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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Early Loss of Ovarian Function May Increase Risk for Cardiovascular Disease

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

SYNOPSIS: Natural and surgical menopause appear to be associated with an increased risk for cardiovascular disease.

SOURCE: Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA* 2019;322:2411-2421.

Even though cardiovascular disease is the leading cause of death among women worldwide, sex-specific risk factors are poorly appreciated.[1] Because recent guidelines from the American College of Cardiology/American Heart Association indicate the need to use a history of premature menopause (defined as menopause prior to age 40 years) to refine cardiovascular risk assessments,[2,3] investigators analyzed data from the observational cohort UK (United Kingdom) Biobank to assess whether early natural or surgical menopause increased the risk for cardiovascular disease. A total of 144,260 postmenopausal women (95.5% white) between the ages of 40 and 69 years (mean age 59.9 ± 5.4 standard deviation [SD] years) were recruited between 2006 and 2010 and followed through August 2016. Of these, 4,904 (3.4%) had natural premature menopause and 644 (0.4%) had surgical premature menopause. In the analyses, those postmenopausal women without premature menopause served as the reference group. The mean (± SD) age at menopause was 50.3 ± 4.2 years among women without premature menopause, 35.4 ± 3.9 years among women with natural premature menopause, and 34.2 ± 4.2 years among women with surgical premature menopause ($P < 0.001$). It is important to note that women with natural and surgical premature menopause were significantly more likely than women without premature menopause to have prevalent cardiovascular risk factors, to have smoked tobacco, and to have used menopausal hormone therapy (MHT) at enrollment.

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Participants were followed for a median of seven years (interquartile range 6.3-7.7).

A total of 5,415 women (3.9%) without premature menopause, 292 (6.0%) with natural premature menopause, and 49 (7.6%) with surgical premature menopause developed one or more incident cardiovascular diseases during follow-up. The incidence rate for the primary outcome (a composite of coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation, ischemic stroke, peripheral artery disease, and venous thromboembolism) was 5.70 per 1,000 woman-years for women without premature menopause, 8.78 per 1,000 woman-years for natural premature menopause, and 11.27 per 1,000 woman-years for surgical premature menopause (both $P < 0.001$ vs. women without premature menopause). After adjustment for conventional cardiovascular risk factors as well as ever use of MHT, both natural premature menopause (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.19-1.56; $P < 0.001$) and surgical premature menopause (HR, 1.87; 95% CI, 1.36-2.58; $P < 0.001$) were independently associated with incident cardiovascular disease. Associations of premature menopause with incident cardiovascular disease remained similar after incorporating ever use of MHT, current MHT use, duration of MHT use, and delayed initiation of MHT use five or more years after menopause.

■ COMMENTARY

These important findings are not easy to interpret because they are somewhat at odds with prior prospective cohort studies. In a study of 121,700 U.S. women 30 to 55 years of age who were followed from 1976 to 1982, women who had undergone bilateral oophorectomy and who had never taken estrogens had an increased risk (rate ratio [RR], 2.2; 95% CI, 1.2-4.2) of coronary heart disease as compared to normal premenopausal women.[4] The use of estrogens in the postmenopausal period appeared to eliminate the increased risk among these women as compared to premenopausal women (RR, 0.9; 95% CI, 0.6-1.6). These earlier data suggested that, in contrast to natural menopause, bilateral oophorectomy increased the risk of coronary heart disease, with the increased risk prevented by estrogen therapy. A much more recent subgroup analysis of the Women's Health Initiative (WHI) estrogen-alone trial of 9,939 women aged 50 to 79 years at the initiation of the study treated with conjugated equine estrogens (0.625 mg or placebo daily for a median of 7.2 years and followed for 18 years) indicated that women with bilateral oophorectomy had an estrogen-associated reduction in all-cause mortality.[5]

In addition, experimental data in cynomolgus monkeys support a beneficial effect of estrogen on the cardiovascular system when the estrogen is begun shortly following bilateral oophorectomy but not when it is begun far removed from the loss of ovarian function.[6] A series of experiments have demonstrated that early and continued estrogen treatment can prevent the development of atherosclerotic plaques in the coronary vessels as well as stabilize further plaque development as documented by histological assessment of the vessels themselves. Experimental studies also have suggested that when initiated late in the atherosclerotic process, estrogen plus progestin (as is administered to women with a uterus) can have adverse effects, destabilizing existing plaques and potentially leading to a coronary heart disease event.

How, then, do we reconcile these disparate findings? It is important to note that the associations reported in the current study from the UK were modest at best. Moreover, associations are precisely that: associations only. Associations cannot establish causality. Large cohort studies such as this one from the UK rely on patient recall regarding the age of menopause and may be subject to recall bias. The reasons for bilateral oophorectomy were not available to the investigators but admittedly were unlikely the result of cardiovascular etiologies. The investigators themselves noted that the UK Biobank has a "healthy participant" selection bias, and the number of resulting cases of incident cardiovascular disease was relatively small. The small number of women in the UK study who had premature menopause also makes establishing associations more difficult with larger confidence intervals. No single study should be considered alone; the data in the entire field should be considered together.

Although the initial report of the WHI findings established that estrogens should not be provided to prevent cardiovascular disease,[7] subsequent analysis of the data indicated that estrogen alone did not increase the risks for women when begun shortly

after menopause onset.[8] Subsequent analysis of data from 27,347 postmenopausal women aged 50 to 79 years and randomized to conjugated equine estrogens and medroxyprogesterone acetate for a median of 5.6 years or to conjugated equine estrogens alone (for women without a uterus) for 7.2 years found no increased risk for all-cause, cardiovascular, or cancer mortality in both arms together or individually during 18 years of cumulative follow-up.[9]

Taken together, then, these data imply to me that women with premature menopause should be offered estrogen therapy at least until the expected age of natural menopause if there are no contraindications to its use. However, whether provided estrogen or not, women with premature menopause should be counseled that they may be at increased risk for cardiovascular disease and should pursue a healthy lifestyle and a healthy diet. When all is said and done, isn't that what we should recommend to all our patients? ■

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ABSTRACT & COMMENTARY

Can We Liberalize Intrauterine Device Insertion Protocols?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she receives grant/research support from Bayer, and is a consultant for Bayer, Mylan, and Merck.

SYNOPSIS: In this retrospective cohort study, the rate of luteal phase pregnancy was 0.4% among 239 women who did not meet pregnancy checklist criteria for intrauterine device insertion.

SOURCE: Castaño PM, Westhoff CL. Experience with same-day placement of the 52 mg levonorgestrel-releasing intrauterine system. *Am J Obstet Gynecol* 2020; Jan. 13. [Online ahead of print].

This is a retrospective cohort study of all women receiving a 52-mg levonorgestrel intrauterine system (LNG-IUS) at Columbia University from July 2009 to April 2012. Women of any age obtaining the device for contraceptive purposes at gynecologic visits or immediately postabortion were included. Exclusion criteria included women undergoing removal and reinsertion the same day and subsequent replacement for women who had experienced an LNG-IUS expulsion. The insertion was performed after a negative urine pregnancy test. Women also could receive emergency contraception (levonorgestrel 1.5 mg orally) if the provider determined them to be at risk of pregnancy from unprotected intercourse. Data were collected at the time of placement and up to 12 months post-insertion to identify failed placements, perforations, luteal phase pregnancies detected after placement, expulsions, and removals. Subjects were evaluated to identify whether they met any of the following pregnancy checklist criteria to be reasonably sure the patients were not pregnant:

- It has been seven days or less since the start of normal menses for the patient.
- The patient has not had sexual intercourse since the start of the last normal menses.
- The patient has correctly and consistently been using a reliable contraception method.
- It has been seven days or less since spontaneous or induced abortion.

• The patient is within four weeks postpartum.
• The patient is fully or nearly fully breastfeeding (exclusively breastfeeding or the vast majority [≥ 85%] of feeds are breastfeeds), amenorrheic, and less than six months postpartum.[1]

The authors identified 886 LNG-IUS placements. Of these, 646 women (73%) met at least one pregnancy checklist criterion (33% within seven days after abortion, 30% correctly and consistently using a reliable method of contraception, 13% within seven days of the start of normal menses, 7% had not had intercourse since the beginning of last normal menses, 2% within four weeks postpartum, and 0% fulfilling criteria for lactational amenorrhea), leaving 239 women who did not meet any of the checklist criteria. A total of 14 women (2%) received emergency contraception prior to LNG-IUS insertion. There only was one placement failure because of uterine fibroids. There was one luteal phase pregnancy (0.4%) that occurred in a woman who did not meet checklist criteria, had irregular menstrual cycles, and had unprotected intercourse two days before LNG-IUS placement. She had a negative pregnancy test, and took emergency contraception prior to placement. She was instructed to repeat a pregnancy test and the pregnancy was detected four weeks after placement. She opted to undergo IUS removal and termination of the pregnancy. There were 28 expulsions, 78 removals, and no perforations identified in the 12 months following insertion, with a 74% rate of at least one follow-up encounter documented in the electronic medical record.

[The Centers for Disease Control and Prevention recommends the provider be reasonably sure that the individual is not pregnant prior to inserting an intrauterine device.]

■ COMMENTARY

According to the Centers for Disease Control and Prevention (CDC), a healthcare provider can be reasonably certain that a woman is not pregnant if she has no symptoms or signs of pregnancy and meets any one of the pregnancy checklist criteria.[1] The goal of this checklist is to be reasonably sure a patient is not pregnant, so that contraception can be initiated.

According to the CDC, for methods other than intrauterine devices (IUDs), even if the provider is uncertain about pregnancy status, the benefits of starting a contraceptive likely outweigh the risks since hormonal contraceptives do not cause birth defects.[1] Before initiating contraception, the provider also can consider checking a urine pregnancy test in certain situations, as well as offering emergency contraception if the patient has had unprotected intercourse in the past five days. Usually, this "quick-start" protocol requires a follow-up pregnancy test in two to four weeks. However, with IUDs there is a concern that a higher risk exists for ectopic pregnancy, spontaneous abortion, septic abortion, preterm delivery, and chorioamnionitis if the IUD is placed when the patient may have a luteal phase pregnancy or early pregnancy. Therefore, the CDC recommends that the provider be reasonably sure that the individual is not pregnant before inserting an IUD.

The authors of this study wanted to evaluate the utility of this pregnancy checklist in a population of patients seeking same-day LNG-IUS insertion. In their practice, a routine urine pregnancy test was performed prior to IUD insertion. Their hypothesis was that the pregnancy checklist was too restrictive and would exclude patients from accessing same-day LNG-IUS insertion.[2] The advantages of same-day LNG-IUS insertion include patient convenience and decreased risk of pregnancy while waiting to come back for another IUD insertion appointment, although bridging contraception could be prescribed. The authors found that a good proportion of patients failed to meet at least one of the pregnancy checklist criteria. These patients had a negative urine pregnancy test and were offered LNG-IUS insertion anyway (with emergency contraception if indicated) and were counseled that they may have a small risk of a luteal phase pregnancy and should repeat a pregnancy test in two to four weeks. Only one woman (0.4%) was found to have a luteal phase pregnancy.

Although these data are reassuring, there are some limitations in that there was no follow-up information for 26% of the sample. In addition, there was no information on the number of women who may have been steered toward using a copper IUD for both emergency and ongoing contraception. Finally, this study protocol requires universal urine pregnancy testing on the day of IUD insertion. Nevertheless, the authors thought their practice style was justified. I would agree, as long as there is shared decision-making with the patient. Patients should be thoroughly counseled on the potential, small risk of an undetected luteal phase pregnancy and the consequences to that pregnancy if an IUD is placed. Some women may not want to take that risk, depending on their values. The authors are to be commended for researching this issue and adding evidence to the literature. It is possible that in the subsequent update to the CDC's Selected Practice Recommendations for Contraceptive Use, changes to the pregnancy checklist requirement will be made. ■

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ABSTRACT & COMMENTARY

Vaginal Dryness: The Keystone Symptom of Postmenopausal Sexual Dysfunction?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: In a large, cross-sectional, multicenter study in Italy that evaluated factors predictive of sexual dysfunction, vaginal dryness correlated independently and negatively with each Female Sexual Function Index domain.

SOURCE: Cagnacci A, Venier M, Xholli A, et al. Female sexuality and vaginal health across the menopausal age. *Menopause* 2020;27: 14-19.

Various factors influence the complex behavior of sexuality. To evaluate changes in female sexuality across the menopausal period, and to test for an association between female sexuality domains and vaginal atrophy (physical findings and symptoms), Cagnacci et al conducted a cross-sectional, multicenter study at 30 outpatient gynecological centers across Italy (the ANGEL study). They recruited healthy women 40 to 55 years of age who reported at least one sexual encounter in the month before enrollment. Key exclusions included virginity, vulvovaginal infections, lichen sclerosus, vaginismus, and vulvodynia. Study staff collected demographic information, data on lifestyle habits, and detailed medical and gynecologic histories, including menopausal symptoms. Eligible participants underwent a pelvic examination; clinicians used vaginal pH > 5, mucosal pallor and dryness, thinning of vaginal rugae, mucosal fragility, and the presence of petechiae as objectives signs indicating vaginal atrophy (VA). They also collected information on subjective symptoms of vaginal dryness, dyspareunia, itching, burning, and dysuria, but did not use these to make the diagnosis of VA. As an objective measure of sexual function, women enrolled in the study completed the Female Sexual Function Index (FSFI). The FSFI provides an overall score and sub-scores for six domains: desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia. Participants respond to each question using a Likert scale from 0 to 6; 0 corresponds to a lack of sexual function and 6 corresponds to full sexual function. The global FSFI score (range 0-36) is calculated as the sum of average scores for each domain (maximum score = 6/ domain). The authors used a previously described cut-off score of < 26.55 to define female sexual dysfunction among the study population.

For the analysis, the authors categorized participants into four age groups: late fertile period (40 to 45 years of age); pre-menopause (46 to 48 years); menopausal years (49 to 51 years); and early post-menopausal years (52 to 55 years). They calculated the prevalence of sexual dysfunction (FSFI < 26.55) across the entire sample and compared the prevalence between age groups.

To identify factors independently related to total FSFI score and the individual domains, the researchers used linear regression. The investigators did not specify a sample size, but reported data collected on 518 women.

The overall prevalence of sexual dysfunction (FSFI score < 26.55) in the sample was 70.6%, and this increased from 55% among women aged 40 to 45 years to 82.8% among those aged 52 to 55 years ($P < 0.01$). Although age, weight, smoking status, sedentary lifestyle, menopausal status, subjective vaginal dryness, dyspareunia, and VA all had an inverse relationship to the FSFI score, only vaginal dryness, postmenopausal status, and weight remained independently associated with FSFI score in the multiple regression model. Only vaginal dryness correlated independently and negatively with each FSFI domain.

Taken together, these results support the idea that the transition from the later reproductive years through menopause is associated with an increasing prevalence of sexual dysfunction, and that vaginal atrophy drives this relationship.

■ COMMENTARY

We know that vulvovaginal atrophy may accompany an increase in sexual discomfort associated with menopause. This cross-sectional study from Italy provides additional evidence that the prevalence of sexual discomfort rises rapidly during the menopausal transition, and that objective signs of vulvovaginal atrophy are the principal drivers of low scores on all the FSFI domains.

The study has many limitations. The authors sought to evaluate changes in female sexuality over the menopausal transition and to test the association between sexuality and vaginal atrophy. Unfortunately, the cross-sectional design does not allow a hypothesis test. Evaluating a potential association required the use of multiple regression to control for differences between women in the various age groups. Correlations do not infer causality. The study tells us nothing about the actual behavior of the women, nor do we have any information on the potential value of any therapy.

Although we have excellent evidence that hormonal therapy improves symptoms of genital atrophy, the effect of postmenopausal hormonal therapy on sexual function

remains an area of ongoing controversy. A recent follow-up study that evaluated sexual activity found no difference in the prevalence of sexual activity following discontinuation of therapy between former participants in the Women's Health Initiative Study randomized to hormonal therapy (36%) and placebo (34%, $P = 0.37$).[1] However, digging deeper into the data, we see evidence for a beneficial effect of hormone therapy. Compared to placebo (9%), women randomized to active hormonal treatment during the intervention period reported a clinically important and statistically significantly higher decrease (20%) in the frequency of intercourse post-intervention. After discontinuing hormone treatment, they also were more likely to report a decrease in desire (17% vs. 6%), arousal (17% vs. 7%), ability to climax (19% vs. 7%), and satisfaction with sexual activity (17% vs. 8%). Along with those symptoms, they also reported an increase in tightness of vagina (12% vs. 3%) and discomfort with intercourse (15% vs. 3%).

Does local estrogen therapy improve sexual function in postmenopausal women? A recent study by Mitchell and colleagues randomized postmenopausal women to vaginal lubrication gel or vaginal estradiol.[2] After 12 weeks of therapy, similar proportions of women in the vaginal estrogen, vaginal gel, and dual placebo reported sexual activity in the past week, and the mean pain scores with sexual activity did not differ between groups. However, significantly more women randomized to the vaginal estradiol reported penetrative sex in the past week and these women showed improvement in vaginal maturation scores and a lowering of vaginal pH, a surrogate for vaginal health. Although the overall comparison did not suggest a decrease in pain between groups, many women did not report a score for sexual pain, presumably because they were not engaging in penetrative sex. More women in the estrogen group reported a score for pain with sexual activity, an important indicator of sexual behavior. My interpretation of the data suggests a positive benefit of estrogen therapy, most likely because of the direct effect of treating vaginal atrophy.

Despite the weakness in study design, the ANGEL study provides some useful information for counseling. Women can expect a decrease in sexual satisfaction as they transition into menopause, and the main driver of this change appears to be vulvovaginal atrophy. Women interested in preserving sexual function should consider local or systemic estrogen therapy. ■

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ABSTRACT & COMMENTARY

17P to Prevent Recurrent PTB in Singleton Gestations: The PROLONG Study

By Camille Hoffman, MD, MSc

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

SYNOPSIS: In this large, double-blind, placebo-controlled, international trial, pregnant women at risk for preterm birth (PTB) between 16-36 weeks gestational age were randomized to an intramuscular weekly injection of either 17-hydroxyprogesterone caproate (17P) or placebo. There was no difference in rates of PTB or neonatal morbidity between these two groups. In comparison to the Meis trial published in 2003, the findings of the PROLONG trial question the use of intramuscular 17P injection as the cornerstone of PTB prevention.

SOURCE: Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A multicenter, international, randomized double-blind trial. *Am J Perinatol* 2020;37:127-136.

The PROLONG study was a double-blind, placebo-controlled, international trial that enrolled women with a previous singleton spontaneous preterm birth. Forty-one of 93 enrollment sites were in the United States and 52 were outside the country. Women were enrolled between 16w0d and 20w6d to receive a weekly intramuscular injection of either 17-hydroxyprogesterone caproate (17P) or placebo. Participants were continued on either the study medication or placebo (in a 2:1 ratio of 17P: placebo) until either delivery or 36 weeks gestation. Co-primary outcomes were preterm birth (PTB) < 35 weeks and a composite neonatal morbidity measure.

Women were enrolled in a 2:1 ratio, with 1,130 women in the 17P group and 578 in the placebo group. Baseline characteristics between the 17P and placebo groups were similar. The racial composition of the PROLONG study

group to the population in the Meis trial was different, with a higher proportion of Caucasian women in this study than in the Meis trial. Unlike the Meis study, the results of the PROLONG study did not show a significant reduction in preterm birth < 35 weeks (11.0% in the 17P group vs. 11.5% in the placebo group, relative risk [RR], 0.95; 95% confidence interval [CI], 0.71-1.26). There were no differences in the neonatal morbidity index (5.6% 17P vs. 5.0% placebo; RR, 1.12; 95% CI, 0.68-1.61) or fetal/early infant death (1.7% 17P vs. 1.9% placebo; RR, 0.87; 95% CI, 0.4-1.81) between groups. When subgroup analyses were done of *only* the women enrolled in the United States (391 total, or 23% of this study cohort), PTB < 35 weeks occurred in 15.6% of the 17P group vs. 17.6% of the placebo group (RR, 0.88; 95% CI, 0.55-1.40). In comparison, in the Meis trial, PTB < 35 weeks occurred in 20.6% of the 17P group vs. 30.7% of the placebo group (RR, 0.67; 95% CI, 0.48-0.93). Of note, the primary outcome of the Meis trial was PTB < 37 weeks, and the authors found a "34% reduction in the incidence of recurrent preterm birth" in the 17P group vs. placebo for PTB < 37 weeks.

The Meis study concluded that "weekly 17P injections result in a substantial reduction in the rate of recurrent PTB among women who were at particularly high risk for PTB and reduced the likelihood of several complications in their infants." In comparison, the PROLONG study concluded that "in this study population, 17P did not decrease recurrent PTB and was not associated with increased fetal/early infant death." This large difference in outcomes — and statistical significance — immediately led to media announcements and major organization proclamations.

■ COMMENTARY

Preterm birth is a major health issue. Since the Meis trial was published in 2003, 17P has been the mainstay of managing pregnancies complicated by a history of prior preterm birth.[1] This medication is a weekly intramuscular injection that pregnant women with a history of prior spontaneous preterm birth receive between 16 to 36 weeks. As part of Food and Drug Administration (FDA) approval of the Makena (hydroxyprogesterone caproate) formulation of 17P, a product created by AMAG pharmaceuticals and that received FDA "orphan drug exclusivity status" in February 2011, a larger randomized, controlled trial was required. The Blackwell/PROLONG study is the result of this requirement.

When the Meis study was published in 2003, findings provided hope toward reducing the risk of PTB as a significant cause of neonatal morbidity and mortality. Thus, it is not surprising that the Meis study was published in the *New England Journal of Medicine* in 2003 and received some media attention. Then, in 2019, the PROLONG study, a potentially more robust trial, was published in the *American Journal of Perinatology*, a lesser-known journal. This may underscore the issue of publication bias and the public's desire for only good news — where only positive results end up in high-impact journals and a bigger, albeit negative, primary outcome trial ends up in the *American Journal of Perinatology*. Nonetheless, within hours of the FDA's advisory committee voting in favor of withdrawing 17P from the market on Oct. 30, 2019, all the major players (i.e., American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine [SMFM]) jumped in to underscore all the ways that the PROLONG study was different from the Meis trial.[2,3]

The excuses cited for the difference in study outcomes ranged from "it was unethical to enroll patients in a placebo-controlled trial when an 'efficacious' treatment already existed" to more data-driven excuses including the race/ethnic differences between study populations, with a much higher proportion of African-American women (who *are* at increased risk for PTB) in the Meis population than in the PROLONG population. Other data-driven differences were variation in the number of previous PTBs, marital status, and reported substance use.

Based on these results, and subsequent commentaries, the SMFM has recommended that obstetric care providers "use an individualized approach as they counsel patients regarding the use of 17P." They also suggest that "it is reasonable to continue use of 17P in the context of a shared decision-making model that includes consideration of risk level for recurrent PTB."

Considering both 2003 and 2019 data, our maternal-fetal medicine division has decided to recommend the following:

- Continue any patient already on 17P at the time of the FDA announcement on this medication through 36 weeks.
- Advise against new starts of 17P in women with a prior PTB unless they have used this medication in the past and have had a later gestational age at delivery ON 17P (and they desire to use it again in the index pregnancy).
- Take an individualized approach and use shared-decision making in African-American women, who are at higher risk for PTB and recurrent PTB.
- Be more consistent with serial cervical lengths and vaginal progesterone use in women with a history of prior PTB. ■

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CME/CE QUESTIONS

1. **Women who lose ovarian function before age 40 may have:**
   a. longer mean lifespans than women with menopause after age 50.
   b. increased risk of developing cardiovascular disease.
   c. markedly lower total cholesterol levels.
   d. decreased risk of stroke.

2. **Analysis of data from the Women's Health Initiative shows that:**
   a. exogenous estrogen should be administered to postmenopausal women to prevent cardiovascular disease.
   b. exogenous estrogen alone increased all-cause mortality in postmenopausal women.
   c. exogenous estrogen appeared to decrease the risk of coronary artery disease following bilateral oophorectomy.
   d. exogenous estrogen alone increased the risk of cancer-related deaths in postmenopausal women.

3. **In the study by Castaño et al, the pregnancy checklist criterion most commonly met by the study population was:**
   a. within seven days of normal menses.
   b. within four weeks postpartum.
   c. within seven days after spontaneous or induced abortion.
   d. correctly and consistently using a reliable method of contraception.

4. **Based on results of the cross-sectional study by Cagnacci et al on the prevalence of female sexual dysfunction in Italian women, which of the following statements is true?**
   a. The prevalence of female sexual dysfunction measured by the Female Sexual Function Index (FSFI) increased from 55% for women aged 40-45 years to 83% for women aged 52-55 years.
   b. Treatment with vaginal estradiol did not improve FSFI scores in women aged 40-45 years.
   c. Vaginal atrophy was not associated with FSFI scores in any domain.
   d. FSFI scores increased with body mass index.

5. **In the PROLONG study, the primary outcome was:**
   a. preterm birth (PTB) < 37 weeks and a composite neonatal morbidity measure.
   b. PTB < 32 weeks and a composite neonatal morbidity measure.
   c. PTB < 35 weeks and a composite neonatal morbidity measure.
   d. PTB < 35 weeks and neonatal death.

6. **In the PROLONG trial, PTB < 35 weeks occurred in:**
   a. 11.0% 17P vs. 11.5% placebo (relative risk [RR] 0.95; 95% confidence interval [CI], 0.71-1.26).
   b. 5.6% 17P vs. 5.0% placebo (RR 1.12; 95% CI, 0.68-1.61).
   c. 1.7% 17P vs. 1.9% placebo (RR 0.87; 95% CI, 0.4-1.81).
   d. 20.6% 17P group vs. 30.7% placebo (RR 0.67; 95% CI, 0.48-0.93).

[IN FUTURE ISSUES]

Does Talcum Powder Cause Ovarian Cancer?