Dysmenorrhea: Basic Research Leads to a Rational Therapy

The discovery of the biochemical abnormality causing dysmenorrhea is finally paying off in an effective therapy

It is not exactly life-threatening, and some people, usually men, do not seem to take it seriously. But for millions of women, dysmenorrhea (menstrual cramps) is a painful—sometimes incapacitating—fact of life. According to textbook estimates, 30 to 50 percent of women of childbearing age suffer from the condition, which results in the loss of more than 140 million working hours every year.

Some cases of dysmenorrhea are caused by known pathological conditions, such as fibroid tumors of the uterus or endometriosis, a condition in which tissue resembling the uterine lining occurs abnormally in various locations in the pelvic area. Many women, however, have menstrual cramps without having any sign of abnormalities such as these. The cause of this "primary" dysmenorrhea is generally considered unknown, although, as it turns out, there have at least been clues to what is going on for more than 15 years.

With the cause of primary dysmenorrhea unrecognized, the treatment has mostly been unsatisfactory. Usually a woman is given either pain-killers, which do not relieve all the symptoms and may cause drowsiness or grogginess, or birth control pills. If the latter, a woman who does not also want to use the pills to prevent pregnancy ends up taking powerful hormones 21 days a month just to treat a condition that occurs 1 or 2 days a month. Even psychotherapy has been tried, on the assumption that dysmenorrhea does not have a physiological basis but is "all in the head."

Contrary to this view, however, an accumulating body of evidence is showing that primary dysmenorrhea does have a physiological basis—overproduction by the uterus of prostaglandins, potent chemicals that have a number of physiological effects and are produced by many tissues of the body. "Not only does a prostaglandin excess help to explain the painful cramps of dysmenorrhea," says gynecologist Arpad Csapo of Washington University Medical School, "but it can readily account for the additional symptoms." These include nausea, vomiting, diarrhea, headache, fatigue, and nervousness.

Recently, this better understanding of the cause of menstrual cramps has begun to be applied to the development of more effective therapies, using a number of drugs known to inhibit prostaglandin synthesis. Clinical trials are now showing that these drugs provide substantial relief of the painful cramping and other symptoms of dysmenorrhea.

Because menstrual cramps resemble labor pains caused by the contracting uterus, uterine contractions have long been under suspicion as the cause of the cramps. The earliest clue that prostaglandins, some of which are powerful stimulators of smooth muscle contraction, might trigger the contractions of the uterus came from the work of V. R. Pickles and his colleagues at the University of Sheffield in England. In 1957 they found in menstrual fluid a lipidlike material that stimulates uterine contractions. They called the material menstrual stimulant, and about 6 years later identified prostaglandins, of both the E and F types, as the active components. Significantly, they often found more prostaglandins in menstrual fluid from dysmenorrheic women than in fluid from women who did not suffer menstrual cramps.

Since then research has revealed that prostaglandins, by triggering uterine contractions, play a pivotal role in the initiation of both menstruation and labor. During pregnancy and the last half of a woman's monthly cycle, says Csapo, this effect of the agents is held in check by high concentrations of the hormone progesterone, which acts to prepare the uterine lining for the implantation of a fertilized egg and then to maintain the pregnancy. For example, during studies of the use of prostaglandins to induce abortion, he and his colleagues found that a delay of several hours must elapse between the time of prostaglandin administration and the start of labor-like contractions.

Progesterone is produced in large quantities during pregnancy, and, apparently, the prostaglandins must first turn off synthesis of the hormone in order to exert their effects on the uterine muscle. The delay is needed to allow progesterone concentrations to fall to a low enough level to let the agents work. Subsequent studies with laboratory animals confirmed the role of the prostaglandins in activating uterine contractions, but only in the absence of progesterone.

One outgrowth of this research has been the use of prostaglandins E and $F_{2\alpha}$ (PGE and $PGF_{2\alpha}$) to induce labor and also to induce abortions between the sixth and seventeenth weeks of pregnancy. Conversely, inhibitors of prostaglandin synthesis are being investigated for preventing labor in women in danger of giving birth prematurely.

High progesterone concentrations also prevent prostaglandins from inducing menstruation, according to Csapo. After ovulation, progesterone production in the ovary increases markedly and prostaglandin production by the uterus goes up somewhat. But toward the end of the cycle, if pregnancy has not occurred, progesterone concentrations drop rapidly and prostaglandin concentrations increase dramatically, causing the uterus to contract and slough off its lining.

Several investigators, confirming Pickles' observation, have now shown an excessive increase in prostaglandin concentrations in menstrual fluid from women with primary dysmenorrhea. The concentrations, say W. Y. Chan and Yusoff Dawood of Cornell University Medical College, are some two to three times higher than those in menstrual fluid from women who do not have the problem and are highest just when a woman's symptoms are most severe, on the first day or two of menstruation. Then they fall off. Accompanying the increased concentrations, according to Csapo, are higher resting pressures in the uterus between contractions and also an increased contraction frequency.

The excessive resting pressure causes pain, especially since it may slow the flow of blood to the uterine muscle just when the demand for it is high because of

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the work the muscle is doing. Such oxygen deprivation produces pain. In addition, both the prostaglandins and some of the substances from which they are synthesized may act directly on pain nerve endings, making them more sensitive.

The other symptoms of dysmenorrhea—nausea, vomiting, diarrhea, headache, and so forth—may be caused by the prostaglandins stimulating contractions of the smooth muscles of the stomach, intestines, and blood vessels. (The latter effect could cause headache by decreasing blood flow to the brain.) All these symptoms are known side effects of PGE and $PGF_{2\alpha}$ administration.

If excessive prostaglandin production does cause primary dysmenorrhea, then prostaglandin synthesis inhibitors would be the logical therapy for the condition. Several such drugs, among them ibuprofen (a product of the Upjohn Company), indomethacin (Merck Sharp & Dohme), mefenamic acid (Warner-Lambert), and naproxen-sodium (Syntex Corporation), have been tested. The agents, which are classified as nonsteroidal, anti-inflammatory drugs, are currently registered by the Food and Drug Administration for the treatment of arthritis, but not, at this time, for dysmenorrhea.

The investigators* who are performing clinical trials on dysmenorrhea are unanimous; the prostaglandin synthesis inhibitors work. Pain is not easy to assess objectively, but whether the rating has been the woman's or the physician's, based on his or her evaluation of the woman's description of her symptoms, the conclusion has always been the same. The drugs provide good—often complete—relief of all the symptoms when compared to inert controls.

In fact, the placebo effects of the controls have generally been slight, an effect militating against the likelihood that dysmenorrhea is strictly psychosomatic. Other indications of the drugs' effectiveness includes less use of pain-killers and fewer days of incapacitating symptoms.

Objective measurements confirmed the effectiveness of prostaglandin synthesis inhibitors. For example, Csapo, with Martti Pulkkinen of Turku University Medical School in Finland, and Chan and Dawood demonstrated marked reductions in the prostaglandin concentrations of the menstrual fluid of women taking naproxen-sodium or ibuprofen, whereas the placebos did not alter the concentrations. Csapo and Pulkkinen also found that ibuprofen and naproxen-sodium reduced the uterine resting pressures and the force and frequency of the contractions. Thus, the reduction in symptoms was paralleled by a decrease in concentration of the suspected culprits.

One prostaglandin synthesis inhibitor that does not appear to control menstrual cramps very well is aspirin. Milan Henzl and his colleagues at the Syntex Corporation directly compared aspirin with naproxen-sodium in a double-blind crossover study. (Each woman took first one drug and then the other; neither the woman nor the clinicians conducting the trial knew which agent she was taking in a given cycle until the trial was over.) Almost 75 percent of the women found naproxen-sodium more effective than aspirin, whereas only 20 percent preferred aspirin to naproxen-sodium. The remainder expressed no preference. Aspirin did only slightly better in this study than placebos in other studies.

Other investigators have shown that aspirin is a weak inhibitor of prostaglandin synthesis. It is only about one-thirtieth as effective as some of the other agents, a finding that may help to explain its poor showing as a therapy for menstrual cramps. Moreover, aspirin itself is inactive and has to be converted to gentisic acid, the active material. The uterus may be less sensitive to this material than other tissues or it may not receive enough of it to do any good.

In the early trials, the drugs were often given one to a few days before menstruation began, on the theory that it was necessary to prevent the buildup of prostaglandins. In the later trials, however, women did not begin to take the drugs until there were signs that the cramps were starting. There was no apparent decrease in the agents' effectiveness as a result of the change. "This is not really surprising," according to Thomas Vecchio of Upjohn, "we always knew that the prostaglandins are broken down very rapidly. We do not need to get a head-start to prevent cramps."

This conclusion is important because the effects of the drugs on very young embryos are not known. Not taking them until menstruation begins makes it very unlikely that a woman will inadvertently take them in the early stages of pregnancy and possibly damage the embryo. The drugs are then taken as needed as long as the symptoms are bothersome, usually only for 1 or 2 days.

The side effects of the various agents, with the exception of indomethacin, are by all accounts minimal. Higher doses of indomethacin caused headaches, gastrointestinal upsets, and mood disturbances in which the patients reported they felt disoriented or "spaced out." The effects tended to disappear at lower doses.

The occasional side effects of the other agents included nausea and light-headedness. Since these are also symptoms of dysmenorrhea, it is hard to tell whether they are truly side effects of the drugs.

Their relative freedom from side effects does not mean that everyone can take prostaglandin synthesis inhibitors. Dawood points out that women who have a history of asthma or ulcers of the gastrointestinal tract should not take them because the agents may aggravate these conditions.

Although birth control pills do not directly inhibit prostaglandin synthesis, they do so indirectly, an effect that may explain why the pill alleviates menstrual cramps. Chan and Dawood determined the prostaglandin concentrations in the menstrual fluid of two women while they were taking oral contraceptives to relieve dysmenorrhea and then after they stopped taking them. While the women were on the pill, the concentrations were low, but they increased to the elevated values seen in other dysmenorrheic women soon after the women stopped taking it. The women's symptoms returned, too.

Birth control pills suppress both ovulation and the growth and thickening of the uterine lining needed for implantation of the fertilized egg. Most prostaglandin synthesis by the uterus is thought to take place in the uterine lining when it is in this proliferative state. Thus the pill indirectly suppresses prostaglandin production and, consequently, menstrual cramps.

But Chan and Dawood do not recommend oral contraception for treatment of dysmenorrhea unless the woman also wants to use it for birth control. Use of prostaglandin synthesis inhibitors, they point out, is a rational and specific therapy for dysmenorrhea. Use of the pill is neither rational nor specific.

Thus, a remarkably consistent body of evidence now indicates that increased prostaglandin synthesis underlies many cases of primary dysmenorrhea—although not all. Chan and Dawood identified two women who had normal concentrations of the chemicals in their menstrual fluid but still had painful menstrual symptoms. But most of the women studied have had an identifiable biochemical abnormality—and, encouragingly, an abnormality that appears amenable to rational treatment.—JEAN L. MARX

*Among the investigators conducting clinical trials of prostaglandin synthesis inhibitors for the treatment of dysmenorrhea are Penny Budoff of the State University of New York, Stony Brook; W. Y. Chan and Yusoff Dawood, Cornell University Medical College; Arpad Csapo, Washington University Medical School; David Halbert and Laurence Demers, Milton S. Hershey Medical Center; Milan Henzl, Syntex Corporation; and Martti Pulkkinen, Turku University School of Medicine, Turku, Finland.