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ABSTRACT & COMMENTARY

Is RhoGAM Needed for Rh-Negative Women Experiencing First-Trimester Pregnancy Loss or Induced Abortion?

By Rebecca H. Allen, MD, MPH, Editor

SYNOPSIS: In this prospective cohort pilot study, the authors validated a flow cytometry protocol for detecting fetal red blood cells and determined that fetal red blood cell exposure in first-trimester uterine aspiration was well below the calculated threshold for maternal Rh sensitization.

SOURCE: Horvath S, Tsao P, Huang ZY, et al. The concentration of fetal red blood cells in first-trimester pregnant women undergoing uterine aspiration is below the calculated threshold for Rh sensitization. *Contraception* 2020; March 3. doi: 10.1016/j.contraception.2020.02.011. [Online ahead of print].

The authors of this study developed a flow cytometry protocol to detect fetal red blood cells (RBCs) that relied on dual staining with hemoglobin F and carbonic anhydrase to distinguish fetal from adult RBCs, and then further distinguished maternal F cells from fetal RBCs by the brightness of staining for hemoglobin F. This flow cytometry protocol then was evaluated with an in vivo pilot study of 42 participants. Based on previous studies, the authors considered 0.1 mL of RBCs the minimum volume of fetomaternal hemorrhage capable of causing Rh sensitization. The average pregnant woman's blood volume in early pregnancy is 4,000 mL. Therefore, the target fetal RBC concentration for detection was 0.1/4,000 mL or 250 fetal RBCs per 10 million total adult RBCs. Women undergoing uterine aspiration for spontaneous or induced abortion less than 12 completed weeks gestation were recruited. Women with hemoglobinopathies or vaginal bleeding prior to enrollment were excluded. Blood was drawn before and after uterine aspiration and samples were run within 72 hours of collection. The authors were able to validate their flow cytometry protocol and then apply it to the study subjects. A total of 37 of 42 participants (88%) had pre- and post-aspiration samples sufficient for analysis. All fetal RBC samples were below the

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A Note from *OB/GYN Clinical Alert*'s New Editor

I am honored to take over the role of editor for OB/GYN Clinical Alert from Dr. Jeff Jensen, a colleague whom I admire greatly. Dr. Jensen invited me to write for this publication back in 2012 and I have contributed articles regularly ever since. I plan to continue in the tradition of evidence-based medicine that Dr. Jensen championed and hope to recruit new writers and cover new topics. I certainly have big shoes to fill with occupying the role held by Dr. Jensen and his predecessor, Dr. Leon Speroff. I will work hard to meet that challenge, and look forward to the future with *OB/GYN Clinical Alert*.

— Rebecca H. Allen, MD, MPH, Editor

calculated threshold for Rh sensitization of 250 fetal RBCs per 10 million adult RBCs. The fetal RBC concentration increased from pre-aspiration (mean 4.5, median 0, range 0-57) to post-aspiration (mean 8.6, median 2, range 0-32). There was no statistically significant difference in fetal RBC concentration by gestational age, use of sharp curettage, pregnancy history, or participant demographics.

■ COMMENTARY

The need for anti-D immunoglobulin (RhoGAM) after first-trimester events, such as threatened abortion, spontaneous abortion, molar pregnancy, and induced abortion, lacks consensus.[1,2]

International recommendations differ, for example, with the Royal College of Obstetricians and Gynaecologists not requiring RhoGAM for abortion less than 12 weeks unless the uterus is surgically evacuated, while the American College of Obstetricians and Gynecologists (ACOG) states that administering a 50 mcg dose in early pregnancy loss "should be considered."[1-4] However, not every facility has the 50 mcg dose available for first-trimester patients and many administer the full 300 mcg dose, which may be a waste of resources. Currently, no synthetic anti-D immunoglobulin is available, and our supply comes from human donors. Since approximately 15% of women in the United States are Rh negative, this recommendation affects new patients, as well as emergency departments, hospitals, and abortion clinics. Therefore, it is laudable that the authors completed this pilot study.

Traditional measurement of fetomaternal hemorrhage with Kleihauer-Betke (K-B) testing is limited because the lower limit of detection is 4,000 fetal RBCs per 10 million adult RBCs. In addition, the K-B test does not distinguish between fetal RBCs and maternal F cells, which can lead to false-positive results. There-fore, the authors opted to use a flow cytometry protocol, which is more sensitive, and then validated it by looking at both maternal F cells and fetal RBCs. Previous studies provided the authors with a plausible threshold concentration for fetomaternal hemorrhage during the first trimester (250 fetal RBCs per 10 million total adult RBCs). The fact that the authors did not find any subject approaching this threshold is encouraging. Luckily, the authors will be pursuing this work with a larger sample of patients; therefore, more data will be accrued.

The National Abortion Federation already changed its guideline in March 2019 to allow for waiving Rh testing and RhoGAM administration for Rh-negative patients undergoing surgical abortion up to eight weeks gestation and medication abortion up to 10 weeks gestation, based on emerging evidence.[2,5,6] This change may allow women seeking induced abortion to pay less out of pocket for the procedure. The change also facilitates medication abortion via telemedicine, which is becoming more important in the COVID-19 pandemic.[7] I suspect many other U.S. providers likely will wait for ACOG to change its recommendation before changing practice in the first trimester. At the very least, I wish more hospitals would stock the 50 mcg dose of RhoGAM to conserve supplies. ■

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ABSTRACT & COMMENTARY

Does a Standardized Recovery Bundle After Cesarean Delivery Decrease Length of Stay?

By Jeanine Mikek, MSN, RN, CEN

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Ms. Mikek reports no financial relationships relevant to this field of study.

SYNOPSIS: Implementation of an enhanced recovery bundle after cesarean delivery reflected diverse positive outcomes. However, length of stay was reduced only by an average of two hours.

SOURCE: Teigen NC, Sahasrabudhe N, Doulaveris G, et al. Enhanced recovery after surgery at cesarean delivery to reduce postoperative length of stay: A randomized controlled trial. *Am J Obstet Gynecol* 2020;222:372.e1-372.e10.

Studies of an enhanced recovery after surgery (ERAS) bundle for postoperative patients in surgical specialties, including but not limited to orthopedics, gastroenterology, and urology, demonstrated positive outcomes, such as reduced length of stay, improved patient satisfaction, and improved fiscal responsibility.[1] However, how an ERAS protocol affects postpartum women after cesarean delivery is unclear. From late 2017 to mid-2018, doctors at an urban academic hospital in Bronx, NY, completed a randomized, controlled trial of 118 women undergoing a cesarean birth to determine if an ERAS bundle would reduce length of stay. These authors primarily were interested in reducing the postoperative length of stay from three days to two days. Secondary outcomes included postoperative pain medicine use, postoperative complications, patient satisfaction, and breastfeeding rates.

Pregnant women with a gestational age of at least 37 0/7 weeks were invited to participate. Exclusions included emergent cesarean births, use of general anesthesia, hypertensive disorders of pregnancy, active intra-amniotic infection, or an adherent placenta. In addition, patients who were not candidates to receive ketorolac were excluded.

One hundred eighteen pregnant women were randomized, with 60 receiving standard care and 58 placed in the ERAS group. Components of the ERAS bundle focused on early oral intake, use of xylitol chewing gum (to promote gastric motility), removal of the surgical dressing by six hours, use of incentive spirometry, removal of urinary catheter with ambulation by 12 hours, and scheduled administration of intravenous ketorolac for 24 hours. The primary outcome was patient discharge on the second day. Other secondary outcomes assessed included postoperative length of stay in hours, postoperative narcotic use, breastfeeding rates, surgical complications, and gastrointestinal issues. Six weeks after delivery, participants used a Likert scale to score their experiences related to the secondary outcomes.

In contrast to other surgical studies evaluating ERAS protocols, a significant reduced length of stay was not observed in this randomized clinical trial. On average, discharge times were reduced by only approximately two hours rather than a full day (73.5 hours vs. 75.5 hours; $P = 0.046$). Interestingly, patients who received standard care had higher rates of hospital readmission (8.3% vs. 0%; $P = 0.10$), hypertensive complications (11.7% vs. 6.9%; $P = 0.38$), and gastrointestinal issues (11.7% vs. 1.7%; $P = 0.06$). Women randomized to the ERAS protocol showed improved patient satisfaction, earlier rates of ambulation, and greater success with breastfeeding. Only 8.9% of ERAS participants stated they did not attempt breastfeeding compared to 26.4% of women who received standard postoperative care ($P = 0.001$). In addition, exclusive breastfeeding at six weeks was significantly higher

in the ERAS group compared to the control group, with a nearly 20% difference (67.2% and 48.3% respectively; $P = 0.046$).

■ COMMENTARY

Postoperative length of stay was not affected by ERAS protocol in a significant way for women delivering by cesarean. However, from personal experience, many mothers who deliver by cesarean birth desire to be discharged home prior to the standard 72-hour mark. So, although these results were not as promising as hoped, with average length of stay reduced by two hours compared to one day, this small difference may be meaningful to some women. Furthermore, a number of the secondary outcomes were positively affected, not the least of which was patient satisfaction. Women randomized to ERAS demonstrated reduced postoperative nausea or vomiting as well as improved perception of pain control. Small improvements in the plan of care, such as introducing chewing gum early to curb nausea, could improve the patient experience and potentially reduce the need for additional medications, such as ondansetron.[2] Less need for medication and an enhanced patient experience could help keep the focus on the maternal-infant dyad, and any factor that allows a woman to return to normal functional capacity is worth considering. A quality improvement project such as this could be a terrific opportunity for nursing staff on the unit to help implement. ■

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ABSTRACT & COMMENTARY

Fezolinetant Shows Positive Response in Vasomotor Symptoms Associated with Menopause

By Nicole Cirino, MD, CST, IF

Reproductive Psychiatrist, Associate Professor of Psychiatry and OB/GYN, Oregon Health & Science University, Portland

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

SYNOPSIS: A phase 2b trial using seven dosing regimens of a novel neurokinin-3 receptor antagonist, fezolinetant, shows statistically significant improvement in vasomotor symptoms vs. placebo in postmenopausal women.

SOURCE: Fraser GL, Lederman S, Waldbaum A, et al. A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause* 2020;27:382-392.

Fezolinetant, a selective neurokinin-3 (NK3) receptor antagonist, is an investigational oral, nonhormonal compound being studied for the treatment of vasomotor symptoms (VMS). It is believed to work on the thermoregulatory center in the hypothalamus, which is stimulated by neurokinin-3 receptor (NK3R) activation and inhibited by estrogen-negative feedback. This balance is disrupted in menopause, producing VMS.[1] Selective NK3R antagonists are suggested to act similarly as gonadotropin-releasing hormone (GnRH) modulators and previously have been studied in benign prostatic hyperplasia and endometriosis.[2] Currently, studies are ongoing for use of this NK3 to treat polycystic ovarian syndrome, uterine leiomyoma, and weight gain.[3]

Previously, a randomized, double-blind, placebo-controlled, phase 2a clinical trial in 87 postmenopausal women showed that single-dose fezolinetant 90 mg twice daily effectively reduced moderate/severe VMS and was well tolerated across 12 weeks of treatment, reducing the frequency of moderate/severe VMS by about 5.0 episodes per day relative to placebo (95% confidence interval [CI], -6.8 vs. -3.3).[1]

This phase 2b study, funded by Astellas Pharma Global Development, Inc., is a randomized, double-blind, placebo-controlled, dose-ranging, parallel group study conducted at 51 sites in the United States. Three hundred fifty-six women were randomized to receive either placebo or fezolinetant doses ranging from 15 mg to 90 mg twice daily or 30 mg to 120 mg once daily. Coprimary endpoints were mean change in both frequency and severity of moderate/severe VMS from baseline to week 4 and from baseline to week 12. Treatment was stopped after week 12. The trial length was 15 weeks.

Women were eligible for inclusion if they recorded ≥ 50 moderate/severe VMS over any seven consecutive days during the 35-day screening period. Mild VMS were defined as sensations of heat without sweating or noting damp sheets or clothing upon awakening. Moderate VMS were defined as sensations of heat with sweating but being able to continue activities, or waking from sleep because of feeling hot. Severe VMS were defined as feelings of intense heat with sweating that disrupts activities or, for night sweats, feelings of being so hot as to require action (e.g., removing layers of clothing, opening a window). Participants continued to record VMS frequency and severity at least twice daily in an electronic diary.

At baseline, participants had an average of nine to 11 moderate/severe VMS per day, which was similar across treatment groups. Participants ranged in age from 41 to 65 years (mean: 54.6 years), and the study population was 73% white, 25% black, 1% Asian, and 1% other races. Body mass index average was 27.3, and 58.1% of participants had undergone natural menopause. Outcomes in frequency and severity were self-reported through diaries.

Most groups showed statistically significant improvement from placebo in mean change in the frequency and severity of moderate/severe VMS at both week 4 and week 12. Results were maintained throughout the 12-week treatment period, with a return to baseline after treatment was stopped at week 15. All treatment groups exhibited a decrease in frequency of moderate/severe VMS. All fezolinetant regimens significantly reduced the frequency of moderate/severe VMS at weeks 4 and 12 compared with placebo, showing a decrease of -1.9 to -3.5 mean change per day from baseline for the twice-daily doses and between -2.3 and -3.0 mean change per day for the once-daily doses at week 4. Fezolinetant reduced moderate/severe VMS by about 62% to 81% at week 4, depending on dose, compared with about a 39% reduction with placebo. At week 12, fezolinetant demonstrated reduced VMS frequency compared to placebo, showing between -1.8 and -2.6 mean change per day for the twice-daily doses and between -2.1 and -2.6 mean change per day for the once-daily doses. Moderate/severe VMS were reduced by about 74% to 87% with fezolinetant vs. 55% with placebo.

Additionally, fezolinetant showed improvement in VMS severity compared to placebo, with a mean change per day range of -0.5 to -1.0 for the twice-daily doses and -0.4 to -0.7 for the once-daily doses at week 4. At week 12, fezolinetant demonstrated improvement in VMS severity compared to placebo, with a mean change per day range of -0.3 to -0.6 for the twice-daily doses and -0.2 to -0.5 for the once-daily doses.

Overall treatment-emergent adverse event (TEAE) rates were similar across groups and mostly mild or moderate. No deaths or treatment-related serious adverse events (SAEs) were reported. Common TEAEs (≥ 5% in any treatment arm) included headache, nausea, urinary tract infection, diarrhea, upper respiratory tract infection, fatigue, viral upper respiratory tract infection, sinusitis, and cough. There were no reports of endometrial hyperplasia. Other reported effects were: increased liver function test values (n = 1, fezolinetant 90 mg twice daily), adjustment disorder with depressed mood (n = 1, fezolinetant 30 mg once daily), cholelithiasis (n = 1, fezolinetant 60 mg once daily), drug-induced liver injury (n = 1, fezolinetant 60 mg once daily), and retinal detachment (n = 1, fezolinetant 120 mg once daily). Nine patients (less than 3%) treated with the higher doses of fezolinetant experienced brief increases in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). There were no cases of bilirubin levels greater than two times the upper limit of normal. Patients returned to baseline levels after discontinuing fezolinetant. No other clinically meaningful changes were noted in the vital signs and laboratory tests, electrocardiogram parameters, or plasma bone marker concentrations.The investigators considered the cholelithiasis and drug-induced liver injury to be treatment-related events. Changes in bone turnover markers were no different across treatment groups.

Although luteinizing hormone (LH) levels remained relatively stable in the placebo group, fezolinetant was associated with dose-dependent LH reductions three hours post-dose compared with either baseline or pre-dose levels. All groups, including placebo, showed small decreases from baseline in follicle-stimulating hormone (FSH) levels, and no treatment- or dose-related effects were observed. There were no clear trends or differences from placebo in estradiol or sex hormone binding globulin (SHBG) levels over the course of the study.

■ COMMENTARY

VMS affect up to 80% of U.S. women and are the most common reason for U.S. women to seek treatment during the menopausal transition.[4] Currently, the only Food and Drug Administration-approved nonhormonal treatment for VMS is paroxetine. Other commonly used nonhormonal medications involve other selective serotonin reuptake inhibitors and gabapentin. The NK3 receptor antagonist is a novel agent believed to work more selectively on VMS by targeting thermodynamic centers implicated in VMS disruption and to work as GnRH modulators.[2] In animal models, NK3 receptor antagonists, such as fezolinetant, have been found to cause a dose-dependently suppression of LH secretion, but not

FSH secretion. Consequently, this has resulted in a dose-dependent decrease estradiol and progesterone levels in women and testosterone levels in men.[2] LH levels were decreased in the treatment arm in this trial, but more data are needed to determine the mechanism in humans. This agent also is being studied in weight management, prostatic hyperplasia, endometriosis, polycystic ovarian syndrome, and uterine leiomyoma. NK3 modulators may be the next phase of management for VMS and may offer an alternative nonhormonal option.

According to Astellas, the pharmaceutical company funding this drug, phase 3 trials now are underway with two doses, fezolinetant 30 mg or 45 mg once daily. The stated goal is to recruit approximately 450 women for a double-blinded, placebo-controlled trial for moderate/severe VMS for the first 12 weeks, followed by noncontrolled 40-week extension periods. This will be followed by a 52-week double-blinded, placebo-controlled study to investigate long-term safety, with a goal of 1,150 participants with VMS.[5] Limitations to this study are the subjective nature of using self-reported diaries to determine hot flash severity and frequency, the number of subjects in each arm, and the short length of the trial. All participants were postmenopausal, not perimenopausal, and there are no plans to study this population. More research needs to be done with longer length of treatment, perimenopausal patients, and head-to-head trials. Timing, dosing, and further study of side effects, such as endometrial hyperplasia, quality of sleep, and mood-related side effects, are important to determine which patient populations would benefit most from this agent. The placebo response rate was as high as 55% in this trial, further highlighting the effect that stress-related factors and stress reduction techniques play in the frequency, severity, and management of VMS. ■

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ABSTRACT & COMMENTARY

A New Treatment for Recurrent Bacterial Vaginosis?

By Rebecca H. Allen, MD, MPH, Editor

SYNOPSIS: In this randomized, controlled trial of 228 women, *Lactobacillus crispatus* CTV-05 (Lactin-V) applied vaginally for 11 weeks reduced the incidence of recurrent bacterial vaginosis from 45% in the placebo arm to 30% in the Lactin-V arm.

SOURCE: Cohen CR, Wierzbicki MR, French AL, et al. Randomized trial of Lactin-V to prevent recurrence of bacterial vaginosis. *N Engl J Med* 2020;382:1906-1915.

Recurrent bacterial vaginosis (BV) is a problem that affects many women, with an estimated 50% of women developing a recurrence within 12 months of treatment.[1] The authors of this study tested the efficacy of a novel product, *Lactobacillus crispatus* CTV-05 (Lactin-V), in reducing bacterial vaginosis recurrence in this phase 2b clinical trial. This product contains a naturally occurring vaginal strain of *L. crispatus* in the form of a powder with 2×10^9 colony-forming units (CFU) preserved with inactive ingredients and administered via a vaginal applicator. Previously, the product was tested successfully in a phase 2a clinical trial.[2] This was a multicenter, randomized, controlled, double-blind trial to assess the efficacy of Lactin-V in preventing a recurrence of BV among women who had received a diagnosis of BV at a screening visit. Women in the study were 18 to 45 years of age who met three of four Amsel criteria (thin, white, homogeneous discharge, > 20% clue cells on wet prep, vaginal pH of > 4.5, and positive whiff test), and were diagnosed with BV and treated with a five-day course of 0.75% metronidazole gel. A swab also was sent for a Gram stain to determine the Nugent score (0-3, normal; 4-6, intermediate; and 7-10, indicative of BV). Nonpregnant women whose Nugent score was 4 or greater and who had negative sexually transmitted infection (STI; HIV, syphilis, gonorrhea, chlamydia, and trichomonas) screening were seen within 48 hours of completing the vaginal

metronidazole treatment. They were randomized in a 2:1 ratio to receive Lactin-V at 2×10^9 CFU per dose or matching placebo. The schedule consisted of four consecutive doses in week 1, followed by twice-weekly doses for 10 weeks. The patients were seen at four, eight, 12, and 24 weeks after treatment. The primary outcome was the percentage of participants who had recurrent BV, defined by three out of four Amsel criteria or a Nugent score of 4 or more at any follow-up visit up to and including week 12. Secondary outcomes included recurrent BV at 24 weeks and acceptability.

From April 2016 through February 2019, 228 women underwent randomization, 152 to the Lactin-V group and 76 to the placebo group. More than half the sample reported a history of five or more episodes of BV. Adherence to the treatment assigned was 77% in the Lactin-V arm and 74% in the placebo arm. In the intention to treat analysis, BV recurrence by week 12 occurred in 46 participants (30%) in the Lactin-V group and 34 participants (45%) in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.44-0.87). Among those without a known recurrence by week 12, an additional 13 (12%) participants in the Lactin-V group and seven (17%) in the placebo group had a recurrence by week 24 (RR, 0.73; 95% CI, 0.54-0.92). There was no difference between the two groups in terms of adverse events, both local (abnormal vaginal discharge, vaginal odor, genital itching) and systemic (abdominal pain, headache, frequent urination).

■ COMMENTARY

L. crispatus is a hydrogen peroxid-producing Lactobacillus that keeps the vaginal pH low and prevents other organisms from proliferating.[3] Lactobacilli predominate in healthy, normal vaginal flora, accounting for 70% to 90% of the microbiome. When this microbiome becomes disrupted, a biofilm infection, primarily consisting of *Gardnerella vaginalis*, adhering to the vaginal epithelium can occur. This biofilm promotes the growth of other anaerobic bacteria, leading to the symptoms of BV and malodorous vaginal discharge. The prevalence of BV varies by the population studied, but it can range from 15% to 40%.[3] First-line treatment options include 0.75% metronidazole gel applied vaginally for five nights, clindamycin cream 2% applied vaginally for seven nights, or 500 mg of oral metronidazole taken twice a day for seven days. Recurrence rates are high, and the optimal strategy to manage recurrence is unknown. One common regimen to treat recurrence is 0.75% metronidazole gel applied twice weekly for four to six months after induction treatment.[4] However, more therapeutic options are needed, and I applaud the authors for taking this issue. Despite BV's prevalence, is not a well-funded disease.

The authors of this study showed a modest reduction in BV recurrence with the use of a novel product, Lactin-V, at 12 weeks and extending through week 24. The use of Lactin-V after treatment with 0.75% metronidazole gel is an attempt to repopulate the vagina with healthy lactobacilli. This makes biologic sense, more so than consuming probiotics orally, and the treatment was well tolerated. Presumably, the authors will continue to study this product in a phase 3 clinical trial and are aiming for U.S. Food and Drug Administration approval. For now, the product is not available commercially.

[Recurrence rates for bacterial vaginosis are high, and the optimal strategy to manage recurrence is unknown. One common regimen to treat recurrence is 0.75% metronidazole gel applied twice weekly for four to six months after induction treatment. However, more therapeutic options are needed.]

Nevertheless, besides the burden of BV on the individual patient, the disease is important because it increases the acquisition of other STIs and has been associated with an increased risk of preterm birth, endometritis after delivery or abortion, pelvic inflammatory disease, and infection after hysterectomy.[3] Although a 15% difference in recurrence rates is not drastic, women may be willing to use a vaginal product with minimal side effects to attempt to decrease their chance of recurrence. It is possible that different doses or lactobacilli products may have a different effect. It is hoped that exploration in this area will continue. ■

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

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- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

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CME/CE QUESTIONS

1. **In the study by Horvath et al, the fetal red blood cell concentration increased:**
   a. as gestational age increased.
   b. with the number of prior pregnancies in the subject.
   c. from pre-aspiration to post-aspiration.
   d. with the use of sharp curettage.
2. **Which effects did the enhanced recovery after surgery bundle have on postpartum women recovering from a cesarean delivery?**
   a. Greater hospital readmission rates, longer breastfeeding, and early mobilization
   b. Increased breastfeeding success, discharge on day 2, and no postoperative narcotic use
   c. Reduced length of stay, less gastrointestinal complaints, and better pain control
   d. Early mobilization, increased breastfeeding rates, and higher percentage of postpartum depression
3. **What is believed to be the mechanism of action of fezolinetant on vasomotor symptoms?**
   a. a GABAergic receptor agonist
   b. an estradiol derivative
   c. a gonadotropin-releasing hormone modulator
   d. a serotonin reuptake inhibitor
4. **In the study by Cohen et al, what was the difference in recurrent bacterial vaginosis between the two study groups at 12 weeks?**
   a. 10%
   b. 15%
   c. 20%
   d. 50%

[IN FUTURE ISSUES]

COVID-19 and Children

Cardiac Complications of Pregnancy