

# Update on Oral Contraceptive Therapy in Acne

While OCPs can be effective against acne, it is important to understand the risks and identify ideal candidates for therapy.

BY JULIE C. HARPER, MD

Oral contraceptive pills (OCPs) represent a common intervention for the treatment of acne in select female patients. Recently, however, some controversy has risen over the safety of OCPs, causing some concern about their use and prompting the US Food and Drug Administration (FDA) to weigh in. Specifically, the FDA funded its own study to evaluate the risk of venous thromboembolism in drospirenone (DRSP)-based agents compared to other hormonal contraceptives. The findings suggested a 1.5-fold increase in the risk of blood clots for women who use OCPs containing DRSP compared to other OCPs. Late last year, an FDA advisory panel met to discuss risks of venous thromboembolic events (VTEs) associated with DRSP-containing oral contraceptives. In their first vote, they posed the question: In the general population of women who desire contraception, do the benefits of the DRSP-containing oral contraceptives for prevention of pregnancy outweigh the risks? Fifteen members voted yes, while 11 voted no. In a second vote, the question asked if members believed the current DRSP levels adequately reflected the risk/benefit profile for these products. Five voted yes and 21 voted no.

Given the recent commotion surrounding OCPs, the time is perhaps salient to reflect on these agents, both in terms of their efficacy in treating acne and their overall safety. Ahead, I will review the literature and assess the role for OCPs in acne care going forward.

## INDICATIONS AND SAFETY

There are four types of OCPs currently approved for the treatment of acne. These include Ortho Tri-Cyclen (norgesti-

mate 0.18mg-0.215mg-0.250mg/ee 35ug, Janssen), Estrostep Fe (Norethindrone acetate 1mg/ee 20-30-35ug and Ferrous Fumarate in hormone-free interval, Warner Chilcott), YAZ (3mg drospirenone/20ug ee, Bayer) and Beyaz (drospirenone/ethinyl estradiol/ levomefolate calcium tablets and levomefolate calcium tablets, Bayer).

Ortho Tri-Cyclen is indicated for the treatment of moderate acne vulgaris in females at least 15 years of age who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical acne medications. Estrostep Fe is also indicated for the treatment of moderate acne vulgaris in females at least 15 years of age who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications. However, Estrostep Fe should be used for the treatment of acne only if the patient desires oral contraceptive for birth control and plans to stay on it for at least six months. On the other hand, YAZ is indicated to treat moderate acne for women at least 14 years old, who have no known contraindications to oral contraceptive therapy and who have achieved menarche. Moreover, YAZ should only be used to treat acne if the patient desires an oral contraceptive for birth control.

Dermatologists frequently use these products off-label; we use them for acne in women who don't need contraception. It is important to note that they are all FDA indicated for acne only if the woman desires contraception. This stipulation has to do with risk. The risk of pregnancy is generally accepted to be higher than the risk of an OCP.

**Side Effects and Risks.** Side effects associated with OCP use may include irregular bleeding, nausea, mood changes, and breast tenderness. Additionally, data has shown that OCP use may be associated with other risks. Apart from venous thromboembolism (which I will address later), risks from using OCPs encompass a number of conditions. Among these is ischemic stroke, which is 2.5 times more likely in women aged 20-24.<sup>1</sup> Data indicate that this risk is directly proportional with estrogen dose and that risk increases with age. In addition, hypertension (HTN), cigarette smoking, and migraine headaches substantially increase risk of stroke. Other potential risks include myocardial infarction; however, 80 percent of heart attacks among OCP users are attributable to cigarette smoking, with the remainder occurring in OCP users with other risk factors such as HTN or diabetes mellitus (DM). Concern has also been expressed for an increased likelihood of breast cancer among OCP users, although this has not been fully substantiated. In a World Health Organization (WHO) meta-analysis of 53,297 women with breast cancer and 100,239 controls, RR of breast cancer is 1.24 for current OCP users. RR of cancer that has spread vs. remained localized is 0.88 (disease tends to be localized).<sup>1</sup>

**Benefits.** OCPs have been associated with several benefits, as well. Most notably among these is a decrease in likelihood of ovarian cancer. In fact, OCP users are roughly at 40-80 percent decreased risk for ovarian cancer.<sup>1</sup> Protection begins after one year of use and increases by 10-12 percent annually with continued use. Moreover, protection persists for 15-20 years after OCP discontinuation.<sup>1</sup>

OCP use has also been associated with an up to 50 percent decreased risk in endometrial cancer. Protection begins after one year, increases with duration of use, and persists up to 20 years after oral contraceptive use is discontinued.<sup>1</sup> Other benefits include protection against pelvic inflammatory disease (PID), uterine leiomyomas, and ovarian cysts, as well as regulation of the menstrual cycle.

## THE LATEST DATA

### Bone Density and Combination Oral Contraceptives.

Diminished bone density represents a recent area of concern regarding OCP use. Bone mineral density (BMD) increases during adolescence and peaks at 20-22 years of age. Peak bone mass is affected by suboptimal bone density accrual during the pubertal years. This can be a predictor for osteoporosis later in life. Estrogen is required for normal pubertal skeletal growth and maturity in adolescent females.<sup>2</sup> The injectable birth control method Depo-Provera received a boxed warning as it is unknown if use of Depo-Provera will reduce peak bone mass. Thus, it should not be used as a long-term birth control method (i.e., longer than two years) unless other birth control methods are considered inadequate.

Studies in recent years have also evaluated a variety of combination contraceptives. In one study that prospectively followed bone mineralization in 370 adolescent girls aged 12-18, patients chose to receive either depot medroxyprogesterone, containing 20ug ethinyl estradiol, or no hormonal contraception. The treated group showed significantly less increase in femoral neck BMD than the control group (0.3% vs 2.3%;  $p=0.03$ ).<sup>3</sup> A follow-up of these patients at two years showed no statistical difference in BMD between contraceptive users and controls at either the lumbar spine or femoral neck. Another study followed 76 women between the ages of 19 and 23 for five years in which patients received either 20ug ee combination oral contraceptive (COC) or no hormonal contraception.<sup>4</sup> There was a significant increase (7.8 percent) from baseline of lumbar spine BMD in the control group, whereas women using COC experienced no change in BMD from baseline ( $p<0.01$ ).

A recent review evaluated several studies concerning the efficacy and safety of COC use.<sup>5</sup> One of the studies it reviewed compared use of a 20ug ee and a 15ug ee pill to non-use of hormonal contraception in young healthy women and found no significant difference in spinal BMD at 12 months between the three groups and in comparison to baseline values.<sup>6</sup> Another compared use of a 30ug ee and a 20ug ee pill to non-users and found no significant difference in spinal BMD values between the three groups and in comparison to baseline values.<sup>7</sup> Similar results were reached in another study that compared the effect of a COC with 30ug ee with a COC containing 15ug ee on BMD in adolescents aged 16-19.<sup>8</sup> BMD values at the hip were unchanged at one-year follow-up and not statistically different between ee groups. Finally, another recent account found that mean BMD in adolescents did not differ by COC duration of use or ee dose.<sup>9</sup> In those aged 19-30, however, mean BMD at spine was lower with longer COC use.

In summary, we should be aware of this potential risk when prescribing OCPs to our youngest adolescent patients. Further studies are needed to evaluate the role of very low estrogen dosages in young adolescents prior to peak bone development.

**Venous Thromboembolism.** Perhaps the area of most concern for clinicians prescribing OCPs is the risk of venous thromboembolic events (VTE), which ultimately led to FDA action. On first glance, the data is alarming. Risk for VTE is tripled in current users of OCPs (increased to four to 18 events per 10,000 woman-years). Additionally, risk increases with higher ethinyl estradiol doses. Moreover, mortality rates double in women ages 35-45.

The most recent focus of attention regarding VTE has involved DRSP-containing OCPs. Several studies have examined the link; notably, the European Active Surveillance Study (EURAS), a prospective, controlled cohort trial, included

## TAKE A THOROUGH HISTORY

The list of contraindications for OCPs include the following:

- Pregnancy
- Breast cancer (current)
- Breast feeding less than six weeks post-partum
- Age over 35 and heavy smoker (15 cigarettes a day)
- Hypertension
- Diabetes mellitus with nephropathy
- Retinopathy
- Neuropathy
- Vascular disease
- Deep vein thrombosis (history or current)
- Heart disease
- Stroke
- Migraine headaches (with focal neurological symptoms at any age or without focal neurological symptoms but over 35 years of age)
- Cirrhosis or liver tumor (benign or malignant)

all VTEs.<sup>10</sup> In total, 58,674 women were analyzed, 16,534 of whom received DRSP, 15,248 of whom received LNG, and the other 26,341 received other oral contraceptives. A total of 142,475 woman years were analyzed. Researchers discovered a total of 118 total VTEs: 26 cases in DRSP cohort (9.1 VTE per 10,000 woman years); 25 cases in LNG cohort (8 VTE per 10,000 woman years); 52 cases in other oral contraceptive cohort (9.9 VTE 10,000 woman years); and finally, three cases in non-oral hormonal contraception cohort (7.4 VTE per 10,000 woman years).

In another study, 22,429 women were initiated on DRSP/ee 30ug versus 44,858 women initiated on other OCPs (including second and third generation progestins).<sup>11</sup> Patients were followed for an average of 7.6 months, during which time researchers discovered 18 cases of VTE in the DRSP group (13 per 10,000 woman years) and 29 cases of VTE in other group (14 per 10,000 woman years).

Two years after these studies, another study was performed in women aged 15-49.<sup>12</sup> In total, 10.4 million woman years were recorded, and 3.3 million woman years in receipt of oral contraceptives. Findings revealed 3.01 VTEs per 10,000 woman years in non-users of OCPs, as compared to 6.29 VTEs per 10,000 woman years in current OCP users, and 7.29 VTEs per 10,000 woman years in DRSP group. These data indicate that the risk of VTE in current OCP users decreases with duration of use and with decreasing estrogen dose. OCPs with desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of VTE than those containing levonorgestrel. Progestin-only pills and hormone release intrauterine devices were not associated with any increase risk of VTE.

More recently, a retrospective nested case-control and

cohort study of PharMetrics database in the US evaluated 186 newly diagnosed idiopathic cases of VTE.<sup>13</sup> Among the 681 matched controls, incidence rates for VTE were 30.8 per 100,000 woman years among users on COCs containing DRSP (95% CI 25.6-36.8), as compared to 12.5 per 100,000 woman years among users on OCPs containing levonorgestrel (95% CI 9.61-15.9).

Taken together, these data indicate that the risk of non-fatal VTE among users of oral contraceptives containing DRSP seems to be around twice that of users of oral contraceptives containing levonorgestrel.

In summary, we must put the risk of VTE into perspective from two vantage points. First, while the statistical risk appears to be real, the absolute risk to our patients is still very low. The risk of VTE in a young woman who is not on an OCP is about three per 10,000 woman years. A young woman on an OCP has a higher risk of VTE, about six per 10,000 woman years. Keeping these baseline numbers in mind, a woman on a drospirenone-containing OCP has a risk of about 10 per 10,000 woman years. Second, the risk of VTE during pregnancy is about 12 per 10,000 woman years and after delivery the risk increases to about 30 per 10,000 woman years.

## THE IMPORTANCE OF BEING THOROUGH

It is important for prescribing physicians to be aware of the risks associated with OCPs. Selecting candidates for OCP therapy must be based on a thorough review of the patient's medical history to ensure no contraindications. Ideal candidates for OCP therapy are women under 35 years of age who do not smoke, do not have migraine headaches, and who are normotensive. While these agents can be very effective in the treatment of acne, the recent data remind of the importance of taking every precaution to minimize risks. ■

*Dr. Harper has disclosed relationships with Allergan, Coria, Galderma, Intendis, Medicis, Ranbaxy, and Stiefel/GSK.*

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