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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Menopausal Hormone Therapy: Useful and Indicated for Vasomotor Symptoms

By Robert W. Rebar, MD

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Dr. Rebar reports no financial relationships relevant to this field of study.

SYNOPSIS: Menopausal hormone therapy is the most effective treatment for symptoms of the menopause, and benefits may exceed risks for most women within 10 years of menopause.

SOURCE: Stuenkel CA, et al. Treatment of symptoms of the menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015;100:3975-4011.

The Treatment of Symptoms of the Menopause Task Force appointed by the Endocrine Society developed a consensus document on the role of menopausal hormone treatment (MHT). Based on the evidence, the task force concluded that MHT is the most effective treatment for vasomotor symptoms (VMS) and improves genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive symptoms, and arthralgias. It further concluded that the benefits may exceed the risks for the majority of symptomatic postmenopausal women < 60 years of age or within 10 years of the onset of menopause. The task force further emphasized the need for health care providers and their patients to use a shared decision-making approach to choose the most appropriate therapy only after a careful assessment of individual risks and benefits. Use of MHT is not warranted to prevent coronary heart disease, breast cancer, or dementia. The task force also noted that there are other, albeit less effective, therapies for individuals with VMS who cannot or choose not to use MHT. Similarly, they noted that low-dose vaginal estrogen and ospemifene are effective in treating the genitourinary syndrome of menopause and that various vaginal moisturizers and lubricants are also effective for those who do not choose hormonal therapy. The task force further emphasized that estrogens alone should be prescribed for women

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without a uterus, and progestogens should be added only for those with a uterus. Starting dosages generally should be lower than those utilized in the Women's Health Initiative (WHI, 0.625 mg conjugated equine estrogens with or without 2.5 mg medroxyprogesterone daily) and should be titrated upward until the appropriate clinical response is achieved. The task force also recommended against the use of custom compounded hormones. Although the use of MHT is recommended for the shortest duration possible, strong evidence to support this conclusion is lacking. Thus, clinicians and their patients should reassess MHT continuation yearly and consider the risks and individual benefits beyond 5 years of use. Continuing therapy can be considered for those who become symptomatic after stopping MHT, those at high risk of osteoporotic fractures, and those for whom alternative therapies are not appropriate and who have no contraindications to continuing therapy. For young women with premature ovarian insufficiency or premature menopause, MHT can be taken until the time of anticipated natural menopause when the use of continued MHT can be reassessed. The task force concluded its recommendations by noting that the most important question for postmenopausal women is how to balance menopausal symptom relief with the prevention of chronic diseases of aging and by emphasizing the need for further research.

■ COMMENTARY

Publication of the initial results of the WHI in 2002[1] changed the use of hormone therapy for menopausal women dramatically. In some sense, the changes that occurred were warranted: No therapy should be provided to any individual without a specific indication, and MHT was being given to women who had no reason to initiate therapy. Simultaneously, however, the report and the ensuing publicity led to a marked reduction in usage of MHT even by symptomatic menopausal women who might well have benefited greatly. That the initial findings of the WHI were misleading and are more complex and difficult to interpret than initially reported was discussed in a recent commentary in *OB/GYN Clinical Alert*.[2] In fact, in a recent reanalysis of the data from the WHI for women 50 to 59 years of age, the benefits for women using estrogen alone or estrogen and progestin seemed to outweigh the risks.[3] To be sure, the WHI was not powered for age-related subset analyses, and none of the data were significant, but the data indicated that all-cause mortality was favorably influenced in both arms of the study for women initiating MHT close to the menopause. When these data are analyzed over a 5-year period, there seems to be similarly beneficial effects.[4]

I chose to call this guideline to your attention because it is such a powerful statement recommending consideration of use of MHT — and it has been provided to a group consisting largely of internist-endocrinologists. Moreover, despite the reanalysis of the WHI data, most clinicians remain wary of the use of MHT, and the majority of symptomatic women in the United States who might benefit from MHT are, in fact, not receiving therapy. As women's health care providers, we have an obligation to educate other clinicians about the responsible use of MHT. We also have a responsibility to provide accurate and appropriate information to our patients.

While this guideline hardly provides all of the answers, it does provide a framework for beginning to discuss the use of MHT with other clinicians and patients. There is clearly a balance that must be struck between ruling out MHT for all women and providing MHT to all. It is now clear that MHT should not be provided to women to prevent chronic diseases, such as cardiovascular disease, but it continues to play a very important role in treating women with VMS. This is particularly relevant in light of recent data from the Study of Women Across the Nation (SWAN), which noted that frequent VMS, defined as experiencing hot flushes or night sweats for 6 days in the 2 weeks before being seen, lasted more than 7 years during the menopausal transition and persisted for 4.5 years following the final menstrual period in women who had such symptoms.[5] Women who were premenopausal or early postmenopausal when they first reported frequent VMS had the longest total VMS duration (median > 11.8 years) and persistence following the final menstrual period (median 9.4 years). Interestingly, the SWAN study noted differences among various ethnic groups, with African-American women having the longest total duration (median 10.1 years). Earlier SWAN data showed that experiencing frequent VMS is highly related to anxiety, depression, sleep disturbances, quality of life, cardiovascular risk, bone health, and

how much VMS bother women. Thus, MHT should be of significant benefit to women with frequent VMS, and frequent VMS can be expected to last for several years. Personally, I have seen an 86-year-old woman who reported having frequent VMS since beginning menopause at age 50! However, such therapy should be provided only after appropriate risk assessment and counseling.

Over time as the information about MHT becomes more widely disseminated, we can only hope that MHT will be used more appropriately when it should and avoided when usage is inappropriate. It is for us the knowledgeable to provide that information. We should also recognize that a single large randomized trial, which was inappropriately analyzed, deprived an entire generation of women from receiving potential benefits of MHT. We should remain vigilant to ensure that this never happens again. ■

REFERENCES

1. Roussouw JE, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
2. Brewer MA. Hormone replacement therapy controversies: Have we harmed women? *OB/GYN Clinical Alert* 2016;32:68-70.
3. Manson JE, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-1368.
4. Santen RJ, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95:s1-s66.
5. Avis NE, et al. Duration of menopausal vasomotor symptoms over the menopausal transition. *JAMA Intern Med* 2015;175:531-539.

ABSTRACT & COMMENTARY

Low-dose Aspirin and Preeclampsia

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: A study comparing outcomes before and after offering low-dose aspirin to patients who were deemed to be high risk by a first trimester protocol showed a decrease in preterm birth prior to 34 weeks and a decrease in early-onset preeclampsia.

SOURCE: Park F, et al. Prediction and prevention of early onset preeclampsia: Impact of aspirin after first trimester screening. *Ultrasound Obstet Gynecol* 2015;46:419-423.

Controversy abounds regarding whether preeclampsia can be prevented with low-dose aspirin (ASA) and, if it does, whether selected high-risk patients or every pregnant patient should be on this medication. An article from Australia by Park et al may shed some light on these issues.[1]

This "before and after" study, which was conducted between April 2010 and March 2012, identified a group of women who were screened for preeclampsia during the first trimester (the observational group) with an already validated algorithm[2] based on demographic history, mean arterial pressure, uterine artery waveform analysis, and pregnancy associated plasma protein A. No treatment was offered to these patients during this time period.

The second (interventional) group was screened between April 2012 and June 2013 using the same first trimester protocol, but those deemed to be at "high risk" (> 2% chance of having early-onset preeclampsia) were offered treatment with a nightly dose of 150 mg ASA up until the 34th week of gestation. The records were then tracked carefully for signs of preeclampsia (elevated blood pressure and proteinuria). Those having elevated blood pressure prior to 20 weeks were labeled as chronic hypertensives.

There were 3066 patients in the observational group (over 24 months) and 2717 patients in the interventional group (over 15 months). When comparing outcomes between the two sequential groups overall (regardless of risk), the only variable showing a significant difference was a decrease in the rate of delivery prior to 34 weeks in the group treated with nightly ASA (0.40% vs 0.04%, $P < 0.01$). However, when comparing the patients in each group at risk for preeclampsia (301 vs 264), the treated (interventional) group had an incidence of preeclampsia that was almost halved in the observational group (2.36 vs 1.42%, $P < 0.01$.) Also, the rate of those needing delivery before 34 weeks was significantly lower (3.6% vs 0.38%, $P < 0.01$) in the interventional group vs the observational group, respectively. There were no significant differences in other variables such as abruption, but there was a trend toward a lower risk of stillbirth (0.29% vs 0.11%) in the group treated with ASA.

■ COMMENTARY

After initiating a policy of offering low-dose ASA (150 mg) early in pregnancy to patients at risk for preeclampsia, there was a significantly reduced chance of preeclampsia and a significant drop in patients delivering prior to 34 weeks, suggesting that the

stronger the predilection for preeclampsia, the stronger the effect of the ASA.

Because of the low prevalence of pre-eclampsia in low-risk patients, it has been hard to prove the benefit of low-dose ASA, and even in the high-risk patients, the results have been inconsistent.[3] However, as sometimes happens, individual randomized, controlled trials (RCTs) may not show differences between ASA treatment and control patients, but a cumulative meta-analysis of these studies did detect a difference.[4] What does seem clear is that the benefit is greatest if the ASA is initiated at, or prior to, 16 weeks[5]: ergo, the move to screen in the first trimester.

So why not give everyone ASA? "ASA-for-all" advocates might say that a low chance of benefit has not discouraged, seemingly, every man in the Viagra-taking age group from taking daily low-dose ASA for prevention of adverse cardiovascular events. Well, in the spirit of "do no harm," there has been a nagging doubt about an increased risk of abruption. This arose from one of the early NICHD (Eunice Kennedy Shriver National Institute of Child Health and Human Development) network RCTs[3] and another later study.[6] Other studies, as well as the above study, have not shown a trend toward an increase in abruptions with ASA, but most were not powered to show a difference. The other problem is a potential allergy to the medication, as well as gastric intolerance. Also, it seems like a dubious undertaking to give ASA to a low-risk population where thousands of patients would be treated to prevent one patient from getting preeclampsia. However, for high-risk patients the numbers can make sense. For example, in the above index study,[1] the authors stated that for every 296 patients screened, 29 high-risk patients would be earmarked to take ASA to prevent one case of "early" preeclampsia. The drawback, of course, is that, if using their protocol, every patient would need first trimester uterine artery wave form analysis and biochemistry, the former being something that is uncommonly done in the United States.

The before-and-after study design is vulnerable to some criticism, but, despite its shortcomings, the findings were worth doing the retrospective analysis. I do question why the investigators chose 150 mg, rather than the 84 mg dose used most commonly. This "if some is good, more is better" approach certainly did not show that 150 mg was superior to the standard dose, and it leaves us in a quandary now regarding which regimen to follow.

Until new information surfaces, it seems reasonable to identify those at greatest risk by whatever protocol one wishes to use and to treat with low-dose ASA before 16 weeks, and preferably by the end of the first trimester. I'll continue to use the one tablet, 84 mg dose, at night and will recommend discontinuing it at 34 weeks, because in some hospitals anesthesiologists are reluctant to administer epidurals in patients with ASA on board, and there is no evidence of prophylactic benefit past this point. It must be realized that with uterine artery screening, there is a very high screen positive rate for preeclampsia, compared with second trimester screening, but then one misses the ideal treatment window with the latter approach. ■

REFERENCES

1. Park F, et al. Prediction and prevention of early onset preeclampsia: Impact of aspirin after first trimester screening. *Ultrasound Obstet Gynecol* 2015;46:419-423.
2. Park F, et al. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease in pregnancy. *Aust NZ J Obstet Gynecol* 2013;53:532-539.
3. Caritis S, et al. Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998;338:701-705.
4. Askie LM, et al; PARIS Collaborative Group. Antiplatelet agents for prevention of preeclampsia: A meta-analysis of individual patient data. *Lancet* 2007;369:1791-1798.
5. Roberge S, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: A systemic review and meta-analysis. *Fetal Diagn Ther* 2012;31:141-146.
6. Yu CK, et al; Fetal Medicine Foundation Second Trimester Screening Group. Randomized controlled trial using low dose aspirin in the prevention of preeclampsia in women with abnormal uterine artery Doppler at 23 weeks' gestation. *Ultrasound Obstet Gynecol* 2003;22:233-239.

ABSTRACT & COMMENTARY

Does a History of D&C Increase the Risk of Premature Delivery?

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: In a meta-analysis, a history of dilation and curettage for management of miscarriage or termination of pregnancy was associated with an increased risk of preterm birth in a subsequent pregnancy but the association is weak and most likely explained by confounding.

SOURCE: Lemmers M, et al. Dilatation and curettage increases the risk of subsequent preterm birth: A systematic review and meta-analysis. *Hum Reprod* 2016;31:34-45.

Since dilation and curettage (D&C) is one of the most frequently performed procedures in reproductive-aged women, any effect of the procedure on outcomes of subsequent pregnancies is important. To evaluate whether D&C increases the risk of subsequent preterm birth, the authors performed a systematic review and meta-analysis of previously published studies. Since no randomized studies exist, they searched the medical literature and selected cohort and case-control studies comparing subsequent preterm birth in women who previously had been managed surgically for first trimester miscarriage or termination of pregnancy to a control group of women without a history of D&C (predominantly suction curettage). From more than 2100 citations identified, only 21 studies met the inclusion criteria. These reported outcomes of 1,853,017 women; 77,231 had a history of at least one first trimester D&C (> 90% were terminations). The control group of 1,781,786 women included 24,977 with a history of medical management of miscarriage/abortion and 1189 with a history of spontaneous abortion. The primary outcome was preterm birth in a pregnancy subsequent to a history of curettage.

Compared to women with no history of D&C, those with a history of suction curettage had an increased odds ratio (OR) for preterm birth < 37 weeks (OR, 1.29; 95% confidence interval [CI], 1.17-1.42). The association strengthened for very preterm birth: < 32 weeks (OR, 1.69; 95% CI, 1.20-2.38) and < 28 weeks (OR, 1.68; 95% CI, 1.47-1.92). A "dose response" was also observed for women with a history of multiple D&Cs compared with those with no D&C (OR for preterm birth < 37 weeks, 1.74; 95% CI, 1.10-2.76). However, when the control group included only those women with a history of medically managed miscarriage or induced abortion, the association weakened (OR, 1.19; 95% CI, 1.10-1.28).

The authors concluded that the increased risk in association with multiple D&Cs indicates a causal relationship, despite that fact that confounding cannot be excluded. They suggested medical management should be considered for termination of pregnancy and management of miscarriage.

■ COMMENTARY

No randomized trials will ever be done to assess the outcome of prematurity after surgical abortion. However, this does not mean that we should accept the conclusion of a flawed meta-analysis. The use of systematic review and meta-analysis can boost our confidence when only small studies with limited power suggest an important association. Given that preterm labor represents an important and costly public health problem, strategies that could reduce the risk should be investigated. However, meta-analysis can also amplify misleading information when studies with similar biases are assessed together. In the words of David Grimes and Ken Schultz, "The validity of case-control studies depends on selection of appropriate control groups. Choosing controls might seem deceptively simple, but it can be treacherous."[1] The conclusions of Lemmers et al that suction curettage is associated with an increased risk of premature delivery in a subsequent pregnancy should be carefully evaluated with this in mind.

Given that women tend to under-report a history of abortion, the weak association observed by the authors is likely the result of bias. Numerous studies have documented a substantial degree of under-reporting on self-reported health exposures and outcomes for sensitive topics in sexual and reproductive health, including abortion.[2,3] This under-reporting is an important source of bias in studies that attempt to evaluate risk factors for poor obstetrical outcomes. It is not difficult to imagine why this occurs. Women interviewed following a bad outcome (in this case preterm birth) are more likely to recall and report a variety of exposures (including history of prior abortion) than women with a normal birth outcome who have no reason to recall events they would prefer not to disclose. This same relationship confounds research into abortion and breast cancer.[4] To be fair, some of the papers included in the Lemmers meta-analysis did use national databases where we would expect accurate reporting of abortion. However, the fact that the meta-analysis included a sample of > 1.8 million women with only 66,000 (approximately 4%) reporting D&C for termination of pregnancy suggests substantial under-reporting overall.

Weak associations (risk ratios < 2) deserve great scrutiny because this is the range in which observed associations are frequently the result of bias and not causality. The purpose of meta-analysis is to increase statistical power to reduce the risk of chance being an explanation for the presence or absence of an observed effect. However, meta-analysis cannot correct observed associations that are the result of confounding bias.[5] For example, women who undergo abortion in many regions have baseline characteristics (e.g., smoking, poverty, black race) that are also risk factors for premature birth.[6] Failure to adjust for these and other factors (e.g., inter-pregnancy interval) could easily lead to a spurious association.

The appropriate control group consists of women with a history of medical abortion or medical management of miscarriage. In the Lemmers paper, the association weakened (OR, 1.12) when medically managed women were used as controls. Männistö et al evaluated data from the Finnish Register of Induced Abortions and the Medical Birth and the Hospital Discharge Registries.[7] Using this national sample, they identified 8294 primigravid women with a history of first trimester termination of pregnancy (3441 medical [MAB], 4853 surgical [SAB]) who had a subsequent pregnancy that resulted in singleton delivery. They found no statistically significant differences in the

incidences of preterm birth (4.0% MAB, 4.9% SAB), low birthweight (3.4% MAB, 4.0% SAB), small for gestational age (SGA) infants (2.6% MAB, 2.9% SAB), or placental complications (2.6% MAB, 2.8% SAB) between the two groups. After adjusting for potential confounders associated with adverse pregnancy outcomes (gestational age at the time of termination, inter-pregnancy interval, maternal age, cohabitation status, socioeconomic status, residence, and smoking during pregnancy), MAB was not associated with significantly decreased risks of preterm birth, low birthweight, SGA infant, or placental complications compared to SAB.

A second large study reported data on pregnancy outcomes from 120,033 women with a history of induced abortion collected from the Scottish Morbidity Record.[8] No difference was seen in the risk of prematurity in a subsequent pregnancy when women with induced abortion were compared to women with a history of miscarriage. Although a small and marginally statistically significant increase in the adjusted risk of prematurity (< 37 weeks) was found with a history of surgical compared to medical abortion (relative risk [RR], 1.25; 95% CI, 1.07-1.45), this disappeared when the analysis was restricted to very preterm (< 32 weeks [RR, 1.13; 95% CI, 0.81-1.58] or < 28 weeks [RR, 1.38; 95% CI, 0.73-2.61]) births.

The take-home message is that risk of premature delivery in a subsequent pregnancy need not be a counseling point when discussing options for management of unintended pregnancy and pregnancy loss. There are many reasons a woman will choose medical or surgical management. Removing confusing and irrelevant information out of this counseling can better inform the discussion. ■

REFERENCES

1. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. *Lancet* 2005;365:1429-1433.
2. Schroder KE, et al. Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports. *Ann Behav Med* 2003;26:104-223.
3. Jones EF, Forrest JD. Underreporting of abortion in surveys of U.S. women: 1976 to 1988. *Demography* 1992;29:113-126.
4. Beral V, et al; Collaborative Group on Hormonal Factors in Breast C. Breast cancer and abortion: Collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries. *Lancet* 2004;363:1007-1016.
5. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-252.
6. Bastek JA, et al. Clinical prediction rules for preterm birth in patients presenting with preterm labor. *Obstet Gynecol* 2012;119:1119-1128.
7. Mannisto J, et al. Medical versus surgical termination of pregnancy in primigravid women—is the next delivery differently at risk? A population-based register study. *BJOG* 2013;120:331-337.
8. Bhattacharya S, et al. Reproductive outcomes following induced abortion: A national register-based cohort study in Scotland. *BMJ Open* 2012;2; pii: e000911. doi: 10.1136/bmjopen-2012-000911.

ABSTRACT & COMMENTARY

Is There a Link Between Miscarriage and Future Cardiovascular Disease?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck, a Liletta trainer for Actavis, and on the advisory board for Bayer, Actavis, and Vermillion.

SYNOPSIS: In this Scottish retrospective cohort study of 60,000 women, two or more miscarriages were found to increase the risk of future ischemic heart disease by two- to three-fold.

SOURCE: Wagner MM, et al. Association between miscarriage and cardiovascular disease in a Scottish cohort. *Heart* 2015;101:1954-1960.

The authors of this retrospective cohort study extracted data from the Aberdeen Maternity and Neonatal Databank to examine all women with at least one singleton live birth or miscarriage from 1950 to 2010. These women were then linked to the Scottish Morbidity Record to identify hospital admissions for cardiovascular conditions and to the National Register of Scotland for deaths using probabilistic record linkage. Women were sorted into four groups: no miscarriage, non-consecutive miscarriage, two consecutive miscarriages, and three or more consecutive miscarriages. The miscarriages could have occurred before or after a live birth. Women without miscarriage who had a least one live birth formed the unexposed control group. The primary outcomes were arterial cardiovascular disease including ischemic heart disease and stroke. Women with pre-existing cardiovascular disease, hypertension, type 1 diabetes mellitus, kidney disease, and any disease of the circulatory system were excluded. Other data collected included age, gravidity, parity, self-reported smoking

(ever/never), social class (based on husband/partner's occupation), and body mass index.

A total of 60,105 women were analyzed in the study, with the majority having at least one live birth and no miscarriage (49,579/82.5%), followed by the non-consecutive miscarriage group (9,419/15.7%), the two consecutive miscarriage group (940/1.6%), and the three or more consecutive miscarriage group (167/0.3%). Median follow-up time was 17 years (range 0 to 62 years). The absolute number of ischemic cardiac events in the control group was 1440 (2.9%) compared to women with nonconsecutive miscarriages (272 [2.9%]), women with two or more consecutive miscarriages (30 [3.2%]), and women with three or more consecutive miscarriages (7 [4.2%]). After controlling for age, body mass index, social class, and smoking, women with non-consecutive miscarriage had no increased risk of ischemic heart disease (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.87-1.13), women with two consecutive miscarriages had about double the risk (HR, 1.75; 95% CI,1.22-2.52), and women with three or more miscarriages had triple the risk (HR, 3.18; 95% CI, 1.49-6.8). A sensitivity analysis performed to examine groups by number of miscarriages, regardless of whether they were consecutive, confirmed these findings, with women experiencing two miscarriages or more having an increased risk of future ischemic heart disease.

■ COMMENTARY

The relationship between obstetric events and future cardiovascular disease is an emerging and fascinating area of study. Already, a history of preeclampsia, pregnancy-induced hypertension, and gestational diabetes are named as risk factors for the development of cardiovascular disease in women in national guidelines.[1] Women with this history are considered "at risk" for cardiovascular disease and placed in the same category as women who smoke or have current hypertension. Cardiologists may view pregnancy as a "stress test" that can possibly unmask early or preexisting endothelial dysfunction and vascular or metabolic disease. The American Heart Association recommends that obstetricians refer patients with a history of preeclampsia, pregnancy-induced hypertension, or gestational diabetes to a primary care physician or cardiologist postpartum so that their other risk factors for cardiovascular disease can be carefully monitored and controlled.[1] Whether miscarriage should be added to the list of obstetric conditions that predisposes women to heart disease is still under study. Several previous studies have suggested a link between these two conditions, and this study adds information about whether consecutive or non-consecutive miscarriages carry the most risk.[2]

Why miscarriage would predispose to cardiovascular disease is debateable. While approximately 15% of pregnant women experience sporadic loss of a clinically recognized pregnancy, only 2% experience two consecutive pregnancy losses and ≤ 1% will have three consecutive pregnancy losses.[3] These numbers are well reflected in the Scottish cohort. It is not known whether miscarriages cause downstream events that increase the risk of cardiovascular disease in women or if both conditions share an underlying pathology. This study is interesting because it addressed both recurrent and sporadic miscarriages. Biologically, it makes more sense that recurrent miscarriages would share an underlying pathology with cardiovascular disease. With recurrent miscarriages, there is more likely to be a maternal component, whether genetic or related to metabolic or immunologic syndromes (e.g., antiphospholipid antibody syndrome). It is difficult to tease this out because many risk factors for miscarriage overlap with risk factors for cardiovascular disease, such as obesity, smoking, and diabetes. Sporadic miscarriages, on the other hand, are usually due to embryonic or fetal genetic abnormalities. Therefore, I would think they would be associated with less future maternal cardiovascular disease risk. Nevertheless, at least two or more nonconsecutive miscarriages in this study also conferred an increased risk of cardiovascular disease in a subgroup analysis. I am skeptical of this result without further studies but it is intriguing. Weaknesses of this study include the fact that type 2 diabetes was not available for use as a variable, and I am not sure of the accuracy of the social class variable. I also found the lack of specificity regarding what trimester the miscarriage occurred troubling, as first and second trimester pregnancy losses tend to have different etiologies. Data were missing for some variables for which sophisticated statistical techniques had to be utilized. But the results do concur with a meta-analysis on the subject.[2] There were too few cerebrovascular events for the study to make a conclusion about the association between miscarriage and future stroke risk.

So what are we supposed to do with this information? It is important to remember that heart disease is the leading cause of death among women in the United States. What threshold of miscarriage history would make a clinician proceed with a cardiovascular disease risk evaluation? I am not sure this study definitively answers that question, but I would not be surprised to see recurrent miscarriage in the next iteration of the American Heart Association guidelines for stratifying women into risk groups for cardiovascular disease. ■

REFERENCES

1. Mosca L, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: A guideline from the American Heart Association. *J Am Coll Cardiol* 2011;57:1404-1423.
2. Oliver-Williams CT, et al. Miscarriage and future maternal cardiovascular disease: A systematic review and meta-analysis. *Heart* 2013;99:1636-1644.
3. American Society of Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: A committee opinion. *Fertil Steril* 2012;98:1103-1111.

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3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After completing the test, a credit letter will be emailed to you instantly.

5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE QUESTIONS

1. Menopausal hormone therapy is indicated for the:

a. treatment of osteoporotic fractures.
b. treatment of frequent vasomotor symptoms.
c. prevention of cardiovascular disease.
d. prevention of dementia.
e. prevention of breast cancer.

2. Which of the following statements is not true regarding the index study of low-dose aspirin prophylaxis for preeclampsia?

a. There were no differences in the rates of preterm delivery prior to 34 weeks when comparing the before and after groups, regardless of risk.
b. The high-risk patients in the second time period had a lower rate of preeclampsia when offered treatment with ASA.
c. The high-risk group in the second time period had a higher rate of delivery prior to 34 weeks of gestation.
d. There was a trend toward a lower risk of stillbirth in the second group when the high-risk group were offered ASA.

3. Following an uncomplicated first-trimester suction abortion, a women's risk of premature delivery in her next pregnancy is:

a. not increased relative to women with a history of an uncomplicated medical abortion
b. double the risk of women who had a prior cesarean section.
c. reduced by 50% compared to women with a history of loop electrosurgical excision procedure excision of transformation zone.
d. increased only if she is also living in poverty.

4. In the study by Wagner et al, which of the following was not associated with an increased risk of future ischemic cardiac disease?

a. One miscarriage
b. Two miscarriages
c. Two consecutive miscarriages
d. Three miscarriages
e. Three consecutive miscarriages

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

[IN FUTURE ISSUES]

By Utilizing In Vitro Fertilization, Pregnancy Rates Can Approach Those in Fertile Women

OB/GYN
Clinical
Evidence-based commentaries
on women's reproductive health
[ALERT]

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