

OB/GYN Clinical [ALERT]

Evidence-based commentaries
on women's reproductive health

ABSTRACT & COMMENTARY

Subcutaneous DMPA: Is It Time for Home Administration?

By *Rebecca H. Allen, MD, MPH*

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

SYNOPSIS: This randomized, controlled trial demonstrates that women are able to self-administer subcutaneous depot medroxyprogesterone acetate at home correctly and without complication.

SOURCE: Beasley A, et al. Randomized clinical trial of self versus clinic administration of subcutaneous depot medroxyprogesterone acetate. *Contraception* 2014;89:352-356.

The authors conducted a randomized, controlled trial of 137 women comparing self-administration and clinic administration of subcutaneous depot medroxyprogesterone acetate (DMPA, 104 mg) between 2010 and 2011 in New York City. Participants were aged ≥ 18 years, seeking DMPA for contraception, and available for follow-up for 1 year. Exclusion criteria were contraindications to the use of DMPA and women who desired pregnancy within 1 year. Participants were stratified according to never, past, or current use of DMPA and then randomized in a 2:1 ratio to self vs clinic administration. Women randomized to the self-administration arm were given instructions, supervised for their initial injection, and

given a packet containing prefilled glass syringes, supplies, a sharps disposal container, and a DMPA calendar giving dates for the next injection. Women were seen at both 6 and 12 months for follow-up and serum medroxyprogesterone acetate (MPA) levels were measured. The primary outcome variable was the continuation rate at 12 months.

In the study, 86 women were randomized to the self-administration group and 46 to the clinic administration group. Of the 132 participants total, 115 (87%) completed follow-up to 12 months. Ten (11.6%) women in the self-administration group and six (13%) in the clinic administration group were lost to follow-up

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and were considered to have discontinued DMPA in the analysis. The two groups did not differ in terms of age, education, and history of self-injection in the past. At study end, 71% of women in the self-administration group and 63% of women in the clinic administration group were still using DMPA for contraception ($P = 0.47$). MPA levels were no different between the two groups in continuous users at 6 and 12 months, indicating compliance with the injections.

■ COMMENTARY

DMPA is an important contraceptive option for women and is highly effective when women are adherent to the injection schedule.¹ The failure rate of DMPA when used perfectly is extremely low (< 1%) and is equivalent to intrauterine devices and implants. While not as long-acting as intrauterine devices and implants, DMPA still affords the user a relatively easy method, with only four required injections per year. Although injectable contraceptives are very popular internationally, currently, only 3% of U.S. women use DMPA for contraception.² DMPA is extremely safe to use and concerns regarding the temporary decrease in bone mineral density during exposure have been overstated. The U.S. Medical Eligibility Criteria for Contraceptive Use rates the use of DMPA as category 1 (no restrictions) in women ages 18-45 and category 2 (benefits outweigh the risks) in younger women.³

Intramuscular DMPA was originally approved for use as a contraceptive in the United States in 1992. Currently, DMPA is available in the United States as a generic 150 mg intramuscular formulation and a branded 104 mg subcutaneous formulation that was released in 2004. In contrast to other subcutaneous injectables like insulin, gonadotropins, and heparin, DMPA is not labeled for self-administration. However, multiple studies have shown that U.S. women would be interested in this option and that returning to clinic every 3 months can be a burden. The Contraceptive Choice Project in St. Louis reported continuation rates of DMPA at 1 year, 2 years, and 3 years to be 56%, 38%, and 28%, respectively.^{4,5,6}

Improving the convenience for women is an important part of increasing continuation rates for DMPA, although bleeding irregularities are still the number one reason for discontinuation.

This randomized, controlled trial demonstrates that women can self-administer DMPA correctly at home by following instructions. This is the first study that measured MPA levels in the participants to confirm adherence. I would have liked to see more information in the report regarding the users' experience with self-injection and their satisfaction levels. The authors only report that two women in the self-administration arm did not like or had discomfort with the injections. Nevertheless, it would behoove the manufacturer of subcutaneous DMPA to change the labeling with the FDA to allow for self-administration. One issue that may impede access is expense. Currently, the subcutaneous formulation is more expensive than the generic intramuscular formulation. Internationally, the 104 mg dose of subcutaneous DMPA is packaged in a format ideal for self-administration in a product called Sayana[®] Press. The drug is packaged in a Uniject device, which is a prefilled injection system using a bubble reservoir and ultra-thin needle. If this product were made to be as affordable as intramuscular DMPA, it could drastically change access to highly effective contraception in Africa and Asia, areas with a high unmet need for contraception.⁷ ■

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Role of Anti-VEGF Therapy in Platinum-resistant Recurrent Ovarian Cancer

By Robert L. Coleman, MD

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

SYNOPSIS: Bevacizumab is a humanized monoclonal antibody targeting vascular endothelial growth factor and has documented single-agent activity in patients with recurrent ovarian cancer. The current study demonstrated that when combined with standard recurrent chemotherapy, bevacizumab can significantly improve progression-free survival and objective response rate without diminishing quality of life.

SOURCE: Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized Phase III trial. *J Clin Oncol* 2014;32:1302-1308.

Patients presenting with platinum-resistant recurrent ovarian cancer are usually treated with single-agent chemotherapy; there are many acceptable options, with previous Phase 3 trials failing to demonstrate a clear “winner.” Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been extensively studied in ovarian cancer, and has clinical activity as a single agent and in combination with platinum-based chemotherapy both in the front-line and in recurrent platinum-sensitive settings. AURELIA is the first randomized, Phase 3 trial combining bevacizumab with chemotherapy in platinum-resistant ovarian cancer.¹ Eligible patients had measurable/assessable disease, progressing within 6 months of completing platinum-based therapy. Patients with refractory disease, history of bowel obstruction, or more than two prior anticancer regimens were ineligible. After investigators selected chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan), patients were randomly assigned to single-agent chemotherapy alone or with bevacizumab (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, depending on the regimen) until progression, unacceptable toxicity, or consent withdrawal. Crossover to single-agent bevacizumab was permitted after progression with chemotherapy alone.

The primary endpoint was progression-free survival (PFS) by response evaluation criteria in solid tumors (RECIST). Secondary endpoints included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes. The PFS hazard ratio (HR) was 0.48 (95% confidence interval [CI], 0.38-0.60; unstratified log-rank $P < 0.001$) representing a median PFS of 3.4 months with chemotherapy alone to 6.7 months with bevacizumab-containing therapy. RECIST ORR was 11.8% vs 27.3%, respectively ($P < 0.001$). The OS HR was 0.85 (95% CI, 0.66-1.08; $P = 0.174$; median OS, 13.3 vs 16.6 months, respectively). Grade 2 or higher hypertension and proteinuria were more common with bevacizumab. Gastrointestinal perforation occurred in 2.2% of bevacizumab-treated patients vs 0 in the chemotherapy-

treated patients. Adding bevacizumab to chemotherapy statistically significantly improved PFS and ORR; the OS trend was not significant. No new safety signals were observed.

■ COMMENTARY

This trial addressed the one previously untested setting for bevacizumab in ovarian cancer, namely, patients with recurrent ovarian cancer, platinum-resistant disease. This cohort of patients represents one of the most challenging because they are identified by their short-term recurrence (6 months or less) from platinum. While it is well recognized that only rarely are patients with recurrent disease cured of their ailment, patients with platinum-resistant recurrence are unlikely to survive more than 2 years, and often are on continuous therapy.² This presents two important contexts for the current trial: clinical efficacy and quality of life. Since *quantity* of life is so difficult to enhance in this setting, *quality* of life becomes a premium endpoint. In addition, since patients with recurrent resistant disease are more likely to be symptomatic than their platinum-sensitive counterparts, resolution of symptoms can be PFS and ORR, which were significantly enhanced. An accompanying article detailing the impact of therapy on patient-reported outcomes and quality of life demonstrated that a significantly greater proportion of patients on combination therapy had a > 15% improvement in their gastrointestinal/abdominal symptoms compared to the standard-of-care arm.³

The impact of the study is dramatic, but not without its criticisms. For one, the study was not blinded. This is a major issue in clinical trials reporting bias-sensitive endpoints, such as ORR and time to progression. Patients and caretakers in the non-combination arm may be more likely to discontinue therapy in ambiguous settings, biasing toward the combination arm. Second, while the choice of standard-of-care regimens was left to the treating physician, the temporal choice was unbalanced. Investigators early in the study favored weekly paclitaxel,

given its track record in this setting, and put better prognosis patients on the trial during that phase. This is visible by looking at the PFS curves in the control arms of each regimen. Third, while billed as a Phase 3 trial, the target sample was adjusted two times during the trial and the three individual chemotherapy arms were ultimately capped at 120 patients each, essentially limiting the power of each analysis to a randomized Phase 2 setting. Fourth, no difference in OS was seen in the initial and (recently presented) final assessment of this long-term endpoint. It is believed this may have been due to the high amount of crossover therapy in the non-bevacizumab arm (40%), but also could represent a different tumor biology induced by bevacizumab exposure. And finally, there is reason to believe that bevacizumab as a single-agent may be efficacious in this setting, but it was not considered.

Fortunately, no new safety signals were identified. There was significant concern that mucositis and palmar-plantar erythrodysesthesia (PPE, a painful blistering eruption of the hands and soles of the feet) could be enhanced with delayed healing in the combination of liposomal doxorubicin and bevacizumab. In the study, the rate was about two-fold higher but overall, high-grade PPE was uncommon (2% vs 4.5%) and was not cumulative. In addition, neuropathy, a noted adverse event of paclitaxel, appeared to be enhanced and cumulative

(grade 2 or higher) when combined with bevacizumab. Some additional toxicities (such as hypertension and neuropathy) represented the longer exposure of therapy due to lack of progression. In all, the trial demonstrates that bevacizumab can enhance the efficacy of standard, single-agent, platinum-resistant chemotherapy. The data now join three previous Phase 3 trials reporting the same findings, increased PFS and objective response without an improvement in OS, and highlight the robust efficacy signal of the agent.⁴⁻⁶ However, the burden of investigation in this disease is on OS, an endpoint that remains elusive in all-comer designed trials. ■

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ABSTRACT & COMMENTARY

Bleeding Patterns and Patient Satisfaction with LNG-IUS

By Jeffrey T. Jensen, MD, MPH

SYNOPSIS: Almost all of the women who elected to continue use of a levonorgestrel intrauterine system by replacement after the first 5-year interval had favorable bleeding patterns during the second 5 years of use, with almost half experiencing amenorrhea.

SOURCE: Heikinheimo O, et al. Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: Results of a prospective 5-year study. *Hum Reprod* 2014;29:1182-1188.

This paper provides extended follow-up of the 2010 study that reported preliminary results from a cohort of European women who requested a second levonorgestrel intrauterine system (LNG-IUS) after 5 years of initial use. A total of 204 women were enrolled in this prospective multicenter study in four European countries and followed up until the end of the first year of the second IUS. At the end of the first year, 170 women continued into the extension phase of the study, and 144 continued up to the full 5 years of use of the second IUS. This paper reports the extension phase of the study. Subjects had a mean age of 39 years and had used the first LNG-IUS for either contraception or treatment of heavy menstrual bleeding. Bleeding patterns were recorded using daily diaries. The authors analyzed

bleeding using 90-day reference periods (RP). For the first year of the second IUS use, all four RPs were assessed. For years 2-5, data were collected for only the last RP of the year. During use of the second LNG-IUS, the proportion of women without bleeding (e.g., spotting only) increased after the first year and remained at 72% during years 2-5. The proportion of women without any bleeding and spotting (e.g., amenorrhea) increased after the first year (34%) and remained at 44-49% during years 2-5. Absence of bleeding was associated with high overall satisfaction and continuation rates. The cumulative expulsion rate during the 5-year study period was 1.2%, and there were no treatment-related serious adverse events.

■ COMMENTARY

Although these same authors presented initial results of this study in 2010,¹ the long-term findings provided in this manuscript add additional evidence useful for counseling women. The bottom line is that women who are doing great with an LNG-IUS will continue to do great after replacement. Although there is some short-term bleeding seen in relation to the replacement procedure, the prolonged bleeding and spotting seen following initial placement (mean days of bleeding and/or spotting during placement of the first device during RP1 is 43²) does not occur following replacement of the device. This is good news for women, as the unfavorable initial bleeding pattern is one of the principle problems seen during initiation of use. Other important information from the initial series of publications includes the finding that most replacements were straightforward, and that misoprostol did not improve the placement experience.³

Use of the LNG-IUS is increasing everywhere that women have access to the device. The main factor motivating women in my area is the desire for light or absent bleeding. The fact that bleeding becomes predictably better during the use of the LNG-IUS is a major advantage of this long-acting method compared to the bleeding pattern seen with the etonogestrel implant. Counseling women that the initial bleeding will be disrupted, but will improve, has been associated with better continuation and satisfaction. When women see this as an investment of time that will result in a tangible health benefit, my experience has been that the acceptability of the initial bleeding disruption is high. Most women become satisfied users, and we regularly see patients return for a second or even third consecutive device. Providing reassurance that the bleeding patterns

will be very acceptable after the change and that replacement is uneventful can ease the stress of the anticipated changeover.

Whether all women desiring continuing use of an LNG-IUS should undergo replacement at 5 years is a hot topic. While there are no studies that assess pregnancy rates with the currently marketed LNG-IUS beyond 5 years, these are likely to remain low. Recall that even inert plastic IUDs are more than 96% effective, and that many women are looking at replacement in their 40s when pregnancy rates are naturally low. While there is no absolute answer to this question, if your patient is amenorrheic and over 35, it may be very reasonable to defer and reassess the decision for replacement after 6 -12 additional months. Younger women have the highest natural fertility and will benefit the most from replacement. However, since bleeding patterns also deteriorate over time, many women may want to choose replacement to take advantage of the stable bleeding seen in this study of consecutive use.

For women in the perimenopausal years, replacement allows for use of the device for endometrial protection. Since this is off-label in the United States, I try to time replacement to the late reproductive years so that insurance coverage as a contraceptive is allowed. ■

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ABSTRACT & COMMENTARY

Passive Smoking Exposure and Preeclampsia

By John C. Hobbins, MD

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

SYNOPSIS: A study that has focused on patients who are exposed to second-hand smoke shows a higher rate of preeclampsia than nonsmokers.

SOURCE: Luo ZC, et al. Plasma cotinine indicates an increased risk of preeclampsia in previous and passive smokers. *Am J Obstet Gynecol* 2014; 210:232.e1-5.

Although smoking during pregnancy is associated with increased rates of fetal growth restriction, preterm birth, and placental abruption, some studies have suggested a lower rate of preeclampsia in smokers.¹ Investigators involved in the Canadian/Mexican study to assess the efficacy of vitamins C and E in preventing preeclampsia (the International Trial of Anti-oxidant Supplementation for the Prevention of Preeclampsia—

INTRAPP)² resurrected banked bloods from 733 patients, obtained at 24-26 weeks, for analysis of plasma cotinine content. This metabolite has been used as an objective method to detect smokers when found in levels above a preset threshold. However, the authors were particularly interested in patients who exhibited lower levels of cotinine, suggesting that they were either passively exposed to cigarette smoke or they had

recently stopped smoking. Specimens from chronic hypertensives were excluded, leaving a final study cohort of 605 patients/samples. The authors then used stringent criteria from patient records to identify those who either developed gestational hypertension or preeclampsia. They applied a currently used plasma cotinine of > 3.0 ug/mL to single out current smokers, 2.0-3.0 ug/mL to define those who recently stopped or had been passively exposed to smokers, and levels < 2.0 ug/mL to signify nonsmokers.

Thirty patients (5%) developed preeclampsia while 67 patients in the study group developed gestational hypertension. The “passive/recently stopped” group had a significantly increased risk of preeclampsia compared with control nonsmokers (odds ratio [OR], 6.06; 95% confidence interval [CI], 2.32-15.85). However, there was no association in this group with the development of gestational hypertension compared with controls (OR, 1.48; CI, 0.54-4.07). In this study, smokers did not seem to be protected from preeclampsia (OR, 1.04; CI, 0.22-4.95), but only 47 smokers were in the analysis.

■ COMMENTARY

It is counter-intuitive that a habit that has such undesirable pregnancy consequences should result in a decreased risk of a condition that is at the heart of the maternal/placental connection. Now it is just as puzzling that those who have recently stopped smoking, or have been exposed to cigarette smoke, are now more vulnerable to preeclampsia. Studies that rely on self-reported data are inherently flawed and the concept of using a metabolite does seem to be a more objective way to study this relationship. Yet, unfortunately, it has been difficult at lower levels of cotinine to separate out the passively exposed women from the recently stopped smokers who may have a low residual level of this metabolite. So the investigators lumped them together. It is clear that there are many more potentially noxious components in cigarette smoke than nicotine — the often blamed culprit — that could affect transport of oxygen

and nutrients to the fetus. For example, carbon monoxide concentrations are quite high in smokers and I recall one study that is now more than 30 years old (and I can't find the citation) that showed carbon monoxide levels in smokers to be as high as workers stationed at that time in the Midtown Tunnel in New York City. However, if looking for a possible protector for preeclampsia, carbon monoxide interferes in vitro with the action of tyrosine kinase, an anti-angiogenic factor whose levels are elevated in preeclampsia. In any case, carbon monoxide has a far shorter half-life than other longer-lasting combustibles in second-hand cigarette smoke that could overmatch carbon monoxide's fading protective effect on the placental bed (if there really is one).

Latest figures show that 10.7% of Americans continue to smoke during pregnancy. Of those who smoke within 3 months of pregnancy, 54% quit when becoming pregnant, but 44% will pick up the habit again postpartum.³ A stunning fact is that 1 in 5 people still smoke in the United States, exposing 88 million nonsmokers to second-hand smoke.⁴ The earlier studies suggesting a lessened risk of preeclampsia in smokers might have sent the wrong message, especially since they might have been tainted by being dependent on self-reported information. This study, using perhaps a more objective measure of cigarette smoke exposure, enforces the message that pregnant patients should even avoid passive cigarette smoke, a situation most commonly occurring in the household or in bars and restaurants that allow smoking. ■

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ABSTRACT & COMMENTARY

Coital Lubricants and Natural Oils as Treatment for Vaginal Dryness

By Michael A. Thomas, MD

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

SYNOPSIS: As a way to indirectly investigate the effects of lubricating products used by infertile women during intercourse on sperm quality, semen from 22 normospermic men was tested against several common lubricants (Pre-Seed®, Astroglide®, K-Y® Sensitive®, K-Y® Warming®, and K-Y® Tingling) and natural oils (baby, canola, sesame, and mustard) at 0, 5, 30 and 60 minutes. Pre-Seed and three of the oils (baby, canola, and mustard) had no deleterious effect on sperm.

Vaginal dryness during intercourse is a common problem often combated with lubricating products. This study was initiated to determine whether over-the-counter lubricants and natural oils when applied intravaginally have an adverse effect on sperm motility in infertile couples. Donated semen samples were obtained from 22 normospermic men (mean age 25.9 ± 4.2 yrs). After centrifugation, the resulting sperm pellets were re-suspended in modified human tubal fluid (mHTF), a standard medium used in inseminations and in vitro fertilization procedures. Aliquots of sperm were standardized to contain a concentration of 20 million sperm per mL. These aliquots were then mixed with mHTF (control) or one of the “synthetic” (Pre-Seed®, Astroglide®, K-Y® Sensitive®, K-Y® Warming®, and K-Y® Tingling) lubricants or “natural” (baby, canola, sesame, and mustard) oils to a concentration of 10% (typical concentration of lubricant remaining in the vagina after intercourse). Total and progressive sperm motility was evaluated using a Makler counting chamber at incubation (0 min), and then at 5-, 30-, and 60-minute intervals.

Control samples co-incubated in mHTF showed no decline in total or progressive sperm motility after 60 minutes. In contrast, all of the synthetic commercial lubricants had a negative effect except Pre-Seed. Although Pre-Seed demonstrated a decline in both total and progressive motility, it did not affect total sperm motility at 60 min ($P = 0.299$). A minimal decrease in progressive motility was noted at 30 (4%) and 60 (7%) minutes ($P < 0.01$); however, this slight diminution in progressive motility was not thought to be clinically significant. The difference found between hHTF and Pre-Seed at these time points was within 2-4 percentage points.

Among the natural products, only sesame oil reduced total (18-22%) and progressive (24-28%) motility ($P < 0.001$). In contrast, baby and canola oils did not produce a change in any of the motility parameters of more than 7%. Incubation with mustard oil demonstrated a persistent hyperactivity of sperm in each of the 22 sperm donors.

■ COMMENTARY

Couples who are attempting to conceive will occasionally use one of the many over-the-counter lubricants or natural oils. The use of a supplemental aid is common among many couples, including couples having timed intercourse. Though vaginal moisturizers, like lubricants and oils, are marketed primarily to perimenopausal and menopausal women, young women also use these products. Lubricants,¹⁻⁵ natural oils,^{1,6} and even saliva⁷ have been studied for their effect on sperm motility and/or chromatin integrity when applied in the vagina. Previously, Pre-Seed, baby oil, and canola oil were found

to have minimal effects on sperm parameters.^{1,5,6} The newer K-Y jelly products (Sensitive, Warming, and Tingling) had not been investigated.

In a recent survey of 900 couples trying to get pregnant, vaginal dryness was a reported problem as “always” by 11%, “often” by 35%, and “occasionally” by 42%.⁸ Of the total number of respondents, 26% admitted that they often or always used a lubricant. Among those reporting lubricant use, 40% used K-Y jelly and 19% used Astroglide.

The current study was the first to evaluate multiple products (lubricants and oils) using a standardized approach that mimicked the natural vaginal environment (10% concentration of lubricant intravaginally). An additional strength of the study included the use of multiple donors and a consistent sperm concentration of 20 million sperm/mL. This eliminated variability between samples. Pre-Seed, baby oil, and canola oil were confirmed to be safe coital adjuvants when used for fertility purposes. The most unique finding was that mustard oil resulted in hyperactivation or exaggerated movement of sperm. We know that mustard oil contains allyl isothiocyanate, which is an activator of the transient receptor potential (TRP) A1 channel.⁹ The TRP channels have been found to effect flagellar activity in human sperm. This may explain the hyperactive motion observed when the sperm came in contact with mustard oil. Sperm hyperactivity previously has been observed with caffeine, pentoxifylline, and 3-deoxyadenosine; however, these compounds were never utilized for routine clinical purposes by couples.¹⁰

Astroglide, the K-Y lubricants (Sensitive, Warming, and Tingling), and sesame oil all decreased total and progressive sperm motility. This provides strong evidence to recommend against their use by couples with fertility problems. Despite this adverse finding, it is unlikely that these specific lubricants and sesame oil would confer a contraceptive effect.

We know that 80-85% of reproductive-aged couples (with normal menstrual cycles) will conceive after 1 year of midcycle intercourse. For most couples experiencing a delay in conception, their primary care provider or gynecologist may suggest a different lubricant as low-level intervention that may result in pregnancy. This paper confirms that commonly used coital lubricants may affect sperm motility in a deleterious way. Having confidence that a lubricant will not affect fertility is important to the couple struggling with fertility since anxiety already takes its toll on intimacy. Now, the practitioner can have confidence that Pre-Seed and natural oils (baby, canola, and mustard) do not adversely affect sperm function and can be safely recommended.

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Whether the sperm hyperactivity documented with mustard oil would have an additional benefit to “boost” or “supercharge” sluggish sperm remains to be determined. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. In the study by Beasley et al, continuation rates of subcutaneous DMPA were statistically significantly higher in the self-administration group compared to the clinic-administration group.
 - a. True
 - b. False
2. Which of the following is an aspect of the design or outcomes in the Phase 3 trial of anti-VEGF therapy in platinum-resistant recurrent ovarian cancer?
 - a. The cohort contained a mixture of platinum-resistant and platinum-refractory patients.
 - b. Patients were allowed to have up to two prior chemotherapy regimens before randomization.
 - c. Overall survival was significantly improved in the bevacizumab containing arm compared to the chemotherapy alone arm.
 - d. Neurotoxicity was observed in both arms to a similar degree.
3. The bleeding pattern seen over the second 5 years of use of a LNG IUS is:
 - a. similar to that observed with the initial LNG IUS; irregular bleeding for 3-6 months followed by amenorrhea in more than 50% of women.
 - b. amenorrhea in more than 90% of women for the full 5 years.
 - c. not able to be assessed in the study because most women were menopausal.
 - d. that the proportion of women with amenorrhea increased from 34% during the first year (34%) and remained at 44-49% during years 2-5.
 - e. important to follow carefully because frequent spotting was associated with endometrial cancer.
4. Which of the following is appropriate regarding the data on women who have been exposed to second-hand smoke or who have been recently quit smoking?
 - a. They had higher rates of preeclampsia.
 - b. They had higher rates of gestational hypertension.
 - c. They had cotinine levels < 2.0 ug/mL.
 - d. They had the highest cotinine levels.
5. In a study of couples attempting to conceive who used a lubricant, what was the most common product used for vaginal dryness?
 - a. Astroglide 50%
 - b. K-Y jelly
 - c. Pre-Seed
 - d. Mineral oil

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