

Aspirin Fails to Prevent Recurrent Miscarriages

BY JANE SALODOF MACNEIL

NEW ORLEANS — Neither aspirin nor a combination of aspirin and low-molecular-weight heparin improved live birth rates in a randomized, placebo-controlled trial conducted in 364 women with unexplained recurrent miscarriages.

An intent-to-treat analysis of the ALIFE (Anticoagulants for Living Fetuses) study showed live birth rates in women seeking to carry a pregnancy to term were not affected by prophylaxis. The rates were 54.5% in 123 women given low-dose aspirin and nadroparin (a low-molecular-weight heparin [LMWH] sold in Europe), 50.8% in 120 women given low-dose aspirin alone, and 57% in 121 women given placebo.

When the investigators looked only at women who became pregnant during the trial, the live birth rates were hardly better and not significantly different: 69.1% in 97 women treated with the as-



'We couldn't find the beneficial effects in our study of three treatment arms—[there was] no difference at all.'

DR. KAANDORP

pirin-LMWH combination, 61.1% in 99 women given aspirin alone, and 67% in 103 women given placebo.

"We couldn't find the beneficial effects in our study of three treatment arms—[there was] no difference at all," Dr. Stef P. Kaandorp said during a press briefing at the annual meeting of the American Society of Hematology.

Despite a dearth of evidence in support of anticoagulant prophylaxis, a large albeit unknown number of physicians give these agents to desperate women in the United States and Europe, according to Dr. Kaandorp and his co-investigators at eight centers in The Netherlands.

The desire to help these women carry a child to term is so strong that colleagues in the United States, France, and Israel had argued that giving a placebo would be unethical in this population, senior author Dr. Saskia Middeldorp said in an interview. Obstetricians warned

VITALS

Major Findings: Neither aspirin nor a combination of aspirin and low-molecular-weight heparin improved live birth rates in a study of 364 women with unexplained recurrent miscarriages.

Data Source: The randomized placebo-controlled ALIFE study.

Disclosures: The ALIFE trial received funding from ZonMW, the Dutch Organization for Health Research and Development (945-27-003); an unrestricted grant from GlaxoSmithKline BV; and study medications (calcium carbasalate and placebo) from Vemedica BV. None of the funding sources were involved in the study protocol preparation, trial management, or data analysis, according to the abstract. Dr. Kaandorp had no financial disclosures. Dr. Middeldorp and another coinvestigator disclosed consultancy, honoraria, and research funding from GSK.

they would not participate if the investigators ignored their advice and went ahead with the trial.

In addition, many pregnant women buy aspirin over-the-counter to prevent miscarriage based on advice from other women in on-line chat rooms, according to Dr. Middeldorp, an internist specializing in vascular medicine at Leiden University Medical Center.

It is not clear whether the trial's findings will put an end to these practices. Dr. Bradford Schwartz, who moderated the press briefing, said the decision in the United States is up to the individual physician.

"I would say this is high-quality data that is likely to influence the way people make their therapeutics decisions. It certainly should influence those decisions," said Dr. Schwartz, a professor of medicine and biochemistry and dean of the University of Illinois College of Medicine at Urbana-Champaign.

Dr. Kaandorp, a research fellow in the department of obstetrics and gynecology at the Academic Medical Center in Amsterdam, sympathized with physicians who want to help these women, but he was emphatic that anticoagulant prophylaxis is not justified in women with unexplained recurrent miscarriages. "To give medication that is potentially harmful is not the way to do it," he said.

None of the participants in the study had excess bleeding events, but the study was too small to detect these, Dr. Kaandorp added in response to a question. About 40% of the women who had been injected with LMWH had skin reactions.

Half of this group also had bruising, compared with 19% in the aspirin-only group and 12% of women on placebo (P less than .001).

The rationale for using aspirin and heparin to prevent miscarriage is based on the possibility that hypercoagulability might contribute to miscarriage. Evidence supports the use of these agents for this

purpose in women with antiphospholipid syndrome (Obstet. Gynecol. 2002;99:135-44), and suggests that recurrent miscarriage might be related to thrombosis risk (Hum. Reprod. 2005;20:1729-32).

A literature review by four of the current authors found, however, "a paucity in studies on the efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia" (Cochrane Database Syst. Rev. 2009 Jan. 21;CD004734).

The ALIFE trial excluded women with antiphospholipid syndrome as well as those with a history of thrombosis, uterus anomaly, abnormal karyotype, or indication for anticoagulants. To be eligible, women aged 18-42 years had to

have two or more unexplained miscarriages and be either trying to conceive or less than 6 weeks pregnant.

Women in the two aspirin arms took calcium carbasalate (Ascal) equivalent to acetylsalicylic acid 80 mg daily from the day of randomization until 36 weeks of gestational age. Nadroparin 2,850 IU was injected after a pregnancy was confirmed by ultrasound from 6 weeks of gestational age until the end of pregnancy.

The average age was about 33 years, and the median number of unexplained miscarriages was three. Among the women who were randomized, 103 completed treatment in each of the aspirin-plus-nadroparin and placebo arms; 104 took all treatments in the aspirin-only group.

The author could find no significant differences in subgroup analyses of women with inherited thrombophilia, preceding live birth, age less than 36 years, or three or more previous miscarriages. The investigators did see a trend toward improved live birth rate in 47 women with inherited thrombophilia, however (relative risk ratio 1.56, $P = .18$).

The study was underpowered to draw a conclusion on whether women with inherited thrombophilia might benefit from anticoagulant prophylaxis, Dr. Kaandorp said, promising to explore this question. "At this moment I think we should not treat those women, but should do another trial in that population," he said. ■

Study Confirms Common Sense

MY TAKE

In women in whom no specific cause is found for miscarriage, no specific treatment should be used. Thus a treatment that is specific for pregnant women with inherited thrombophilia or antiphospholipid syndrome should not be given to pregnant women without such diagnoses. If you use aspirin in mid-pregnancy, you increase the risk of pregnancy loss and placental abruption. So if there is no proven benefit to this treatment, this seems like a bad deal. On the other hand, if a woman comes into an ob.gyn.'s office having had two miscarriages and says, "Do something," some physicians may say, "Give them what they want."

But this study has shown that aspirin does not prevent recurrent idiopathic miscarriages and does cause bruising. Low-molecular-weight heparin is probably even worse in terms of potential risks and complications.

If you do not find the problem you are looking for—that is, inherited thrombophilia or antiphospholipid syndrome—treat-

ment is dangerous and not helpful.

Are these data new? Prior studies of aspirin use in pregnancy have demonstrated an increased risk of placental abruption in aspirin-treated women. The current study confirmed what logic told you was the right thing to do: Don't use them.

In practice I occasionally see physicians prescribe a treatment for a pregnant patient, saying, "What harm can it do?" It was that kind of thinking that led to the DES debacle some 40 years ago. When dealing with pregnancy, you can't say, "What harm can it do?" because the results can be disastrous. It is good that these researchers performed this study because it confirmed what most rational physicians know: We should use only treatments definitely shown to work, especially during pregnancy.

GERSON WEISS, M.D., is the chairman of the department of obstetrics and gynecology at New Jersey Medical School, Newark. He said he had no relevant disclosures.

Ob.Gyn. News

THE LEADER
IN NEWS
AND
MEETING
COVERAGE

#1

Thanks For
Making Us

Source: PERQ/HCI Corp., Focus® Medical/Surgical June 2009 Readership Summary; Obstetrics and Gynecology Section, Office-Based, Table 702 Projected Average Issue Readers