“Effectiveness of Oral Contraceptive Pills in a Large U.S. Cohort Comparing Progestogen and Regimen”

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1. Review the source of support for this study and identify which medications used in this study are manufactured by the supporting organization.

2. Review the details of the International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC) INAS-OC Study at ClinicalTrials.gov. This trial is listed as a Phase IV trial. Discuss the definitions of clinical trial phases. Develop reasons why a drug manufacturer might want to sponsor a large Phase IV trial of one of their products. Discuss the obligation of drug manufacturers to provide postmarket drug safety information (including post-authorization safety studies) after a drug has been approved by the Food and Drug Administration (FDA).

3. Contrast the INAS-OC study with the European Active Surveillance on Oral Contraceptives (EURAS-OC) study. Are there significant differences? What aspects of the INAS-OC study are novel and relevant to the patients you presently see?

4. Were all women using oral contraceptive pills (OCP)s for contraception? For what other purposes do you prescribe OCPs? What effect would enrollment of women using OCPs for non-contraceptive reasons have on estimation of contraceptive effectiveness?

5. Discuss the use of the Pearl Index in evaluating contraceptive effectiveness. How is it calculated? Contrast actual use Pearl Index with perfect use Pearl Index. What assumptions are inherent in the Pearl Index? Why might these assumptions be invalid in this study? What have the authors done to adjust for any invalid assumptions? Discuss whether the Pearl Index would be the same for OCP starters as for recurrent users.

6. Review the four levels of the authors’ follow-up procedure. Compare the loss to follow-up rate of the EURAS-OC study and the European arm of the INAS-OC study with the rate in the US arm of the INAS-OC study. Discuss possible explanations for any differences.

7. What was the duration of participation by the women in this study? Were there any differences among groups for duration of participation? Would any differences in duration of participation affect the failure rate by Pearl Index? By life-table estimates? Discuss how data from a woman who switched OCP formulations during the study should be handled in calculating the Pearl Index and in calculating the life-table estimates.

8. The authors report that there was a fourfold increase in failure rate in this study compared with the EURAS-OC study. Discuss possible explanations for their observation.

9. What was the main outcome of interest in this study? How was that outcome defined and confirmed? Who reported the outcome for each study participant? Did the authors convince you that the outcome was reported accurately by questionnaire? If not, how would you design the study differently?
10. What was used to estimate noncompliance by the women who reported pregnancy? Discuss what the authors meant by “intensive questioning by investigators.” The authors do not report noncompliance classification criteria as “forgot to take the pill on time,” “used antibiotics,” and “episode of diarrhea or vomiting.” Discuss what criteria would be appropriate for each classification.

11. What is (are) the route(s) of excretion for drospirenone and norethisterone acetate? What is the half-life for each progestin?

12. Review the dosages of ethinyl estradiol in the OCP formulations evaluated in this study. Discuss whether the dosage of ethinyl estradiol is associated with failure rates with actual use. Explore methods to determine whether there is an interaction for failure rate among dosage of ethinyl estradiol, type of progestin, and duration of regimen.

13. Read the UpToDate topic, “Overview of the use of estrogen-progestin contraceptives.” In light of the results in the present study, should this summary be changed? Do you plan to change your approach to prescribing oral combined hormonal contraceptives? If so, how?