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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Is an Atraumatic Tenaculum on the Cervix Less Painful than a Single-tooth Tenaculum?

By Rebecca H. Allen, MD, MPH

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

SYNOPSIS: In this randomized, controlled trial, there was no difference in pain scores between the standard single-tooth tenaculum (mean 33/100) and the atraumatic vulsellum tenaculum (mean 35/100) ($P = 0.58$). The time to control bleeding at the tenaculum site differed with 1.1 minutes in the single-tooth tenaculum group and 0.4 minutes in the atraumatic vulsellum tenaculum group ($P = 0.001$).

SOURCE: Doty N, MacIsaac L. Effect of an atraumatic vulsellum versus a single-tooth tenaculum on pain perception during intrauterine device insertion: A randomized controlled trial. *Contraception* 2015;92:567-571.

This is a single-blind, randomized, controlled trial comparing the use of the atraumatic vulsellum tenaculum to the single-tooth tenaculum to grasp the cervix during intrauterine device (IUD) insertion at one center in New York. Eighty women without contraindications to IUD insertion were enrolled and randomized in a 1:1 ratio. Pain was measured at seven points during the procedure on a 0-100 mm visual analog scale: 1) prior to start, 2) speculum placement, 3) tenaculum placement, 4) uterine sounding, 5) IUD insertion, 6) speculum removal, and 7) 3 minutes post-procedure. IUDs were inserted by four experienced providers and two second-year OB/GYN residents. Forced coughing was performed at the time of tenaculum placement and the tenaculum was closed completely and "without audible clicks."

Eighty women were randomized; however, three women in the atraumatic vulsellum group and one woman in the single-tooth tenaculum group did not receive the allocated intervention and were excluded from analysis. There was no difference between the two groups in terms of age, race, body mass index,

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IUD chosen, history of dysmenorrhea, preoperative anxiety score, or previous vaginal delivery. A similar number of women in each group had taken pre-procedure medications at home (17 ibuprofen, 2 opioids, 2 benzodiazepines, 1 acetaminophen, 1 diphenhydramine). There was no difference between the groups with pain at the time of tenaculum placement (33.3 single-tooth tenaculum vs 35.0 atraumatic vulsellum tenaculum, P = 0.58). Provider-reported ease of placement did not differ between the two groups (19 vs 19 out of a 0-100 mm visual analog scale). The length of time needed to control bleeding from the tenaculum site was longer in the single-tooth tenaculum group (1.1 minutes) compared to the atraumatic tenaculum group (0.4 minutes) (P = 0.001). Approximately 29% of women in the single-tooth tenaculum group required pressure and/or silver nitrate to control bleeding compared to 14% in the atraumatic vulsellum group (P = 0.1).

■ COMMENTARY

The vulsellum atraumatic tenaculum (also known as a Teale or Bierer tenaculum) has multiple small teeth that are not intended to puncture the cervical mucosa. It is similar to an Allis clamp but longer and angled in order to be used vaginally. The authors of this study report that the vulsellum atraumatic tenaculum was favored in their institution because providers believed it caused less pain and bleeding than the single-tooth tenaculum. Nevertheless, there were no data in the literature supporting this preference. Therefore, the authors undertook this simple trial that was powered to detect a 20 mm difference in pain scores on the 0-100 mm scale. While the authors did substantiate slightly longer procedure durations with the single-tooth tenaculum due to the time it took to control bleeding from tenaculum puncture sites, there was no difference in the pain experienced by the patient. It is admirable when our practices are examined in an evidence-based fashion, as we all tend to believe "our way" is the best way of doing a particular procedure.

The question of tenaculum type and pain experienced by women is a topic of interest to those of us who research interventions for pain control for gynecologic office procedures. In most procedures involving uterine instrumentation, a tenaculum is used for stabilization and traction of the cervix and to decrease the flexion of the uterus to ease passage of instruments into the endometrial cavity. I find two points of the authors' technique interesting. First, they described that both groups of patients were instructed to cough with tenaculum placement. While this common technique has been found to decrease pain with cervical biopsy,[1] it has not been studied for tenaculum application. Second, they also reported closing the tenaculum completely without "audible clicks." Presumably, avoiding the clicking sound lessens the patient's anxiety. The decision to close the tenaculum completely, however, is different from what I have seen in the past for teaching IUD insertions. My experience is that most experts advise closing the tenaculum very slowly to only one ratchet as a technique to decrease pain.

> […these authors debunk the myth that atraumatic tenaculums or other similar instruments are less painful when applied to the cervix than single-tooth tenaculums..]

At any rate, other studied interventions to reduce pain with tenaculum placement include topical and injected local anesthetics. A recent randomized, controlled trial among 70 women compared a 2 mL injection of 1% lidocaine and 1 mL of 2% lidocaine gel to the anterior lip of the cervix for tenaculum placement.[2] The tenaculum was placed immediately after medication administration. The results showed that women who received the injection had significantly less pain at the time of tenaculum placement compared to women who received the topical gel (12.3 vs 36.6 out of 100, P < 0.001). Nevertheless, the product label for 2% lidocaine gel states that onset of action occurs in 3 to 5 minutes when used on mucosal surfaces.[3] While it is not surprising that the topical gel had no effect in this study, most providers are unwilling to wait a full 3 minutes for the gel to work, so this aspect of the study is more true to practice. To this end, Rapkin et al evaluated patient self-administration of 2% lidocaine gel vaginally 5 minutes prior to IUD insertion

and found that mean pain scores for tenaculum placement were 32 in the lidocaine arm and 56 in the placebo group out of 100 ($P = 0.030$).[4] Because this technique does not require a speculum exam for gel application, it may be more acceptable to patients. It is unclear why the women in this study had a higher pain report with tenaculum placement than other studies.

In sum, reducing pain at time of tenaculum placement is a worthwhile endeavor. Injected lidocaine is effective in reducing pain with tenaculum placement and is convenient to perform when a paracervical block is planned. Topical agents typically are not effective unless a longer period of time elapses between administration and tenaculum placement. Doty et al examined yet another nuance of pain at time of tenaculum placement. I commend these authors for debunking the myth that atraumatic tenaculums or other similar instruments, such as ring forceps, are less painful when applied to the cervix than single-tooth tenaculums. ■

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ABSTRACT & COMMENTARY

Molecular Diagnostics: A Step Forward in Breast Cancer Treatment?

By Jeffrey T. Jensen, MD, MPH, Editor

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Dr. Jensen reports he is a consultant for and receives grant/research support from HRA Pharma, Bayer Healthcare, Merck, Agile Pharm, Population Council, AbbVie, Evofem, and ContraMed; and is a consultant for Teva Pharmaceuticals and Microchips.

SYNOPSIS: Use of a gene-expression assay to predict prognosis may reduce the need for adjuvant chemotherapy in some women with early stage invasive breast cancer.

SOURCE: Sparano JA, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015;373:2005-2014.

This paper reports initial results from the Trial Assigning Individualized Options for Treatment (TAILORx) study, a prospectively conducted clinical trial designed to evaluate the clinical usefulness of the 21-gene assay (Oncotype DX Recurrence Score, Genomic Health) in low-risk women with hormone-receptor–positive, HER2-negative, axillary node–negative invasive breast cancer. Subjects had to meet National Comprehensive Cancer Network guidelines for adjuvant chemotherapy; a primary tumor size of 1.1-5.0 cm in greatest dimension (or 0.6-1.0 cm for high-grade tumors); an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (no or mild symptoms); and normal hematologic, bone marrow, hepatic, renal, pulmonary, and cardiac function. The clinical trial was sponsored by the National Cancer Institute (NCI), and patients were recruited from NCI-supported research centers. Eligible patients at these sites received counseling about the study, and consenting subjects agreed to have their breast cancer treatment determined by results of a genetic test, the Oncotype DX Recurrence Score. The score (0 to 100) was calculated using a reverse-transcriptase–polymerase chain-reaction 21-gene assay performed on RNA extracted from the formalin-fixed paraffin-embedded tissue from each patient. Subjects with a score of < 10 received endocrine therapy (tamoxifen and/or aromatase-inhibitor) alone, those with a score of > 25 received chemotherapy plus endocrine therapy, and those with a midrange score of 11-25 were randomly assigned to receive either chemotherapy plus endocrine therapy or endocrine therapy alone. The primary trial endpoint was a time-to-event analysis of the rate of survival free from invasive cancer. This paper presented only the results from the cohort with low-risk scores (0-10) assigned to receive endocrine therapy only.

Of the 10,253 women eligible for the study, 1629 (15.9%) had a low-risk score (< 10) and received endocrine therapy only. At 5 years, the rate of invasive disease-free survival was 93.8% (95% confidence interval [CI], 92.4-94.9), and the rate of overall survival was 98.0% (95% CI, 97.1-98.6), but most of

the events were due to a second primary cancer and deaths from causes unrelated to the primary breast cancer. In other words, use of the genetic tests safely eliminated the need for chemotherapy in 16% of women with early-stage breast cancer.

■ COMMENTARY

With the diagnosis of a true invasive breast cancer, the use of highly aggressive therapies seems justified, even when the overall benefit looks marginal and the morbidity of treatment can compromise quality of life. The use of advanced molecular techniques could improve results by identifying the heterogeneity of prognoses associated with an individual diagnosis. While the promise of personalized medicine is vast, these diagnostics must undergo prospective validation.

Sparano et al evaluated whether a molecular biology approach could determine which women would benefit from adjunctive chemotherapy. The proprietary test evaluates the expression patterns of 21 breast cancer-associated genes to calculate a risk score of low, intermediate, and high risk for recurrence based on earlier retrospective evaluations outcomes associated with these patterns.[1-4] The test, OncotypeDx, is currently approved on the basis of these retrospective evaluations. Although the prospective validation of a test to screen low-risk women unlikely to benefit from chemotherapy is an important step forward, there are several limitations to this study. The test was marketed based on results from the retrospective studies that suggest the addition of chemotherapy provides little benefit to women with low-risk scores. Women with high-risk scores represent a poor prognosis group that benefits the most from chemotherapy. Whether women with tumors of intermediate scores benefit from aggressive chemotherapy is the subject of the prospective randomized, clinical trial currently in progress. Since women with intermediate gene scores represented 67% of the study population, results of the randomized, clinical trial will be extremely important. Unfortunately, the test is already in clinical use with a cutoff point for low risk of 18 rather than the 10 reported in this paper, so these results cannot be considered a validation of the higher cutoff point in the approved test. Still, 16% of the approximately 10,000 node-negative, hormone-receptor–positive breast cancer patients enrolled in the study had a score of < 11, and the prospective results confirmed that this is a good prognosis group that can avoid chemotherapy. Let's hope that the randomized, clinical trial supports expanding this simplified treatment for women with intermediate scores. Until then, clinicians should be cautious about the predictive power of this test for women with high gene scores.

More work is needed to develop low-cost diagnostics to improve cancer diagnosis and personalized therapies. The title of Clifford Hudis's accompanying editorial in the same issue of the journal gets it right: "Biology Before Anatomy in Early Breast Cancer — Precisely the Point."[5] Companies developing these approaches will make a lot of money, but advanced diagnostics will hopefully save money and lives by reducing the use of expensive, toxic, and ineffective chemotherapy protocols. Making cancer therapy "smart" will require the joint effort of scientists, clinicians, and regulators to prevent false and misleading claims. ■

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ABSTRACT & COMMENTARY

Hormone Replacement Therapy Controversies: Have We Harmed Women?

By Molly A. Brewer, DVM, MD, MS

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Dr. Brewer reports that she receives grant/research support from the National Cancer Institute.

SYNOPSIS: The interpretation of hormone replacement therapy in postmenopausal women has varied dramatically before and after the publication of the Women's Health Initiative study in 2002. New studies question the validity of the conclusions reached by the investigators.

SOURCE: Shapiro S, et al. Risks and benefits of hormone therapy: Has medical dogma now been overturned? *Climacteric* 2014;17: 215-222.

In the past, hormone replacement therapy (HRT) was thought to prevent cardiovascular disease (CVD), the number one cause of mortality in women after menopause. Epidemiologic data had shown that the risk of CVD in women was lower than men prior to menopause but increased after menopause to become equivalent to men. Hormones associated with ovarian function, particularly estrogen, were believed to play a large role in the prevention of postmenopausal CVD. Therefore, researchers concluded that if postmenopausal women were given HRT, it would decrease their CVD risk.[1-4] Over and above the protection against CVD, data also showed the preventive effects of HRT on osteoporosis,[5] adding to the argument that postmenopausal HRT served multiple protective effects.

Since the publication of the Women's Health Initiative (WHI) study in 2002,[6] the use of HRT has changed dramatically. Up to this time, most clinicians caring for postmenopausal women thought that HRT reduced the risk of CVD and prevented osteoporosis. The majority of women were prescribed HRT, unless a woman had breast cancer. Following the release of the WHI manuscript (and the subsequent negative publicity), Dr. Rossoue, the lead author, stressed the importance of understanding how the risk to an individual woman can be low, but the risk to the population at large can be great:

> The WHI results tell us that during 1 year, among 10,000 postmenopausal women with a uterus who are taking estrogen plus progestin, 8 more will have invasive breast cancer, 7 more will have a heart attack, 8 more will have a stroke, and 18 more will have blood clots, including 8 with blood clots in the lungs, than will a similar group of 10,000 women not taking these hormones. This is a relatively small annual increase in risk for an individual woman. Individual women who have participated in the trial and women in the population who have been on estrogen and progestin should not be unduly alarmed. However, even small individual risks over time, and on a population-wide basis, add up to tens of thousands of these serious adverse health events.[7]

The study was stopped early due to a 24% increase in the risk of breast cancer in the estrogen-progestin (E-P) arm. The results of the WHI study were widely publicized and women were universally warned through the media that taking HRT was damaging to their health.

Women either voluntarily stopped taking HRT or their physicians recommended they stop HRT as a result of this study. A 2003 publication determined that most regular users of HRT attempted to stop treatment based on the mass media discussion about the risks of HRT without really understanding the real individual risk of continuing their HRT.[8] Aside from the individual risk of breast cancer and CVD, there were multiple other outcomes published from the WHI, most of which showed a detrimental effect of E-P on women's health.[9-11] This furthered the argument that postmenopausal HRT may be harmful to women.

A recent publication has challenged much of the data published from the WHI study. In a 2014 manuscript,

[Despite the fact that this was a randomized, controlled trial, the flaws in the study and the overinterpretation of the results have significantly affected women's health. In addition, the wide media coverage and numerous commentaries have frightened women and clinicians.]

Shapiro et al questioned both the study design and the conclusions reached by the WHI group.[12] They suggested that the primary endpoints (i.e., CVD, breast cancer) changed multiple times throughout the study. This is worrisome since it implies that the authors were manipulating the data. The authors of the 2014 study said that the global index, which included CVD, breast cancer, stroke, pulmonary embolus, colon cancer, endometrial cancer, and fracture risk as a conglomerate score of risk vs benefit, is not valid because there was little similarity in these outcomes. Instead, they suggest that hazard ratios can be weighted to determine an overall risk or benefit. Multiple modifications of the index were made during the study, which the authors suggest biased the results. Women were informed of the risk of CVD and a large number of the E-P women were unblinded (44%), which would increase the surveillance for CVD and potentially diagnose more CVD. In addition, there was a 42% rate of nonadherence in the E-P group and 10% of the women in the placebo group crossed over to the treatment group. Analyzing women in the group to which they were randomized when there was such a high rate of nonadherence and a high rate of crossover introduced significant confounding factors, particularly if the risk is found to be elevated (i.e., causation will be inferred when no causation may exist). In addition, the hazard ratios are quite low for the risk of breast cancer (1.24), CVD (1.18), and stroke (1.39), the outcomes that were the most worrisome. The clinical significance

of a hazard ratio < 2.0 is questionable. There is an epidemiologic concern that this low strength of association (low hazard ratio) is due to confounding factors and is not a real effect.[13] The authors concluded that the WHI study, despite its wide impact, may not have demonstrated an increase in the risk of either CVD or breast cancer given the study design and statistical issues, and that as a result of these flaws, women have been harmed.

■ COMMENTARY

I have had significant concerns about the conclusions reached by the WHI study since its publication in 2002. The average age of the women enrolled was 63 years, an age that generally has not been associated with starting HRT, and 34% of women had a body mass index > 30 kg/m^2, a known risk factor for breast cancer. With the large nonadherence in the E-P group (44%) and the 10% crossover from the placebo group, it is probable that at least 55% of the women did not receive the treatment to which they were allocated. Thus, the conclusion that HRT caused poor outcomes may, in fact, be spurious. As a result of this study, most women would rather suffer with severe atrophic vaginitis that interferes with their sexual and urinary tract function than take hormones because of their fear of breast cancer, CVD, and stroke. Many women will develop osteoporosis but will not take hormone replacement and instead opt for other osteoporosis drugs that are found to possibly have limited benefit. It is unfortunate that the questionable results of this study could have such a large impact on women.

Despite the fact that this was a randomized, controlled trial (the most powerful study design in terms of showing causation), the flaws in the study and the overinterpretation of the results have significantly affected women's health. In addition, the widespread media coverage and the numerous commentaries by the authors have frightened both women and clinicians. There were six more CVD events, nine more breast cancer cases, nine more strokes, and nine more pulmonary embolisms per 10,000 women. It is not clear if this difference could have occurred more commonly in the women who did not take their HRT (the 44% nonadherence in the E-P group) because the increase is relatively low.

It is always important to weigh the risk and the benefits of any intervention. However, to do so, the results must be interpretable to patients and clinicians. As clinicians, we must always be guided by the caveat to first do no harm. In the case of the WHI, the debate continues as to the true value of this large and impactful study. ■

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ABSTRACT & COMMENTARY

Recurrence Rate for Placental Abruption

By John C. Hobbins, MD

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

SYNOPSIS: A study from the Netherlands involving more than 1 million patients has shown that recurrence of placental abruption happens more frequently in those patients whose first abruption occurred at term and/or in their first pregnancy, as well as in those with a history of hypertension.

SOURCE: Ruiter L, et al. Incidence and recurrence rate of placental abruption: A longitudinal linked national cohort study in the Netherlands. *Am J Obstet Gynecol* 2015;213:573.e1-8.

Placental abruption can be associated with devastating results but even if the outcome is favorable, the process of getting through the pregnancy leaves an indelible impression on most patients. Before or soon after becoming pregnant again, most will seek answers regarding the chances of having a recurrence. Unfortunately, there has been little in the literature to help with the answer — until now.

Investigators searched the Netherlands Perinatal Registry for pertinent data from 1999 to 2007 regarding documented cases of abruption.[1] They then tracked these patients' reproductive histories looking for recurrences. Fortunately, the database was robust enough to search for possible risk factors that could be linked with recurrent abruption.

Of the 1,570,635 patients in the database, 3496 patients had an abruption (0.22%). Follow-up information was available on 264,424 patients, representing 528,848 deliveries. The authors found 520 patients had abruptions in their first pregnancies (0.20%), compared with 214 (0.08%) in their later pregnancies. Of those experiencing abruption, 30 had a recurrence in another pregnancy (5.8%) vs those without this history (0.07%).

Interestingly, those having abruptions at term were more likely to have a recurrence than those with preterm abruptions (32-37 weeks) or early preterm (< 32 weeks), with odds ratios (OR) of 188, 52, and 39, respectively. Not surprisingly, hypertensives had a higher rate of abruption than normotensive women (0.44% vs 0.26%). Of the entire group having abruptions in their first pregnancies, 12.6% had hypertension, while 6.6% of second pregnancy abruption patients had hypertension. Surprisingly, there was a nonsignificant trend toward a lower recurrence rate in hypertensives compared with normotensive women (OR, 0.68; 95% confidence interval, 0.27-1.6).

■ COMMENTARY

The most important message for a patient who has had an abruption, and who often feels like she is sitting on a powder keg, is that the overall recurrence rate is 5.8%. Or if presented in a "this glass is way more than half full" approach, she has a 19 in 20 chance of sailing through the pregnancy without a recurrence. The most striking findings were the parallel relationship between the gestational age at the time of the first abruption and the incidence of a recurrence, and in the fact that most abruptions were likely to happen after 37 weeks. This even stimulated the authors to recommend induction at 37 weeks for patients with a history of previous abruptions, the deck being loaded even further if the first abruption occurred at term.

The most frustrating part of caring for patients with previous abruptions is that little can be done to prevent the condition or to treat it once it happens. However, there are early clues available to identify those at greater risk. For example, first trimester (low pregnancy-associated plasma protein A)[2] and second trimester (elevated alpha-fetoprotein)[3] biochemistry have been linked with abruptions later in pregnancy. Also, abnormal uterine artery waveforms have been associated with an increased risk of abruption.[4] While abnormal results can raise the antennas of providers, negative results might at least provide the patient with some reassurance against another abruption. ■

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CME/CNE QUESTIONS

1. **In the study by Doty et al, atraumatic vulsellum tenaculums were found to be:**
   a. less painful than single-tooth tenaculums.
   b. associated with shorter procedure times than single-tooth tenaculums.
   c. more painful than single-tooth tenaculums.
   d. associated with more bleeding than single-tooth tenaculums.

2. **The OncotypeDx test evaluates breast cancer prognosis and need for chemotherapy:**
   a. by evaluating the expression of 21 breast cancer-associated genes in tumor samples using reverse transcriptase polymerase chain reaction.
   b. by comparing cancer gene expression in a pre-surgery and post-surgery blood sample.
   c. by calculating a risk score derived from age, tumor size, grade, and seven breast cancer-associated genes.
   d. is only valid when the tumor specimen is flash frozen and shipped on dry ice within 72 hours.

3. **What is the risk of breast cancer in women taking combined hormone replacement therapy with conjugated estrogens and medroxyprogesterone acetate?**
   a. Two times the population risk
   b. Increased with age
   c. 24% increased over the baseline
   d. Reduced by 15%

4. **In the index study, abruption reoccurred more frequently in patients:**
   a. having the first abruption in their first pregnancies.
   b. who had hypertension.
   c. in whom the first abruption occurred at term.
   d. All of the above

5. **In the study group of more than 264,000 patients where follow-up data were available, placental abruption reoccurred in about one in 10 pregnancies.**
   a. True
   b. False

CME/CNE 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]

Updates in Infertility