled population despite the lack of studies examining this use. Further research is needed to assess acceptance of this method especially with respect to family and patient acceptance of the initial nuisance bleeding and to quantify risks of uterine perforation and PID in this population.

Conclusion

The various medical treatment options available for menstrual suppression in adolescent women with developmental disabilities include DMPA, extended regimen of OCP or the transdermal contraceptive patch, and LNG IUS. Each option presents a variety of advantages and disadvantages, which must be considered for each individual patient. Furthermore, these methods are reversible and, therefore, if one option does not work to the satisfaction of the patient and caregiver, another option may be considered. While the contraceptive vaginal ring is yet another option

for menstrual suppression, practical aspects regarding administration limit its application in this patient population.

Further research is required with each of these treatment modalities in the developmentally disabled population for whom duration of treatment might be substantially longer and in whom medical comorbidities may affect treatment. While a variety of surgical approaches remain possible, they should be approached as secondary options, to be used only in recalcitrant cases not amenable to these multiple medical options.

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