"IN THE NEWS, NOW ON THE SHELF: A NOVEL ESTRADIOL BASED OC"
ROBERT L. BARBIERI, MD
(EDITORIAL; SEPTEMBER 2010)

A few questions about the new multiphasic OC

Having read Dr. Barbieri's September editorial on the recently approved Natazia oral contraceptive (OC), I have several concerns:

- A common complaint among women using an OC is early breast soreness, which has been attributed to the week-long hormone-free interval followed by a sudden increase in estrogen when active pills are resumed. Estrostep was developed years ago to address this issue by starting with a low dose of estrogen and gradually increasing the level of ethinyl estradiol to stabilize the endometrium. With Natazia, a starting dose of 3 mg of estradiol would seem to be rather large, with the potential for "early-pack" breast soreness, a common reason for discontinuing an OC.
- The half-life of estradiol is very short. When micronized estradiol is given for menopausal symptoms, sometimes a twice-daily dosing pattern is required to smooth out the peaks and valleys of blood levels and minimize the bottoming out of the estrogen level. How does Natazia address this issue?
- Early triphasic (progestin-phasing) pills are notorious for their association with breakthrough bleeding due to the step up in progestin. How does the breakthrough-bleeding rate of Natazia compare with that of other triphasic (progestin) pills and monophasic pills?
- Why are there two estrogen-free days at the end of the Natazia pack? Women who have menstrual migraines often benefit from a low dosage of estrogen during the entire menstrual placebo week. In the case of Natazia, why not have a low dosage of estradiol for the entire menstrual week?

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Jeffrey Musson, MD
Racine, Wisc

›› Dr. Barbieri responds:

Effects of Natazia are best viewed in comparison with an EE-LNG pill

Dr. Musson raises many important clinical issues concerning the estradiol valerate–dienogest contraceptive, Natazia. From my perspective, his clinical questions are best addressed by reviewing the data from the head-to-head randomized trial of Natazia versus a standard, monophasic 21/7, ethinyl estradiol (20 µg) plus levonorgestrel (100 µg) (EE-LNG) contraceptive.[1] Some of the clinical highlights of this study:

- *Natazia treatment was associated with significantly fewer scheduled (withdrawal) bleeding days than the monophasic EE-LNG pill.*
- *Natazia and the monophasic EE-LNG pill had a similar number of unscheduled (breakthrough or intracycle) bleeding days.*
- *Amenorrhea was reported by 15% of the women taking Natazia and 5% of the women taking a monophasic EE-LNG pill.*
- *Breast pain was reported by 3.3% of the women taking Natazia and 1.0% of the women taking the monophasic EE-LNG pill.*

Estradiol has a half-life of about 160 minutes.[2] Estradiol valerate is metabolized to estradiol, estrone, and estrone sulfate. The pools of estradiol valerate, estrone, and estrone sulfate help to stabilize the estradiol levels, through interconversion. The average concentration of estradiol in a user of Natazia is about 50 pg/mL, which is similar to the relatively modest estradiol concentrations observed in the early follicular phase.

I appreciate Dr. Musson's help in further characterizing the effects of Natazia in clinical practice.

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"2 HPV VACCINES, 7 QUESTIONS THAT YOU NEED ANSWERED"
EXPERT PANEL WITH NEAL M. LONKY, MD, MPH, MODERATOR
(AUGUST 2010)

Show me the data behind a panelist's remarks!

I would be interested to know the specific data that support the following statement by Dr. Diane M. Harper in the roundtable on the human papillomavirus (HPV) vaccine (page 42):

> Vaccine protection must last at least 15 years to reduce the rate of cervical cancer. Otherwise, the development of cervical cancer will only be postponed, if boosters are not

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implemented. It is now widely recognized that Cervarix induces high antibody titers, offering 100% efficacy even after 8.4 years, making it very likely that the protection it provides will continue for at least 15 years. It is also widely acknowledged by immunologists that Gardasil-induced titers for HPV 6, 11, and 18 are much shorter-lived, so protection is likely to wane 5 to 10 years after vaccination. That means that Gardasil provides excellent protection against one cancer-causing type of HPV. In addition, it protects against genital warts caused by HPV types 6 and 11 for at least 5 years. In comparison, Cervarix protects against five cancer-causing types of HPV, thereby preventing about 90% of cervical cancers, and is likely to remain effective for at least 15 years. There are 10 times as many women who have an abnormal Pap test as there are women who have genital warts, so one would think that Cervarix would be the vaccine of choice in preventing the life-threatening disease of cervical cancer.

I would like to disclose that I was a clinical investigator for Merck's Future III trial, and I have served as a speaker for Merck in regard to Gardasil.

Larry Glazerman, MD
Tampa, Fla

›› Dr. Harper responds:

Data are plentiful

I am happy to provide the data Dr. Glazerman requested. In regard to the need for a minimum of 15 years of protection for a vaccine to reduce the rate of cervical cancer, see Barnabas and colleagues and Berkhof and coworkers.[1,2]

For data on the high antibody titers associated with Cervarix, see De Carvalho and coworkers, Paavonen and colleagues, and the GlaxoSmith-Kline HPV-023 Study Group.[3–5]

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Data on the shorter-lived titers induced by Gardasil for HPV 6, 11, and 18 can be found in Olsson and colleagues and Rowhani-Rahbar and associates.[6,7] *And data on Cervarix's protection against five cancer-causing types of HPV are available in a report from the PATRICIA Study Group.*[8]

As for the rate of abnormal Pap tests versus the incidence of genital warts, see Eversole and coworkers and Insinga and colleagues.[9,10]

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Which vaccine would the panelists choose?

I enjoyed reading the differing opinions of the expert panelists who participated in the HPV vaccine roundtable discussion—but I found the discussion slightly confusing, too. I wish someone had asked the panelists whether they'd be willing to vaccinate *themselves*, and, if so, which vaccine they would choose.

I know the option of choosing both vaccines is not cost-effective, but there are patients who can afford to do so and who would be willing to do so. What are the benefits and risks of this approach?

Dennis A. Fito, MD
Liberal, Kans

They're asking about getting both vaccines

Patients have asked me whether there are any data on the benefits and risks of taking both Gardasil and Cervarix. How would the panel respond?

James W. Browne, MD
Andrews, Tex

How might the HPV vaccines affect other cancers?

Would Dr. Lonky or any of the panelists care to comment on the prevalence of HPV in oral and esophageal cancers and how the quadrivalent and bivalent vaccines (Gardasil and Cervarix) might affect it?

What about the efficacy of one dose of Cervarix followed by the full series of Gardasil? Are there any studies of the practice of administering one or two doses of each vaccine?

Helen Sandland, MD
Morristown, Tenn

›› Dr. Lonky responds:

Context is everything

It is not realistic to ask a male panelist who is in his 50s which vaccine he would choose for himself. Even so, I would not "endorse" either vaccine. In fact, I think the data on cancer prevention and overall safety are too controversial for me to advocate for either vaccine at this time.

Were I a young woman (and assuming that the vaccines have similar side-effect profiles), my choice would likely be based upon which vaccine is more affordable, a lower cost making it easier to complete the series. Were either vaccine to demonstrate clear-cut superiority in terms of efficacy or a streamlined vaccination schedule, it would have the advantage.

If I were the director of a health plan or medical group and thus had data on the total cost of managing both premalignant and benign HPV-related disease, that information would drive my recommendations to the patient. We know that both vaccines should prevent encounters related to colposcopic evaluation. The costs associated with encounters for benign genital warts, if reduced by vaccinating early against HPV types 6 and 11, would provide additional savings to the patient and the healthcare system as a whole. As a result, I would lean toward advocating for Gardasil (which has had a commercial head start). If clear-cut evidence later revealed that Cervarix is similarly effective in preventing benign HPV disease, or offers a superior vaccination regimen, the scale would tip back toward Cervarix.

Ultimately, however, it is up to the patient to decide, after being informed about cost, risk of malignancy, morbidity of HPV-related disease, and so on. If she does not agree with her insurer's choice, she is free to go elsewhere, perhaps even to have the vaccine covered or subsidized by the government.

›› Dr. Felix responds:

The prevalence of HPV in oropharyngeal cancers ranges from 20% to 40%, depending on the series. Most recent series estimate prevalence closer to 40%. The most prevalent HPV types are 16 and 18—these two strains account for almost 80% of oropharyngeal carcinomas that are caused by HPV.

Although there have been no clinical trials assessing the efficacy of either vaccine in preventing oropharyngeal HPV, either should work as well as it does in the cervix. Both vaccines provide coverage against HPV 16 and 18, so they would be equally effective.

›› Dr. Harper responds:

All of the panelists are older than 26 years, and three of them are men, which means that none of them have the option of choosing vaccination for themselves.

It is most important that each woman be given the choice of including HPV vaccination in her regular Pap screening program. If she decides to be vaccinated, then it is her value system, not the physician's that determines which vaccine is chosen. Does she want a vaccine that provides superior cancer coverage or one that provides less cancer coverage along with some protection against genital warts for an unknown length of time?

The benefits of being vaccinated with both vaccines would be that the woman gains some wart protection for 5 years and better cancer protection for an unknown length of time. The risks would be that the safety of taking both vaccines is unknown. Acellular pertussis vaccines were given to many teens and young adults to boost protection, although these patients had already been given a combination of pertussis and tetanus.

Before a woman opts to take both vaccines, she needs to understand that data on safety and lack of safety are lacking.

›› Dr. Huh responds:

There are no published data on administration of both Gardasil and Cervarix to a single patient. Moreover, it would be challenging to demonstrate any clinically significant additional benefit in this setting.

›› Dr. Smith-McCune responds:

There are no data on the efficacy of administering both vaccines to an individual patient. Full efficacy is best achieved by administering the full series of either vaccine. In the specific scenario Dr. Sandland described, the patient would receive full protection against HPV 6, 11, 16, and 18 by virtue of having received the full series of Gardasil. It is not possible to say anything about the potential for added protection from one shot of Cervarix because this approach has hardly been studied.