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OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

The Complexity of Health Care Disparity: The Geographic Effect

By Robert L. Coleman, MD

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

SYNOPSIS: Barriers to guideline-adherent care for advanced ovarian cancer are impacted by geographic proximity to a high-volume hospital and travel distance. However, these geographic barriers disproportionately affect racial minorities and women of lower socioeconomic status.

SOURCE: Bristow RE, et al. Spatial analysis of adherence to treatment guidelines for advanced-stage ovarian cancer and the impact of race and socioeconomic status. *Gynecol Oncol* 2014;134:60-67.

Several factors are known to impact access to National Comprehensive Cancer Network (NCCN) guideline-compliant care for the management of advanced ovarian cancer. The current study interrogates geographic location and the impact of travel distance to care in relation to race and socioeconomic status (SES). Patients diagnosed with stage IIIC/IV epithelial ovarian cancer (1/1/96–12/31/06) were identified from the California Cancer Registry, which captures 99% of the state's index cases and has follow-up completion rates of more than 95%. Generalized additive models were created to assess the effect of spatial distributions of geographic location, proximity to a high-volume hospital (defined as treating 20 or more cases per year), distance traveled to receive care, race, and SES on adherence to NCCN guidelines. Of the 11,770 patients identified, 45.4% were treated according to NCCN guidelines. Black race (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.21-1.83), low-SES (OR, 1.46; 95% CI, 1.24-1.72), and geographic location more than 50 miles from a high-volume hospital (OR, 1.88; 95% CI, 1.61-2.19) were independently associated with an increased risk of non-adherent care, while high-volume hospital treatment

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(OR, 0.59; 95% CI, 0.53-0.66) and travel distance to receive care more than 20 miles (OR, 0.80; 95% CI, 0.69-0.92) were independently protective. SES was inversely associated with location over 50 miles from a high-volume hospital, ranging from 6.3% (high-SES) to 33.0% (low-SES) ($P < 0.0001$). White patients were significantly more likely to travel more than 20 miles to receive care (21.8%) compared to blacks (14.4%), Hispanics (15.9%), and Asian/Pacific Islanders (15.5%) ($P < 0.0001$). The study highlighted that geographic proximity to a high-volume hospital and travel distance to receive treatment are independently associated with NCCN guideline-adherent care for advanced-stage ovarian cancer.

■ COMMENTARY

Access to health care is a complex issue and involves several contexts that extend beyond availability of care.[1] To this end, health care in the United States is largely available, but how it is gainfully accessed is profoundly and disproportionately limited by factors that include financial, organizational, social, and cultural barriers. These well-described factors define utilization; much effort has been expended to not only understand how these factors impact utilization, but also how health care services may be consumed under limitations of any one, or all, of these factors. This has been the center of the ongoing and highly contentious debate of the Affordable Health Care Act.[2] One frequently cited example of disproportionate health care utilization is emergency department (ED) visits. The absence of regular primary health care access, which disproportionately affects minorities and lower socioeconomic classes, leads to higher utilization of the ED for routine care. At least one state, where more universal health care access has been enabled, has greatly altered the character and frequency of inappropriate utilization of the ED.

In the June 2013 issue of *OB/GYN Clinical Alert*, I presented a provocative article that demonstrated compliance with NCCN guidelines for ovarian cancer care was significantly related to access to a gynecologic oncologist.[3] This was one of the first articles to also clearly demonstrate the impact of compliance on expected survivorship from the disease and included data on approximately 70% of all patients cared for in the United States. Other reports have also highlighted survivorship related to the hospitals in which these patients were cared for; higher ovarian cancer patient volume closely tracks with significantly higher compliance with NCCN guideline treatment and leads to improvement in overall survival.[4] The correlation of hospitals with high ovarian cancer patient volume and access to a gynecologic oncologist is expectedly strong. The current study closely examines a new feature, geography. While the majority of people live in urban areas where highly specialized care can be accessed, Bristow and colleagues nicely demonstrate the disparity of non-adherent ovarian cancer care throughout the state of California based on geographical distance to high-volume centers. In addition, they demonstrate that geography disproportionately affects racial minorities (African American, Hispanic, and Asian/Pacific Islander). In this study, white patients were significantly more likely to travel over 20 miles to receive care in high-volume centers. So, while geographic proximity to high-volume hospitals significantly impacts the opportunity to receive the best appropriate care, this distance is disparate among racial minorities and patients of lower SES status.

This study, as the others, highlights that patients face significant barriers and challenges to receiving appropriate standard of care therapy. This is the case even with equal opportunity to access but is confounded even more by geographic

factors. The solution to this problem is not simple, but has been tackled in other countries where universal health care is available. In these situations, a mandated and quality-controlled process of centralization of specialty services (centers of excellence) has been enacted. Removing geographical and financial barriers leads to higher compliance of treatment standards, which are significantly impacted by specialty care. In the case of ovarian cancer, surgical resection and pathology expertise are more disparate among high- and low-volume centers than the type of chemotherapy that can be delivered in these settings. Methodical evaluation of the critical factors impacting survivorship can help to define how to begin the process to harmonize effective care in ovarian cancer management. ■

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ABSTRACT & COMMENTARY

Predicting Painful IUD Insertion

By Rebecca H. Allen, MD, MPH

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Dr. Allen is a retained consultant for Bayer.

SYNOPSIS: In this prospective cohort study of 161 nulligravid women, there was no reliable threshold of uterine length or flexion angle measurements that were predictive of painful or difficult insertions. History of severe dysmenorrhea was the only predictor of insertion pain.

SOURCE: Kaislasuo J, et al. Predicting painful or difficult intrauterine device insertion in nulligravid women. *Obstet Gynecol* 2014;124:345-353.

This is a prospective cohort study of 161 nulligravid women naïve to intrauterine device (IUD) insertion recruited in Helsinki, Finland, between January 2011 and July 2012. Participants chose the IUD they desired: either the copper IUD or the levonorgestrel (LNG) IUD. Women with contraindications to IUD use were excluded. Women were instructed to take either 800 mg ibuprofen or 1000 mg acetaminophen 1 hour before insertion. Misoprostol was not routinely used. All the IUD insertions were performed by a single experienced physician. Of note, all insertions were performed during menses except for women who had amenorrhea from prior contraceptive use. Before insertion, uterine position was determined from bimanual exam and transvaginal ultrasound was performed to measure the uterine length (length of uterine cavity plus cervical length) and width (cornu to cornu). Flexion angle between the cervix and uterus was also calculated. The length of the uterus as measured by metallic uterine sound was recorded. Insertion pain was evaluated immediately after insertion by the woman and physician, and insertion difficulty was rated by the physician.

The majority of women (68.5%) chose the LNG-IUD, and they were slightly younger (23 years vs 25 years, $P = 0.03$) and reported more menstrual bleeding (heavy flow 36.4% vs 7.8%, $P = 0.001$) and pain (severe dysmenorrhea 25.5% vs 3.9%, $P = 0.001$) than women choosing the copper IUD. The mean uterine sound measurement was 75 ± 7.6 mm and the mean total uterine length by ultrasound was 64.1 ± 8.4 mm for a difference of 11.7 ± 7.9 mm. The mean fundal width was 23.1 ± 3.9 mm. The mean flexion angle was 119.6º (range 61º to 173º). Most insertions (89.4%) were classified as easy. In 15 women, the insertion was difficult; 13 of these women used the LNG-IUD. In 10 of these, cervical dilation was required with metallic Hegar dilators, with six women receiving a paracervical block and three women receiving misoprostol. Only two insertions failed, one because of pain (copper IUD) and one because of a uterine sound measurement of 45

mm (LNG-IUD). In multivariable analysis, insertion difficulty was correlated with smaller total uterine length and smaller flexion angle even when controlling for type of IUD, age, body mass index (BMI) > 30 kg/m^2, uterine position, bleeding status at insertion, and other uterine measurements. Nevertheless, there were no threshold measurements that were adequate predictors of insertion difficulty. All women reported pain during insertion — 18 women (11.2%) had mild pain, 49 (30.4%) had moderate pain, 91 (56.5%) had severe pain, and 3 (1.9%) had intolerable pain. In multivariable analysis, the only predictor of pain was a history of severe dysmenorrhea, even when controlling for uterine measurements, type of IUD, bleeding at insertion, uterine position, age, BMI, smoking, dyschezia, dyspareunia, other abdominal pain, and prior cervical procedures.

■ COMMENTARY

National organizations have endorsed the use of IUDs in adolescents and nulliparous women.[1-3] As more nulligravid and nulliparous women are choosing IUDs for contraception, it is important to elucidate factors that may contribute to more painful or difficult insertions. There has been concern that the size of a nulligravid woman's uterus would be too small to accommodate the copper T380A IUD or the higher dose LNG-IUD, both of which measure 32 mm × 32 mm.[4,5] This may lead to more complaints about pain and bleeding leading to removal requests. Additionally, while the inserter for the copper IUD is the smallest, measuring 3.65 mm in diameter, the inserter for the LNG-IUD currently measures 4.75 mm (a 4.4 mm inserter will be released shortly). The newly released, smaller, lower-dose LNG-IUD measures 28 × 30 mm and has a 3.8 mm inserter. The size of the inserter has been correlated to pain and difficulty with insertion in some studies.[6]

This study attempted to determine whether uterine position or uterine size by ultrasound could predict difficulties with and pain at insertion for nulligravid women. It is one of the first studies attempting to accomplish this in a prospective fashion with the IUDs currently available. A previous study by radiologists reported that the mean uterine cavity width of premenopausal nulliparous women was 27 mm compared to those with one birth (30 mm) and those with more than one birth (31 mm).[7] The radiologists concluded that "physicians should consider ultrasonography to measure the uterine cavity before inserting an intrauterine device." However, while this would certainly increase business for radiologists, it would significantly add to the cost and increase barriers to IUD insertion.

Similarly, in the current study, it is interesting to note that most of the women had uterine cavity sizes smaller than the copper IUD and higher-dose LNG-IUD. One-third of women had a cavity length that was smaller and nearly all had a cavity width that was narrower. Despite this, 90% of insertions were assessed as easy. Indeed, although more acute flexion angles were associated with insertion difficulty, there was no threshold ultrasound measurement that was able to reliably predict difficulty or pain with insertion. As this study shows, given an experienced inserter, difficult insertions are likely accounted for by a tight cervix and not uterine size. Most difficult insertions can be solved with cervical dilation and straightening the uterus with a tenaculum to reduce flexion. Therefore, providers planning to insert IUDs in nulligravid and nulliparous women should have the ability to provide cervical dilation as well. I am relieved to know that pre-insertion ultrasounds are not necessary for this population. After insertion, previous studies have shown that the majority of nulliparous women are very satisfied with IUDs and have continuation rates equal to multiparous women.[7,8]

Finally, the use of the smaller, lower-dose LNG-IUD in this population would not necessarily solve the size issue, as approximately 20% had a shorter cavity measurement and 90% had a narrower cavity measurement. However, the inserter is more narrow than for the higher-dose LNG-IUD, which may facilitate insertions in this population. The fact that history of severe dysmenorrhea predicted pain with insertion is no surprise given that the insertion can irritate the uterus. This may be one variable to ask our nulliparous patients about and, if positive, offer them a paracervical block with insertion. ■

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ABSTRACT & COMMENTARY

News from the KEEPS Study: HRT Does Not Decrease Progression of Atherosclerosis Over 4 Years of Treatment

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: Although treatment with oral conjugated estrogens or transdermal estrogen improved some surrogate markers of cardiovascular disease risk, no reduction in the progression of atherosclerosis was seen over 4 years of treatment.

SOURCE: Harman SM, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: A randomized trial. *Ann Intern Med* 2014;161:249-260.

The KEEPS (Kronos Early Estrogen Prevention) study was a randomized, controlled trial of postmenopausal hormone therapy designed to assess the effects of treatment in women who were within 36 months of their last menses, the typical time interval for initiation of therapy. Healthy (no history of cardiovascular disease [CVD]) recently postmenopausal women were randomized to receive oral conjugated estrogens o-CEE 0.45 mg/d (Premarin®, Pfizer Pharmaceuticals), transdermal estradiol 50 mcg/d (t-E2, Climara®, Bayer HealthCare), or placebo. Estrogen-treated subjects also received oral progesterone capsules, 200 mg/d (Prometrium®, Abbott), on days 1-12 of each month. The treatment allocation was double-blinded; all estrogen-treated subjects received both a patch and daily pill that were active or placebo according to assignment, plus the monthly progesterone capsules. To conceal allocation, placebo-treated subjects also received a placebo patch, pill, and capsule. The primary outcome was the annual change from baseline in carotid artery intima–media thickness (CIMT) measured by ultrasonography. Secondary outcomes included changes from baseline in other markers of cardiovascular risk including coronary artery calcium (CAC) score (measured by chest CT scan at baseline and end of study) and several biochemical endpoints; HDL-C, LDL-C, triglycerides, interleukin-6, C-reactive protein, sex hormone-binding globulin, glucose, and insulin. A total of 727 women were randomized: o-CEE (230, 31.6%), t-E2 (222, 30.5%), placebo (275, 37.8%). Participants had a mean age of 52.7 years and were an average of 1.4 years after menopause. At 48 months, CIMT was available for 580 women (79.8%); of these 464 (63.8%) were still using the assigned study medications. The mean duration of treatment was 37.4 months for o-CEE, 34.6 months for t-E2, and 37.6 months for placebo.

A similar increase in mean CIMT (approximately 0.007 mm/year) was seen in all three groups during the 4 years of observation. The change in CAC scores (an increase of 17.4% o-CEE, 18.9% t-E2, and 21.0% placebo group) were also not statistically significant. Treatment with o-CEE resulted in a decrease in LDL-C and an increase in HDL-C, C-reactive protein, and SHBG. The insulin resistance score decreased with t-E2. About half the subjects (o-CEE 49.1%, t-E2 47.3%, and placebo 47.6%) experienced at least one adverse event, but most of these were mild. The study was not powered to assess serious adverse events.

■ COMMENTARY

The KEEPS study was designed to determine whether early initiation of hormonal replacement therapy (HRT) could prevent the development of CVD in postmenopausal women. One of the major criticisms of the Women's Health Initiative (WHI) study is that the population studied was asymptomatic and approximately 10 years postmenopausal — a decade older than the age at which women commonly start HRT. The difference from the positive benefits seen in observational studies suggests that a critical window for initiation of treatment may exist. In fact, follow-up reanalysis of the WHI combined CEE/medroxyprogesterone acetate treatment group documented a nonsignificant trend toward protection from CVD in women < 10 years postmenopausal in contrast with the elevated risk observed in women starting therapy more than 20 years after menopause.[1]

Since the investigators in the KEEPS study did not have the resources or time to enroll a cohort as large as WHI, the enrollment and outcomes were more modest. Only surrogate measures of CVD were evaluated. Treatment was divided between an oral and transdermal approach. But all women received an oral treatment with micronized progesterone. The PEPI study demonstrated that the favorable effects of oral CEE on lipids were attenuated with medroxyprogesterone acetate, but not affected with micronized progesterone.[2] However, we still don't understand the role of postmenopausal progestin replacement therapy outside of endometrial protection.

Our current understanding of HRT is that thrombosis is the principle risk.[3] Thrombosis is related to estrogen-induced changes in hepatic globulins. Current research supports the use of non-oral routes of administration of estrogen and the use of estradiol rather than ethinyl estradiol to avoid the first pass effect of oral therapy on the liver.[4]

The KEEPS study evaluated the factor through which thrombosis mediates most heart attacks, the development of atherosclerotic plaques. Although no difference was seen in this study, there are several limitations that might explain the results. The first is that, in contrast to WHI, the investigators were too careful to exclude women at risk for CVD from the study. By enrolling a healthy low-risk population, the ability to demonstrate a difference may have been limited. All women in the study were required to have a baseline CIMT of < 50 Agatston units. These women may be at lower risk for progression. Another explanation is that the time for follow-up was too short. However, there is no indication from the data that any trend toward protection with either treatment was emerging during the later years of the study. All of the treatment groups showed a slow trend toward progressive arterial narrowing.

While the negative results of KEEPS do not settle the question about the critical window of treatment hypothesis, they do demonstrate that combined HRT does not increase atherosclerotic progression. Given this, I remain convinced that transdermal (or vaginal) estradiol treatment makes sense for women using estrogen replacement, as the thrombosis mechanism remains an important factor. Data from the ESTHER study showed no increase in the risk of DVT in users of transdermal estradiol compared to non-users, but an increase in risk in women using oral products.[5] It would take another large study the size of WHI to evaluate whether an alternative HRT regimen actually protects against CVD. I am not optimistic about seeing this funded.

The take-home clinical message is that reduction in CVD is not a primary indication for HRT or a secondary health benefit. However, the results from KEEPS are consistent with other studies that suggest otherwise healthy women initiating HRT at or shortly after menopause do not increase their risk of adverse cardiovascular outcomes. ■

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ABSTRACT & COMMENTARY

When Prolapse Become Symptomatic

By Chiara Ghetti, MD

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

SYNOPSIS: Prolapse occurs along a spectrum from early and asymptomatic to advanced and symptomatic. The authors define anatomic cutoffs that are likely to result in symptomatic and clinically significant prolapse.

SOURCE: Dietz HP, Mann KP. What is clinically relevant prolapse? An attempt at defining cutoffs for the clinical assessment of pelvic organ descent. *Int Urogynecol J* 2014;25:451-455.

The objective of this study was to determine the relationship between symptoms of prolapse and anatomical measurements and to define anatomical points that predict symptomatic prolapse by using receiver operator characteristic (ROC) statistics.

This was a retrospective study of archived data from 764 women evaluated for lower urinary tract symptoms and pelvic floor dysfunction. The main outcome measure was presence of prolapse symptoms defined as a "sensation of a lump or bulge" and/or a "dragging sensation in the vagina." The degree of prolapse was quantified using three specific points of the Pelvic Organ Prolapse Quantification (POP-Q) examination, a standardized metric for evaluating pelvic organ prolapse. Specifically points Ba, C, and Bp were used. These points correspond

to the lowest point (or most distal measurement) of the anterior vaginal wall, measurement of the cervix (or vaginal cuff in women who have had a hysterectomy), and the most distal measurement of the posterior wall, respectively. Logistic regression was used to model the relationship between symptoms of prolapse and POP-Q measurements of anterior, central, and posterior vaginal compartments. The authors wanted to use the POP-Q points like a diagnostic test to see if there is specific value for each point that could accurately distinguish symptomatic from asymptomatic prolapse. In order to do this, they used receiver operator characteristic (ROC) analysis.

The study included 764 patients seen during a 21-month period. The mean age was 57 years (range, 19-87). Four hundred ninety-two subjects (64%) were postmenopausal, 566 (74%) reported stress incontinence, 570 (75%) reported urge incontinence, and 407 (53%) reported symptoms of prolapse. POP-Q examination scores were available in 760 women, of which 605 (80%) had prolapse stage ≥ 2 in any compartment. POP-Q points Ba, C, and Bp were all strongly associated with symptoms of prolapse on univariate analysis. ROC curves were calculated using the complete data set for Ba, C, and Bp. To account for confounding variables, the authors repeated the analysis by only including data from women with dominant prolapse in each of the three compartments.

In the repeated analyses, 557 patients were included for Ba, 363 for C, and 486 for Bp. Improved predictions were found for all three points. The accuracy of an ROC analysis is measured by calculating the area under the curve (AUC). An area of 1 defines a perfect test, while an area of 0.5 represents a very poor test. This analysis found an AUC of 0.768 for Ba (95% CI, 0.73-0.81), 0.724 for C (95% CI, 0.67-0.78), and 0.686 for Bp (95% CI, 0.64-0.73). Cutoff values for prolapse that are likely to be symptomatic, with maximal sensitivity and specificity, were defined as follows: for Ba = -0.5 (sensitivity 69%, specificity 71%), C = -5 (sensitivity 67%, specificity 64%), Bp = -0.5 (sensitivity 63%, specificity 62%).

■ COMMENTARY

ROC curve analyses are often used as a tool to evaluate diagnostic tests, in particular to evaluate a test's ability to distinguish diseased from non-diseased states.[1] In theory, a test would be both highly sensitive and highly specific. The ROC curve shows the tradeoff between sensitivity and specificity of a test. Prolapse occurs along a spectrum from early and asymptomatic to advanced and symptomatic. POP-Q measurements for Ba, C, and Bp have continuous numeric values and are considered continuous outcomes. The authors wanted to use the POP-Q points like a diagnostic test to see if there is specific value for each point that could accurately distinguish symptomatic from asymptomatic prolapse.

Pelvic organ prolapse is a common condition. Women with prolapse experience a myriad of symptoms including a sensation of vaginal bulging, a vaginal lump, pelvic heaviness and/or pelvic pressure, and lower urinary tract symptoms. Women are estimated to have a 10-20% lifetime risk of surgery for prolapse, a significant risk considering women are living well into the eighth decade of life. In 2002, the Standard International Continence Society created the POP-Q system as a standardized metric to quantify prolapse.[2] It consists of nine points measured in centimeters; seven defined points are measured using the hymen as a reference point. The points allow for the individual assessment of the anterior, posterior, and apical vaginal compartments as well as the measurement of length of genital hiatus and perineal body.

Some studies have found it difficult to correlate symptoms of prolapse with anatomic findings.[3] By modeling the likelihood of symptoms as a function of clinical measurements in the anterior, apical, and posterior compartments by using Ba, C, and Bp measurements, respectively, the authors attempted to identify anatomic cutoff points to reliably distinguish symptomatic and asymptomatic prolapse.

The authors found fairly accurate anatomic cutoffs that are likely to result in symptomatic and clinically significant prolapse. The cutoff values are different by compartment and are Ba = -0.5, C = -5, and Bp = -0.5. For those of us not used to routinely using the POP-Q system, this translates into values that correspond to the anterior wall 0.5 cm proximal to the hymen (Ba), the cervix or vaginal cuff (C) 5 cm proximal to the hymen, and the posterior wall (Bp) 0.5 cm proximal to the hymen. At one of these anterior, apical, or posterior points, a woman is very likely to be symptomatic, and as these values worsen (or come closer to the hymen), it is more likely that a woman will become increasingly symptomatic and, hence, have more clinically significant prolapse. These cutoff values are helpful as anatomical reference points that when seen on exam may prompt us to further inquire about prolapse symptoms or help guide our counseling of women who are still asymptomatic. ■

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CME QUESTIONS

1. **Which of the following was independently associated with a protective effect against receiving non-adherent care?**
   a. Black race
   b. Low socioeconomic status
   c. Lack of a gynecologic oncologist
   d. Travel distance to receive care > 20 miles

2. **In the study by Kaislasuo et al, which of the following was a predictor of pain with IUD insertion?**
   a. Uterine position
   b. Short uterine length
   c. Age
   d. History of severe dysmenorrhea
   e. Short fundal width

3. **The primary objective of the KEEPS study of postmenopausal hormone therapy was to:**
   a. evaluate the rates of cardiovascular mortality between users of oral and transdermal estrogen.
   b. evaluate all-cause mortality.
   c. evaluate progression of surrogate markers of cardiovascular disease.
   d. evaluate quality of life and sexual function.

4. **A recent study attempting to define clinically relevant prolapse found:**
   a. there is no way to predict symptomatic prolapse.
   b. prolapse is only symptomatic once it is 2 cm distal to the hymen.
   c. cutoffs for symptomatic prolapse are different based on compartment.
   d. urinary symptoms were the main symptoms described by women with prolapse.

CME 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]

Use of Cervical Length and Fetal Fibronectin in Preterm Labor