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Mini-Review

Primary Dysmenorrhea in Adolescent Girls and Treatment with Oral Contraceptives

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Abstract. This review examines the prevalence, associated morbidity, and treatment of primary dysmenorrhea in adolescent girls. Relevant literature was examined by systematic, evidence-based review using MEDLINE and Cochrane Collaboration databases. Dysmenorrhea is highly prevalent during adolescence. Despite differences in measurement methods, 20%–90% of adolescent girls report dysmenorrhea and about 15% of adolescents describe their dysmenorrhea as severe. During adolescence, dysmenorrhea leads to high rates of school absence and activity nonparticipation. Most adolescents with dysmenorrhea self-medicate with over-the-counter preparations; few consult healthcare providers. Combined oral contraceptives (COC) are an accepted treatment for dysmenorrhea in nonadolescent women. However, data supporting the efficacy of COC is limited. Very small studies show decreased prostaglandin in menstrual fluid associated with high-dose COC use. Larger studies are limited to cross-sectional comparisons showing lower prevalence of dysmenorrhea in low-dose COC users compared to non-COC users. One small, randomized controlled trial including some adolescents demonstrated an improvement in dysmenorrhea with high-dose COC treatment compared to placebo. The efficacy of low-dose COC in the treatment of adolescent dysmenorrhea has yet to be determined. If effective, well-established safety and noncontraceptive health benefits may make COC an ideal treatment for dysmenorrhea in adolescent girls.

Key Words. Dysmenorrhea—Adolescents—Oral contraceptives

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Introduction

Primary dysmenorrhea is defined as pain during menses in the absence of an identifiable pathologic lesion. This menstrual pain can be associated with nausea, vomiting, diarrhea, and headache. The cause of dysmenorrhea remains unclear. Dysmenorrhea is highly prevalent among adolescent girls and has been identified as a leading cause of morbidity in this population, leading to school absence and activity nonparticipation. Combined oral contraceptives (COC) are a widely used treatment for primary dysmenorrhea in women. If effective, COC could be an ideal treatment for adolescent dysmenorrhea for the following reasons: COC are safe during adolescence, COC use is associated with several noncontraceptive health benefits important to adolescents, and adolescence is characterized by a high rate of unplanned sexual activity, pregnancy, and abortion. This systematic, evidence-based review will examine the prevalence and impact of primary dysmenorrhea in adolescent girls, and the efficacy of treatment of primary dysmenorrhea with COC.

Materials and Methods

The following search strategy was used to conduct a systematic review of existing evidence. First, MEDLINE was searched from 1966 to current using the medical subject heading dysmenorrhea with subheadings of classification, complications, prevention and control, physiopathology, diagnosis, drug therapy, economics, epidemiology, and therapy. The search was limited to human research published in English. A total of 775 citations were identified; 52 of these were selected for detailed review based on the title or the content of the abstract. Second, the Cochrane Collaboration Database was searched for protocols and reviews related to treatment of dysmenorrhea. The

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search identified one protocol (review pending) for treatment of dysmenorrhea with nonsteroidal anti-inflammatory agents (NSAIDS) but none relating to treatment with COC. A hand search of bibliographies from reviewed publications was also used to identify additional references.

Prevalence

Primary dysmenorrhea is highly prevalent among adolescent girls (Table 1). Most dysmenorrhea prevalence data come from convenience samples of varied populations. More representative and generalizable prevalence data come from two large cross-sectional studies. Klein[6] conducted the only population-based study of dysmenorrhea including younger adolescent girls using a national probability sample from the third cycle of the National Health Examination Survey. Andersch[7] examined the prevalence of dysmenorrhea in older adolescents by using a population registry to randomly sample one in four of all 19-yr-old females in Goteborg, Sweden. Of the 656 adolescents identified, 91% responded to the questionnaire. Despite differences in measurement methods, a majority of adolescents report experiencing dysmenorrhea and about 15% of adolescents describe their dysmenorrhea as severe. Klein[6] reported the lowest prevalence of severe dysmenorrhea among the youngest adolescents. This finding supports the widely held idea that dysmenorrhea is related to the establishment of ovulatory menstrual cycles.

Impact (Morbidity)

Dysmenorrhea is a major cause of activity restriction and school and work absence in adolescent girls. In a questionnaire study of 182 U.S. high school girls, 59% reported that cramps caused them to be less active, 45% reported ever missing school or work due to cramps, and 40% reported missing class in the past year due to cramps.[8] In a sample of Swedish school girls ages 14–19 yr, 15% reported being unable to participate in normal activities, 10% reported school absence, and 5% reported staying in bed due to dysmenorrhea.[1] Among 54 Norwegian factory workers aged up to 19 yr, 24% reported being absent from work in the previous 6 months.[9]

In a prospective cohort study, Harlow[4] collected menstrual diary data during the first year of university from 165 college entrants aged 17–19 yr. During the study, 1,396 bleeding episodes were observed. Those using COC were excluded. Menstrual pain led to ever missing any activity in 42% and ever missing school in 25% of subjects. Of the reported pain episodes, 10% were associated with missing any activity, 4% were associated with missing school, and 10% were associated with staying in bed.

In a larger, representative sample of U.S. adolescents aged 12–17 yr, 14% frequently missed school because of cramps.[6] Those with severe cramps (50%) were more likely to miss school than those with mild cramps (17%), and African-American girls (24%) were more likely than white girls (12%) to miss school due to cramps after adjustment for socioeconomic status. Some authors have estimated that dysmenorrhea is the single greatest cause of lost working hours and school absence in adolescent girls, although no systematic studies have prospectively examined the impact of dysmenorrhea on quality of life or cost.[10]

Dysmenorrhea may have an especially dramatic impact in adolescent girls due to undertreatment or no treatment in this group. In a national probability sample, Klein[6] reported that only 14% of U.S. adolescents aged 12–17 with dysmenorrhea sought help from a physician, including only 29% of those reporting severe dysmenorrhea. In a convenience sample of 182 white U.S. high school girls, 73% reported dysmenorrhea but only 16% had spoken to a doctor or nurse.[8] More, but still a minority, of girls who missed work or school because of cramps reported talking to a doctor

Table 1. Prevalence of Dysmenorrhea in Adolescents

Author year	Population	N	Mean age (years)	% reporting dysmenorrhea	% reporting severe dysmenorrhea
Svanberg 1981	Sweden, school	502	15	43%	8–18%[a]
Wilson 1989	U.S., school	88	15	91%	23%
Robinson 1992	U.S., family planning clinic	308	16	80%	18%
Harlow 1996	U.S., university	165	18	71%	14%
Campbell 1997	Canada, school	291	16	93%	5%
Klein 1981	U.S., NHES[b]	2699	(12–17)[c]	60%	9%
Andersch 1982	Sweden, 19-yr-olds	596	19	72%	15%

[a]reported as range by age

[b]NHES = National Health Examination Survey

[c]age reported as range

or nurse (26%). Of dysmenorrheic subjects who had not seen a physician or nurse, 68% felt their cramps were not severe enough, 20% thought it would not help, 5% were fearful of a pelvic exam, and 5% did not know where to seek care. In small studies from different populations, 30%–60% of girls report at least occasionally self-medicating with over-the-counter (OTC) preparations.[8,5,1,7] These studies have not evaluated the efficacy of OTC preparations in providing pain relief. One study reported that a majority of adolescents use nonpharmacologic methods such as heat, rest, or distraction to treat dysmenorrhea, with associated efficacy of 60% or less.[11]

Etiology

The cause of primary dysmenorrhea has not been clearly elucidated. However, prostaglandins (PGs) probably play an important role. PGs are a family of compounds derived from arachidonic acid, which is itself a derivative of membrane phospholipids.[12] Arachidonic acid is converted into prostaglandins via a system of enzymes referred to as the cyclooxygenase pathway.[12] Nonsteroidal anti-inflammatory agents (NSAIDS) inhibit enzymes of the cyclooxygenase pathway.

Small observational laboratory studies support a causative role of PGs in dysmenorrhea. In an early study, Chan[13] measured PGF2α activity in menstrual fluid from tampons. Unblinded investigators collected menstrual fluid from two women without dysmenorrhea and one woman with dysmenorrhea. PG activity was twice as high in the dysmenorrheic as in the nondysmenorrheic subjects. Lundstrom[14] noted that PG production increases in the presence of blood, and used a gas-chromatography technique to measure a primary PGFα metabolite not affected by blood in the sample. PGs were measured by unblinded investigators in plasma and endometrial samples from women the first day of the menstrual cycle. Women with dysmenorrhea receiving no medication had PGF2α levels three to four times as high in plasma ($n = 9$) and endometrium ($n = 5$) as nondysmenorrheic subjects receiving no medication ($n = 5$ and $n = 5$, respectively). PGs are commonly used in obstetrics to induce labor, and may lead to dysmenorrhea by causing contractions that induce uterine ischemia. Studies measuring intrauterine pressure have not consistently identified increased pressure in dysmenorrheic compared to nondysmenorrheic women.[15]

Treatment and Oral Contraceptives

Interventions such as herbal preparations,[16] transcutaneous nerve stimulation,[17] and exercise[18] have been reported to improve dysmenorrhea in small observational studies, but most research has focused on NSAIDS and COCs. NSAIDS probably decrease dysmenorrhea via direct inhibition of PG production. In early studies, Chan[19] and Lundstrom[14] found that PGF2α decreased and pain improved in small numbers of dysmenorrheic women ($n \leq 9$) treated with NSAIDS. Subsequent larger, randomized placebo-controlled trials have shown NSAIDS, including meclofenamate sodium ($n = 18$), zomepirac sodium ($n = 47$), ketoprofen ($n = 43$), ibuprofen ($n = 60$), and naproxen sodium ($n = 64$), to be effective treatments for primary dysmenorrhea.[20–25] These trials included some adolescents, but most subjects were in their twenties or older. At least one controlled trial has examined the efficacy of NSAIDS among adolescents. DuRant[26] randomized 45 girls with a mean age of 15 yr to five naproxen sodium dosing regimens for the treatment of dysmenorrhea. All regimens included naproxen for the first loading dose; placebo was incorporated into subsequent doses. A loading dose of 550 mg was associated with more improvement of dysmenorrhea than a loading dose of 275 mg by the third treatment month. The study lacked power to detect other dose-response effects.

The physiologic mechanism of COC impact on primary dysmenorrhea probably involves PGs and may be complex. Menstrual fluid PGs, serum PGs, serum arginine vasopressin (AVP), and intrauterine pressure all change with COC use. Chan[19] reported that PGF2α levels in menstrual fluid were lower in two women with dysmenorrhea effectively treated with COC than in six women with untreated dysmenorrhea or normal controls. Neither the type of COC used nor the PGF2α level before COC treatment were reported. Serum levels of AVP and 15-keto-PGF2α from seven women with moderate to severe dysmenorrhea before and after one cycle of treatment with a low-dose COC containing 30 μg ethinyl estradiol (EE) and 0.15 mg levonorgestrel were highly variable.[27] No difference in either PGF2α or AVP was seen when levels from the first day of control-cycle bleeding were compared to the first day of treatment-cycle bleeding, although subjects reported pain relief. Creatsas[28] also used serum levels of PGF2α and PGE2 before and after one cycle of treatment with a higher-dose COC (50 μg EE and lynestranol 2.5 mg) in 10 adolescent girls with dysmenorrhea. PG levels were slightly lower on the first day of bleeding after COC treatment than before COC treatment, and subjects reported pain relief. In two small studies by Ekstrom, intrauterine pressure as measured by total pressure amplitude decreased and pain improved on the first day of menstrual bleeding following treatment with low-dose COC.[30,29] Taken together, these small studies suggest COC may decrease pain by decreasing PG production and intrauterine pres-

sure. However, these studies were limited by the lack of a placebo-control group and the unblinded status of the investigators.

Observational studies support an association between COC use and decreased dysmenorrhea. Milsom[31] selected 596 Swedish women aged 19 yr, chosen at random from a population registry, and questioned them regarding dysmenorrhea and related absenteeism. A verbal multidimensional scoring system and a visual analog scale were used to grade dysmenorrhea. Oral-contraceptive users were grouped into those taking progesterone-dominant (levonorgestrel 0.15 mg with ethinyl estradiol (EE) 0.03 mg or levonorgestrel 0.25 mg with EE 0.05 mg) or low-progesterone-activity pills (lynestrenol 1.0 mg with EE 0.05 mg, lynestrenol 2.5 mg with EE 0.05 mg, or norethisterone 1.0 mg with mestranol 0.05 mg). Most reported use of pills containing 0.03 mg ethinyl estradiol. Results showed reduced prevalence and severity of dysmenorrhea as well as reduced absenteeism in the progesterone-dominant COC group compared to non-COC and non-IUD users. No differences were noted between the low-progesterone-activity group and the non-COC and non-IUD groups. The direct effect of COCs on dysmenorrhea is difficult to interpret due to the cross-sectional nature of the data and the relatively arbitrary distinction of progesterone activity between pills.

Robinson[32] followed a group of inner-city adolescents with a mean age of 16 yr attending a Baltimore family planning clinic after starting COCs for contraceptive purposes. The presence and severity of dysmenorrhea at baseline and at 3 and 6 months were determined by interview using a verbal multidimensional scoring system. Among the 56 girls with severe dysmenorrhea, 70% experienced either reduction in menstrual pain or menstrual bleeding after starting COCs. Those experiencing these positive side effects were eight times more likely to be consistent COC users than those who did not. The direct effect of COCs on dysmenorrhea is difficult to determine secondary to the lack of a control group and lack of information on which pills the subjects used.

Prospective, open-label studies also suggest improvement of dysmenorrhea after initiating COC use. In a study designed to determine the effect of COC on menstrual blood loss, Larsson[33] followed 20 Swedish women with a mean age of 24 yr for 6 months after initiating a COC containing 0.03 mg EE and 0.15 mg desogestrel. Fourteen women reported any dysmenorrhea before COC, which decreased to four women by 6 months of use. Weber-Diehl[34] followed 1933 German women for up to 36 cycles after starting a triphasic pill containing EE and gestodene. Eighteen percent of these subjects were less than 20 yr old. Compared to the pretreatment cycle, mild dysmenorrhea decreased from 20% to 4% and severe dysmenorrhea decreased from 5% to $<1\%$ by cycle 24. Ulstein[35] followed 367 Norwegian women for 12 months after starting a triphasic pill containing EE and levonorgestrel. Nearly 30% of the subjects were less than 20 yr old. Light dysmenorrhea decreased from 42% to 14% and heavy dysmenorrhea decreased from 10% to $<1\%$. Overall, the consistency of effect across populations and with different pill formulations, and the persistence effect over time, support the efficacy of COC in the treatment of dysmenorrhea. The placebo effect, however, may be substantial among volunteers for pill studies, and none of these studies included a placebo-control group. Also, few adolescents were included in these trials; results may not be generalizable to that population.

Together, these laboratory and observational studies suggest COCs are an effective treatment for primary dysmenorrhea. The lack of a placebo-control group in all of these studies is a major limitation. Studies designed to evaluate the efficacy of NSAIDS in the treatment of dysmenorrhea in women have consistently documented placebo-group response rates of 20%–50% with outcomes of pain relief and improvement of activity restriction during one to six treatment cycles.[25,21,24,23] The placebo effect probably attenuates over time. In a comparison of NSAID vs placebo, Fedele[36] showed that while 84% reported an excellent response to placebo in the first treatment cycle, only 10% reported an excellent response to placebo by the third treatment cycle.

Only one double-blind, randomized, placebo-controlled trial has examined the effectiveness of COC in the treatment of primary dysmenorrhea. In 1968, Matthews[37] conducted a randomized, double-blind controlled trial comparing the COC Sequens to placebo. This COC contained much higher doses of estrogen (80 μg) than pills currently in use, and unlike modern pills with progesterone and estrogen given simultaneously, progesterone (2 mg chlormadinone) was added only to the last five estrogen-containing pills. All subjects enrolled reported dysmenorrhea. Symptoms experienced at baseline and during 6 months in a crossover design were recorded. Patients were randomized to receive either COC or placebo during month 1 and 2, followed by 2 months of washout, then were assigned to the other treatment for the remaining 2 months. The mean age was 19 yr. Of the 59 subjects randomized, only 29 completed the trial. Total days of abdominal discomfort were slightly lower in the COC (2.9) than the placebo group (3.5), although this difference did not reach statistical significance. Maximum pain intensity rating after two months of treatment was lower in the COC group than in the placebo group ($P < 0.02$). The high dropout rate may have resulted in an overestimate of the COC

effect if those who discontinued did not experience improved dysmenorrhea.

Conclusions

Important gaps in knowledge remain in the treatment of dysmenorrhea. No randomized, placebo-controlled trial has examined the efficacy of modern, low-dose COC. The small laboratory studies and observational data supporting a positive effect of COC have included few adolescent girls, and even fewer have included minority adolescent girls. Inclusion of adolescents in dysmenorrhea trials is especially important given undertreatment and high morbidity in this group. Also, studies conducted with adults may not be generalizable to adolescents, who experience unique psychosocial stresses. Psychological factors could influence adolescents' response to COC for dysmenorrhea. In a study of NSAID therapy for dysmenorrhea, DuRant[26] found that more life-crisis events and lower self-concept ratings were associated with less pain relief among adolescent girls. Depression could also be an important predictor of response to treatment among adolescents.

NSAIDS have been established as an effective therapy for dysmenorrhea. However, if effective, COC may be a superior treatment among adolescents. COC use in healthy adolescent girls is safe,[38] and COC are effective in treatment of acne, irregular menstrual cycles, iron deficiency anemia, prevention of ovarian cysts, prevention of pelvic inflammatory disease (PID), and most importantly, prevention of pregnancy.[39] Many adolescents in the United States are sexually active and unplanned pregnancy, abortion, and teen childbearing rates are high compared to other industrialized nations.[40] Noncontraceptive benefits may help to improve adolescent compliance with COC and therefore decrease risk of pregnancy. Robinson[3] found that among inner-city adolescents in Baltimore, girls who experienced improvement in dysmenorrhea were eight times more likely to continue COC than those who did not.

In summary, dysmenorrhea leads to important, undertreated morbidity in adolescent girls. The great potential benefits of COC use in this population should make the study of COC as a primary treatment for adololescent dysmenorrhea a research priority.

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