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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

The Best Medical Treatment for Endometriosis? The Debate Continues

By Robert W. Rebar, MD

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

SYNOPSIS: In a "before and after study," the proportion of satisfied and very satisfied women did not change from the "before" period, during which women with endometriosis were treated with norethindrone acetate, to the "after" period during treatment with dienogest.

SOURCE: Vercellini P, Bracco B, Mosconi P, et al. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: A before and after study. *Fertil Steril* 2016;105:734-743.

Progestins, with or without estrogens, are approved by the FDA and used frequently for treating women with symptomatic endometriosis.[1] However, because therapy for endometriosis generally is long-term, there are still questions about which medications are best to use. In this unusual study, Italian investigators attempted to assess the effectiveness of norethindrone acetate (NETA), a 19-nortestosterone derivative progestin that has been available for many years, and dienogest, a semisynthetic 19-nortestosterone derivative progestin recently approved for the treatment of endometriosis in Europe, Australia, Malaysia, Singapore, and Japan. Before June 6, 2013, the group recommended treatment with NETA as the first-choice progestin; after that date, dienogest was recommended as highly effective and particularly well tolerated. The investigators compared the satisfaction of the last 90 patients with endometriosis between 18-40 years of age for whom treatment with NETA (2.5 mg/day) was initiated with the first 90 similar patients treated with dienogest (2 mg/day) at their academic medical center.

Three women in the NETA group and eight in the dienogest group discontinued therapy in less than six

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months, largely because of side effects or perceived ineffectiveness. After six months of therapy, 25 of 87 women treated with NETA discontinued treatment (side effects, n = 15; persistent pain, n = 6; desire for pregnancy, n = 4) compared with 31 of 82 treated with dienogest (side effects, n = 12; cost, n = 8; persistent pain, n = 5; desire for pregnancy, n = 6). In an intention-to-treat analysis of all 180 patients, 71% of women who received NETA were either very satisfied or satisfied with the therapy compared to 72% of those treated with dienogest. Dienogest was no more effective than NETA in improving health-related quality of life, sexual function, and psychological status, or in providing pain relief. Although there were no major adverse events, 55% of the women using NETA and 41% of those using dienogest reported side effects. The most frequently reported side effect was weight gain in 31% of NETA users and in 16% of dienogest users. Overall tolerability as assessed by a numeric rating scale was statistically significantly better in women using dienogest, and the proportion of women who reported that their medical treatment was well or very well tolerated was statistically significantly higher (80% vs. 58%) in the dienogest users as well. Despite the increased tolerability, the authors concluded that the high cost of the drug relative to the cost of NETA indicated that dienogest should be used selectively in women who do not tolerate NETA.

■ COMMENTARY

At first blush, this study may seem largely irrelevant to American readers because dienogest has not been approved by the FDA for the treatment of endometriosis in the United States. So why did I decide to review this particular study? This study documents, yet again, how difficult it is to provide adequate and appropriate therapy to young women suffering from endometriosis, and further emphasizes how common are the side effects of therapy. The most common complaints of women with endometriosis are chronic pelvic pain, dyspareunia, and infertility. Surgery only sometimes provides a definitive cure for those women desiring to preserve or improve their fertility, necessitating the use of medical therapy for symptomatic relief. All medical therapies commonly used, including progestins, combined oral contraceptives, and GnRH analogs, have side effects and are not entirely effective in alleviating all symptoms. This study also highlights the need for new drugs for use in the treatment of symptomatic endometriosis.

Today, endometriosis often is defined as "an estrogen-dependent inflammatory disease" and is thought to affect 5-10% of reproductive-aged women in the United States.[2,3] The prevalence may be as high as 50% in infertile women[4] and may be approximated as 75% in women with chronic pelvic pain.[5] The recognized defining feature is the presence of endometrium-like tissue in sites outside the uterine cavity, primarily on the pelvic peritoneum and on the ovaries. The pathogenesis is complex and not yet completely understood.[2] The attachment and implantation of endometrial glands and stroma on peritoneal surfaces is associated with the aberrant expression of endometrial genes and altered hormonal responses.[2] The endometrial lesions produce a chronic inflammatory disorder with increased numbers of macrophages, proinflammatory cytokines, metalloproteinases, chemokines, and prostaglandins that cause the symptoms and findings associated with endometriosis. The altered inflammatory and immune responses associated with endometriosis, as well as estrogen, favor the survival and growth of endometriotic tissue. In contrast to the unfavorable role of estrogen in perpetuating endometriosis, the role of progesterone is less well defined. It appears that the eutopic endometrium in women with endometriosis exhibits progesterone resistance, which may account for the diminished fertility observed in many women with even mild endometriosis.

There is evidence that all the changes outlined originate from two distinct epigenetic changes that affect the transcription factors SF1 and estrogen receptor ß, both of which are found in extraordinarily high levels in endometriotic tissue. In response of the endometriotic cells to prostaglandin E2, SF1 binds to the promoters of several steroidogenic genes, including aromatase, and leads to the formation of large quantities of estradiol locally. The estradiol in turn stimulates COX-2 through activation of estrogen receptor ß and results in overproduction of prostaglandin E2. Thus, inflammation and estrogen are linked in a continuous feedback cycle that involves the overexpression of genes that encode the aromatase and COX-2 enzymes

and formation of estradiol and prostaglandin E2. Moreover, estrogen receptor ß suppresses progesterone receptor levels, leading to progesterone resistance and disruption of a paracrine pathway that inactivates estradiol.

Based on this knowledge, what drugs can be used to treat endometriosis? Evidence indicates that the pain associated with endometriosis can be reduced with a variety of medications: nonsteroidal anti-inflammatory drugs (NSAIDs), progestins, combined oral contraceptives, GnRH agonists, androgens, aromatase inhibitors, and selective progesterone-receptor modulators.[1,2] NSAIDs would be expected to have variable effectiveness, as they do. Progestins and combined OCs probably act by suppressing ovulation. In this regard, antiprogestins with a mix of agonist and antagonist properties might be expected to be more effective than progestins.[6] Aromatase inhibitors[7] and GnRH analogs might be at least as effective as other means of suppressing ovulation because they lower circulating estrogen levels even more than progestins and combined OCs. Androgens, such as danazol, also suppress estrogens and ovulation and are effective in treating the symptoms associated with endometriosis, but their side effect profile generally is more severe than that of other available drugs. No doubt NETA has more side effects than does dienogest because NETA is the more androgenic progestin. Drugs targeting COX-2, aromatase, estrogen receptor ß, and progesterone receptors will continue to be investigated for their ability to treat the symptoms associated with endometriosis.

What is clear from this discussion is that there is no magical medical bullet to treat symptomatic endometriosis at present. We will continue to need to use the multidisciplinary approach to pain, even as new drugs are developed and promoted for the symptomatic treatment of endometriosis. ■

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ABSTRACT & COMMENTARY

The Effect of Major Depression on Quality of Life After Surgery for Stress Urinary Incontinence

By Chiara Ghetti, MD

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

SYNOPSIS: Women with major depression undergoing surgical treatment for stress urinary incontinence have worse condition-specific quality of life than non-depressed women. Postoperatively, depressed and non-depressed women have similar incontinence severity and quality of life.

SOURCE: Siff LN, Jelovsek JE, Barber MD. The effect of major depression on quality of life after surgery for stress urinary incontinence: A secondary analysis of the Trial of Midurethral Slings. *Am J Obstet Gynecol* 2016;215:455.e1-9.

The main objective of this study was to determine whether baseline major depression affects urinary incontinence severity and incontinence-specific quality of life after midurethral sling surgery. This was a secondary analysis of the Trial of Midurethral slings (TOMUS) study, a multicenter, randomized equivalence trial that assigned women with stress UI to either retropubic or transobturator midurethral sling surgery. The aim of the primary TOMUS analysis was to compare 12-month cure rates between each type of midurethral sling. The reported analysis included all TOMUS subjects who completed Patient Health Questionnaire (PHQ-9), underwent midurethral sling, and completed one year of postoperative follow-up. The main outcome measures for this analysis included the PHQ-9, which has been validated for the diagnosis of depression in primary care and specialist medical outpatient settings. Subjective

outcome measures also included the following validated self-report questionnaires: the International Consultation on Incontinence Questionnaire (ICIQ) measuring incontinence severity, Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI) measuring incontinence-specific quality of life, and Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) measuring symptom-specific sexual function.

The analysis included 526 patients, and 79 women (15%) had major depression at baseline. Depressed subjects were more likely to be younger, obese, diabetic, and current smokers. They were less likely to be white, have education level higher than high school, or have "very good" or "excellent" health. At 12 months, only 4% of the population met criteria for major depression. At baseline, depressed subjects had higher urinary incontinence severity and worse incontinence specific quality of life. At 12 months postoperatively following midurethral sling, there was no difference in incontinence severity between subjects who were or were not depressed at baseline. Postoperative condition-specific quality of life was worse in women with depression at baseline; however, after adjusting for differences between the depressed and non-depressed groups, these differences were not statistically significant. Subjects depressed at baseline maintained worse sexual function following surgery compared to the non-depressed at baseline. After adjusting for differences between groups, multivariable analyses did not show an independent association between baseline major depression and postoperative incontinence severity or quality of life. However, an independent association was found between baseline major depression and 12-month sexual function.

[Depressive symptoms improved following surgery for urinary incontinence .... This study further highlighted the importance of identifying depressive symptoms in patients with pelvic floor symptoms and women undergoing surgery. The presence of depressive symptoms contributed to individual women's quality of life and likely affected goals and expectations of surgery.]

■ COMMENTARY

Depression is very common and has been estimated to affect about 18% of people. Depression is known to affect overall physical health, surgical outcomes, and quality of life. It has been found to affect subjective outcomes following different types of procedures. It also has been shown to affect the perception of symptoms in patients with chronic illness. In women with pelvic floor symptoms, major depression has been associated with both incontinence and prolapse symptoms and has been associated with worsened condition-specific quality of life. In a study conducted in women undergoing surgery for pelvic organ prolapse, we found a significant decrease in depressive symptoms following surgery.[1]

This secondary analysis of women undergoing surgery for urinary incontinence also demonstrated a decrease in depressive symptoms following surgery. At 12 months following surgery for urinary incontinence, 83% of those with major depression at baseline no longer met criteria for depression. Interestingly, incontinence severity in women with baseline depression following surgery was no different than in non-depressed women. However, sexual function remained worse in women with baseline depression, despite overall improvement in depressive symptoms.

The main limitation of this study was that the authors did not evaluate whether women held a past or current diagnosis of depression or were in treatment for depression. In interpreting the findings, it is difficult to control for the natural history of the disease within these women followed prospectively for 12 months following surgery. In addition, it is not possible to establish causality in the associations between mood and incontinence symptoms and the effect of surgery on mood.

Despite several limitations, this study further adds to the body of literature investigating the complex relationship of mood and pelvic floor symptoms. Interestingly, depressive symptoms improve following surgery for urinary incontinence. These findings are similar to those found in women undergoing surgery for other pelvic organ prolapse. This study further highlighted the importance of identifying depressive symptoms in patients with pelvic floor symptoms and women undergoing surgery. The presence of depressive symptoms contributed to individual women's quality of life and likely affected goals and expectations of surgery. Being aware of the presence of depressive symptoms in women with pelvic floor symptoms may allow providers to better individualize treatment goals. ■

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ABSTRACT & COMMENTARY

When to Start Progestin-only Contraceptives After Medical Abortion

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck and a Liletta trainer for Actavis, and she has served on advisory boards for Bayer and Pharmanest.

SYNOPSIS: In this randomized, controlled trial, provision of depot medroxyprogesterone acetate on the same day as mifepristone for medical abortion decreased efficacy a small amount and had no effect on repeat pregnancy at six months. Whether this is clinically relevant will depend on individual patient counseling and the woman's desire for convenient contraceptive coverage.

SOURCE: Raymond EG, Weaver MA, Louie KS, et al. Effects of depot medroxyprogesterone acetate injection timing on medical abortion efficacy and repeat pregnancy: A randomized controlled trial. *Obstet Gynecol* 2016;128;739-745.

The authors of this multicenter, randomized, controlled trial compared the administration of depot medroxyprogesterone acetate (DMPA) on the same day of mifepristone for medical abortion to DMPA given after the medical abortion was confirmed to be complete. The medical abortion regimen consisted of 200 mg of mifepristone followed 24-48 hours later by 800 mcg of buccal misoprostol. Women were followed for seven months after enrollment and asked to complete a urine pregnancy test before the final contact. Women who were appropriate candidates for medical abortion at the site (gestational age ≤ 75 days) did not have recognized nonviable pregnancies, desired DMPA for contraception, and did not plan on using hormonal contraceptives before receiving DMPA were enrolled. The study was powered to detect a surgery rate (to complete the abortion) of no more than 5% higher in the immediate DMPA arm compared to the regular DMPA arm. At six months, evidence of non-pregnancy was defined as a negative pregnancy test at 197 days or later or use of sterilization, intrauterine device (IUD), contraceptive implant, or injectable method at 183 days. Otherwise, a participant who was followed for at least 183 days without a reported pregnancy was considered to have "no evidence of pregnancy."

A total of 461 women were recruited and randomized, three-quarters of whom were from Mexico and the remainder from the United States. There were 225 women in the immediate DMPA group (five excluded for missing abortion outcomes) and 236 in the regular DMPA group (seven excluded for missing abortion outcomes and three who may have used hormonal contraception prior to DMPA). For the primary outcome, 14 (6.4%) women in the immediate DMPA group required surgery (seven for ongoing pregnancy and seven for other reasons) compared to 12 (5.3%) women in the regular DMPA group (one for ongoing pregnancy and 11 for other reasons) (difference 1.1%; 95% confidence interval, -2.8 to 4.9). The confidence interval approached 5%, and a sensitivity analysis determined that if just one of the five women with unknown abortion outcomes in the immediate DMPA group required surgery, then the upper limit of the 95% confidence interval would have crossed 5% and the investigators could not have concluded that giving DMPA immediately was noninferior to giving it at the regular time after medical abortion completion. In addition, there were more ongoing pregnancies (positive fetal heart beat) in the immediate DMPA arm (8, 3.6%) compared to the regular DMPA arm (2, 0.9%). There was no difference between the two groups in the proportion of women who had evidence of non-pregnancy through six months (93% immediate group vs. 93% regular group, $P = 0.64$). Of the reported pregnancies by six months, there were five (2.3%) in the immediate DMPA group and seven (3.2%) in the regular DMPA group ($P = 0.64$). Only half of the participants were still using DMPA at six months.

■ COMMENTARY

Medical abortion with mifepristone followed by misoprostol accounts for approximately 36% of all abortions before nine weeks' gestation.[1] In March 2016, the FDA updated the mifepristone label to reflect the evidence-based regimen that already was being used (200 mg mifepristone followed by 800 mcg buccal misoprostol) and also expanded medication abortion up to 70 days' gestation. The success of this medical abortion regimen is 98% at ≤ 49 days, 97% at 50-56 days, 95% at 57-63 days, and 93% at 64-70 days' gestation.[2] The rate of surgical intervention for ongoing live pregnancies also is related to gestational age: 0.3% at ≤ 49 days, 0.8% at 50-56 days, 2% at 57-63 days, and 3.1% at 64-70 days' gestation. Because of the small risk of ongoing pregnancy and the fact that misoprostol is associated with congenital anomalies, most facilities in the United States require follow-up for medical abortion in the form of an in-

person ultrasound or serum B-HCG follow-up at a laboratory.

Initiating contraception following medical abortion is important for patients. Typically, the contraceptive pill, patch, and ring can be started the day after misoprostol use. Other methods that are administered in the clinic require that the patient return for DMPA injection, implant placement, or IUD insertion when the abortion is complete. The authors of this study attempted to determine whether immediate administration of DMPA would affect the efficacy of medical abortion, given that mifepristone is an anti-progestin, and whether it would decrease repeat pregnancy rates at six months. The authors previously had shown that immediate placement of the etonogestrel implant on the day of mifepristone had no effect on medical abortion efficacy.[3] The results from this study, however, were not so clear cut. Based on the data, there is a possibility that immediate DMPA decreases medical abortion efficacy slightly. This may be because DMPA is a higher dose of progestin than the etonogestrel implant. Overall, however, the authors reported that the success rate was still more than 93% for women in the immediate DMPA arm. In addition, women preferred receiving the DMPA on the same day as the mifepristone rather than returning to the clinic.

I wish the authors would have reported outcomes by gestational age. About 47% of the subjects were ≤ 49 days' gestation, 40% were between 50-63 days, and 13% were ≥ 64 days (up to 75 days). It may be that they believed they didn't have enough subjects to report on the group that was ≥ 64 days, but this would be important information for counseling patients regarding this option. For example, if failure rates were much higher at greater gestational ages with immediate DMPA, then the patient may opt to defer DMPA until the follow-up visit. It is also interesting that the maximum gestational age was 75 days when the usual cutoff is 70 days.

When comparing the contraceptive continuation rates of this study to their etonogestrel implant study, the authors noted that only 50% of women were still using DMPA at six months. This was much lower than the proportion who continued the etonogestrel implant (> 91%) at six months. In this respect, which method the woman chose was more important than the timing of administration. Facilitating access to contraceptive implants and IUDs should be a priority anytime a woman undergoes an abortion. ■

Editors note: The bottom line from this study is that DMPA reduced the success of medical abortion with a clinically important real increase in ongoing pregnancies. We should not be mislead by the confusion that this increase did not cross the predefined non-inferiority margin. The coadministration of a massive dose of DMPA, a progesterone-receptor agonist, with mifepristone, a progesterone-receptor antagonist makes no pharmacological sense. The further evidence that neither DMPA initiation or continuation was increased by early administration begs the question of "Why take this additional risk"? Although the same day use of the low-dose etonogestrel implant makes sense and seems to work, same day DMPA is a bad idea.

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ABSTRACT & COMMENTARY

Extending Life of LARCs: More Years for Your Implant

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: An international study found that continued use of an etonogestrel contraceptive implant for up to five years, two years longer than the current labeling approval, did not increase the risk of pregnancy.

SOURCE: Ali M, Akin A, Bahamondes L, et al. Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: Comparison to levonorgestrel-releasing subdermal implant. *Hum Reprod* 2016;31:2491-2498.

Regulatory approval of the etonogestrel (ENG) contraceptive implant supports use of this highly effective reversible contraception for up to three years, but pharmacokinetic data demonstrate stable ENG levels up to five years. Since cost and inconvenience to women could be reduced by extending the recommended duration of use, the World Health Organization (WHO) sponsored this study to evaluate the safety and efficacy of ENG implant use for up to five years.

The study population represents a subset of women originally enrolled in a multicenter international study designed to evaluate the clinical performance of the three-year single-rod ENG implant and the five-year, two-rod levonorgestrel (LNG)-releasing implant over three years. In the original study, women were randomized in an open label fashion to receive either implant (ENG = 1,003, LNG = 1,005), and the authors also included a separate cohort of copper intrauterine device (IUD) users (n = 974) for comparative purposes (nonhormonal controls).[1] The overall clinical performance of the two implants over three years was similar. Both implants had a three-year cumulative pregnancy rate of 0.4/100 woman-years (WY) of use compared with 5.7/100 WY among users of the copper IUD.

To obtain data in support of extended use, the investigators invited subjects to consent to two additional years of participation, which represented off-label use for the ENG implant group only. A subset of 390 ENG, 522 LNG, and 416 IUD participants agreed. Of these, 204 ENG, 330 LNG, and 256 IUD users completed the full five years of use of their respective methods.

No pregnancies occurred in either of the implant groups during year 4 or 5, compared with three additional pregnancies in the copper IUD control group, yielding five-year cumulative Kaplan-Meier pregnancy rates of 0.6/100 WY (95% confidence interval [CI], 0.2-1.8) for the ENG implant, 0.8/100 WY (CI, 0.2-1.8) for LNG, and 4.1/100 WY (CI, 2.5-6.5) for the copper IUD. As previously reported during the initial three years of follow-up, ENG implant users reported more bleeding complaints than LNG, but this association was significantly increased only for heavy bleeding (12% vs. 9%; relative risk, 1.32; CI, 1.01-1.73) during years 4 and 5. Clinicians rated removal of the single-rod ENG system as significantly easier and faster.

The authors concluded that the results support extended use of the ENG implant for up to five years, and recommended that the WHO adopt this policy in family planning programs.

■ COMMENTARY

The widespread use of highly effective long-acting reversible (LARC) methods of contraception has been a game changer in the United States. The increased use of LARCs correlates with a drop in teen pregnancy and unintended pregnancy that began to 2008.[2,3] These user-friendly "forgettable" methods have high continuation rates and extremely low method failure. Any strategy that makes obtaining or continuing a LARC method easier should result in a hefty return on investment.

Worldwide, access remains one of the great barriers to LARC use. Both IUDs and implants require a skilled healthcare provider for placement and removal. Since all LARC methods have an approved duration of use, replacement is required for continuation of the method after expiration. Our most highly effective LARC method, the ENG implant, is approved for three years of use. Since many women find the placement and/or removal of implants unpleasant, extending this duration could increase the acceptability of the method. Increasing the duration of use also would greatly reduce costs associated with long-term implant use.

Substantial evidence now exists to support extending the duration of use. Circulating ENG prevents ovulation as the primary mechanism of implant action, with 90 pg/mL considered sufficient for suppression.[4] According to the full prescribing information for Nexplanon, mean levels of ENG decline from around 1,200 pg/mL in the first two weeks after placement, to 202 pg/mL at 12 months, 164 pg/mL at 24 months, and 138 pg/mL at 36 months of use. However, using the cohort of implant users enrolled in the CHOICE study, McNicholas et al reported median (range) ENG levels of 188.8 (CI, 63.8-802.6) pg/mL and 177.0 (CI, 67.9-470.5) pg/mL at the end of three and four years of use, with no effect of body mass index on drug levels.[5] Similar to the results reported by the WHO group, no pregnancies have occurred among implant users in the CHOICE studies who consented to continue the method beyond three years, although this study remains in progress.

Once a product receives regulatory approval, pharmaceutical companies have little incentive to change the label unless this would result in increased sales or new evidence of risks require additional information. I suspect that strategies designed to encourage individuals to use a current product longer rather than buy a new one are not taught in business schools. Although a five-year LNG two-rod implant exists in most of the world outside of the United States, the world cost of the system is similar to the ENG implant, and there is no interest in introducing the LNG product to the U.S. market. Thus, we should not expect to see an application from Merck to change the labeling for Nexplanon. However, if such an application were to be filled, the FDA would require data on at least 200 women using the product for the new interval. The results of the Ali study satisfy this requirement.

The results of our recent election threaten to undermine the gains in contraception coverage achieved due to the Affordable Care Act. If so, many women using a LARC method in the United States may find difficulty accessing a new device at the scheduled replacement interval. The literature now provides strong and convincing evidence to recommend that women using the ENG implant continue use of the

same device for up to five years. This may help some survive until the next election. ■

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CME/CE QUESTIONS

1. **In women undergoing surgery for stress incontinence, women with major depression:**
   a. at baseline, have a lower body mass index and fewer medical problems.
   b. have less incontinence severity compared to non-depressed at baseline.
   c. have higher sexual function compared to non-depressed following surgery.
   d. may have improved depressive symptoms after surgery.
2. **In the study by Raymond et al on medical abortion, there were more ongoing live pregnancies in the immediate DMPA administration arm compared to the regular DMPA administration arm.**
   a. True
   b. False
3. **All of the following support extending the duration of use of the etonogestrel contraceptive implant to a full five years *except*:**
   a. the FDA has agreed to change the approved label for Nexplanon for five years of continued use.
   b. data from the CHOICE study demonstrates therapeutic serum ENG concentrations at the end of year 4.
   c. no pregnancies occurred during year 4 and 5 among more than 200 women using the ENG implant in the WHO study.
   d. no pregnancies have occurred among implant users from the CHOICE study who consented to continued use up to five years.

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]

Who Needs an Endometrial Biopsy?

Ovarian Cancer Screening