REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Cardiovascular risk and combined oral contraceptives: clinical decisions in settings of uncertainty

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Although generally safe, combined oral contraceptives (COCs) are associated with risks, including an estimated 2-fold increased relative risk of cardiovascular events. For most women taking COCs for contraception, absolute cardiovascular risks are very low, and the overall risks of COCs are outweighed by the risks of unwanted pregnancy. Nonetheless, risks of COCs may be excessive in some women, and both the American College of Obstetricians (ACOG) and the World Health Organization (WHO) have offered contraindications for COC use. Complicating this issue, COCs are commonly used for reasons other than contraception (eg, polycystic ovary syndrome, which is associated with subfertility and cardiovascular risk factors). Thus, in some clinical scenarios, ACOG and WHO guidelines may offer incomplete guidance regarding whether COC use would be associated with an unacceptable risk-benefit ratio. We propose that cardiovascular risk calculators may be helpful in some patients, as an adjunct to ACOG and WHO guidelines, by allowing physicians to estimate the attributable risk of COC-related cardiovascular events.

Key words: cardiovascular risk, combined oral contraceptives, myocardial infarction, polycystic ovary syndrome

Combined oral contraceptives (COCs) are widely prescribed to reproductive-age women for contraception. COCs are also effective treatments for a variety of medical conditions, including hyperandrogenism (most commonly related to polycystic ovary syndrome [PCOS]) and menstrual cycle disorders (eg, menorrhagia, dysmenorrhea). Although generally safe, the use of COCs is not without risk. For example, COCs have been associated with increased risks of venous thromboembolism and lipid abnormalities.[1]

Additionally, low-dose (ie, ethinyl estradiol dose less than 50 μg) COCs may increase the risk of myocardial infarction and ischemic stroke approximately 2-fold in the general population of COC users.[2,3] Fortunately, the baseline risk of cardiovascular events in most women of reproductive age is very low, so the absolute risk remains very low, even while taking COCs.[4] Moreover, for most women taking COCs for contraception, the risks of unwanted pregnancy appear to outweigh the risks of COCs.[1] However, it remains unclear how to identify women in whom the cardiovascular risk associated with COCs would outweigh the benefits.

This consideration may be especially relevant when COCs are used mainly for reasons other than contraception. A prime example is the use of COCs for the classical symptoms of PCOS; as a group, these women have subfertility and are ostensibly at increased baseline risk of cardiovascular events.[5,6]

Both the World Health Organization (WHO)[7] and the American College of Obstetricians and Gynecologists (ACOG)[8] have formally offered contraindications to the use of COCs (for contraception). Although eminently valuable, these guidelines may at times provide incomplete guidance regarding COC use in women with elevated cardiovascular risk. Relevant contraindications offered by both WHO and ACOG include smoking in women 35 years old or older and history of ischemic heart disease or stroke. Although the WHO suggests that any hypertension is a general contraindication to COC use, ACOG guidelines would allow COC use in women with well-controlled hypertension as long as they were nonsmokers, 35 years old or younger and had no evidence of end-organ vascular disease. Similarly, ACOG guidelines state that COC use in women with diabetes should be limited to nonsmokers younger than 35 years old without hypertension or known micro- or macrovascular disease; the WHO guidelines would generally permit COC use in women with diabetes for less than 20 years as long as they have no known micro- or macrovascular disease. In both WHO and ACOG guidelines, dyslipidemia can represent a contraindication, depending on severity and presence/absence of additional risk factors.

The aforementioned contraindications are based on characteristics clearly associated with increased cardiovascular risk. However, the guidelines do not provide estimates of actual risk for individual patients, which limits their utility for balancing COC risks and benefits. Also, these guidelines were predicated on the idea that COCs would be used for contraception with avoidance of pregnancy (and its attendant risks), justifying the acceptability of some cardiovascular risk. These guidelines therefore may not be as useful when COCs are used primarily for reasons other than contraception, such as in women with PCOS who often have subfertility. Also of great importance, the absence of the WHO and ACOG contraindications does not necessarily imply that COC-related cardiovascular risk is acceptable. A patient example will highlight these issues.

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Consider a 30 year old woman on no medications with a well-established diagnosis of PCOS. Her primary complaints are moderate hirsutism and oligomenorrhea. She has never been pregnant despite episodic sexual activity without contraception; she does not currently desire pregnancy. She has no personal or family history of cardiovascular or venous thromboembolic disease, but she smokes one half pack of cigarettes daily. A physical examination reveals a blood pressure of 135/85 mm Hg, body mass index of 35 kg/m^2, and moderate hirsutism without virilization. Laboratory testing while fasting discloses the following: glucose, 98 mg/dL; hemoglobin A1c, 5.9%; total cholesterol, 220 mg/dL; high-density lipoprotein (HDL), 45 mg/dL; low-density lipoprotein, 135 mg/dL; and triglycerides, 200 mg/dL.

Patients like this are not uncommon in clinical practice. Should this patient's metabolic abnormalities, including the metabolic syndrome,[9] influence decisions regarding long-term COC treatment? Or does her status as a young woman, generally implying a low absolute risk of cardiovascular events, and the absence of clear contraindications according to the WHO and ACOG guidelines alleviate concern? By necessity, available guidelines cannot offer specific guidance for such highly complex clinical scenarios.

The aforementioned patient does not have any conditions that, in isolation, would prohibit COC use according to the WHO or ACOG guidelines. However, one clarification from the WHO guidelines may possibly be relevant to this patient: "When a woman has multiple major risk factors, any of which alone would substantially increase the risk of cardiovascular disease, use of [low-dose combined oral contraceptives] may increase her risk to an unacceptable level."[7] Nonetheless, the helpfulness of this statement is limited by its vagueness. For example, a physician may be uncertain about which of this patient's risk factors represent major risk factors and to what degree said factors increase the risk of cardiovascular disease (either in isolation or in composite). Must the physician rely on general impressions regarding this patient's baseline cardiovascular risk?

Fortunately, easy-to-use tools for estimating the 10 year risk of cardiovascular events are readily available and routinely used by physicians when making decisions regarding lipid-lowering therapy.[9,10] These tools may also be helpful, as an adjunct to the WHO and ACOG guidelines, when considering COC use for patients who may have a higher risk of cardiovascular events (eg, some patients with PCOS), primarily because they would help physicians estimate 10 year risk of cardiovascular events that could be directly attributable to COC use.

One such tool is the Framingham risk calculator, a multivariable risk prediction calculator incorporating age, sex, blood pressure and use of antihypertensive medications, cholesterol levels, and the presence of diabetes.[9] Using this calculator, the aforementioned patient would have a 2% estimated 10 year risk of myocardial infarction and coronary death at baseline. If one assumes that this risk estimate is valid for this particular patient and that COC use for 10 years would double this risk, then there would be a 4% likelihood that this patient would experience a myocardial infarction and/or coronary death if taking COCs over the next 10 years; 2% of this risk would be directly attributable to the COC (ie, absolute risk of 2%, number needed to harm of 50). This would likely give pause to many physicians and patients, especially when there are other effective treatments for the symptoms of PCOS.

It is more difficult to determine baseline risk of ischemic stroke, which may also be doubled with COC use,[3] in premenopausal women. One may estimate the 10 year risk of general cardiovascular disease, which incorporates risk of both coronary heart disease and ischemic stroke.[10] However, it remains unclear how COCs influence other components of this composite endpoint (eg, hemorrhagic stroke, intermittent claudication, heart failure), so the utility of this approach is uncertain.

Overall, physicians must continue to individualize COC use based on patient goals along with the various risks and benefits of COCs (and their alternatives). It seems prudent to counsel patients, especially those with cardiovascular risk factors, that current COC use may double the risk of myocardial infarction and ischemic stroke. However, it seems preferable to provide patients with an estimate of absolute risks whenever possible because relative risks may be difficult for patients to fully comprehend.

For some physicians and patients, such estimates of absolute risk, considered in the context of other risks along with likely benefits, may discourage COC use. In contrast, some physicians and patients may decide that even relatively high (estimated) risks are justified in light of likely COC benefits (including contraceptive and noncontraceptive benefits). In general, though, patients should be given an opportunity to weigh the desirability and likelihood of COC benefits against the acceptability and likelihood of COC risks.

An understanding of alternative treatments for hyperandrogenism (eg, hirsutism) and endometrial protection, the primary noncontraceptive benefits of COCs in patients with PCOS, is integral to the risk-benefit decisions cited in earlier text. When patients with PCOS are felt to be at increased cardiovascular risk, physicians and patients should consider alternative treatments that do not further increase cardiovascular risk.

- First, in women with PCOS who are overweight or obese, efforts should be focused on weight loss via dietary modification and increased physical activity because such changes can improve hyperandrogenemia and ovulatory function[11-13] in addition to providing other health benefits that are especially important for patients with cardiovascular risk factors.
- Alternative treatments for hirsutism[14] include direct hair removal via photoepilation (laser and intense pulsed light therapy), shaving, waxing, plucking, topical depilatory agents, and electrolysis. Eflornithine hydrochloride topical cream can also be used to slow hair growth. The oral antiandrogen spironolactone is an additional option for treatment of hirsutism, but because of potential teratogenicity, antiandrogens must be used only in the setting of reliable contraception.
- For a number of reasons (eg, chronic anovulation), women with PCOS are at increased risk of endometrial hyperplasia and, most likely, endometrial cancer.[15] Intermittent administration of proges-

tins (eg, micronized progesterone) to induce withdrawal menses is felt to provide reliable endometrial protection[15] while avoiding the increased cardiovascular risk of COCs. Restoration of regular ovulation would also reduce risk of endometrial hyperplasia, and ovulatory function may be improved with weight loss[11] and insulin-sensitizing agents such as metformin.[16,17] However, apparent eumenorrhea may not be a reliable indicator of regular ovulation in hyperandrogenic patients,[18] so confirmatory testing (midluteal progesterone measurements) may be required when menstrual regularity improves with the latter interventions.

- Although women with PCOS are subfertile as a group, reliable contraception remains an issue for those not desiring pregnancy. Non-COC options for contraception include barrier methods, intrauterine devices, and progestin-only oral contraceptives. For women with PCOS who cannot take COCs, the progestin-releasing intrauterine device and progestin-only contraceptives may be attractive options because they also provide endometrial protection. In terms of cardiovascular risk, progestin-only oral contraceptives are believed to be much safer than COCs.[7,8]

The Framingham risk calculator has been validated in multiple populations, although the women included in these validation studies were at least 44 years old.[19] Although the accuracy of the Framingham risk calculator in young women is not proven, it is important to note that the original Framingham Heart Study, the basis for the Framingham risk calculator, was a very large, population-based, longitudinal study that included women aged 30 to 74 years at the time of initial assessment. Similarly, although the Framingham risk calculator has not been specifically validated in women with PCOS, the original Framingham Heart Study almost certainly included a large number of such women. Thus, the suggested use of the risk calculator has a sound basis; and at the present time, such risk calculators represent the best way to estimate short-term (10 year) cardiovascular risk in young women, both with and without PCOS, and the Framingham risk calculator is routinely used as a guide for dyslipidemia treatment in such women.

Finally, in the setting of long-term COC use (eg, long-term contraception, symptomatic treatment of PCOS), the risk-benefit ratio of COC use should be periodically reevaluated because the baseline risk of cardiovascular events increases with age. However, COC use itself can influence cardiovascular risk factors (eg, HDL cholesterol, blood pressure), and it is unclear how such COC-induced changes translate to changes of cardiovascular risk. Thus, the accuracy of such risk estimates could possibly be diminished for those already on COCs. Of importance for those who discontinue COCs, available data suggest that past COC use is not associated with higher cardiovascular risk.[2,3]

In summary, although the WHO and ACOG guidelines provide important contraindications for the use of COCs related to cardiovascular risk, there is still some uncertainty as to whether these guidelines will identify all patients in whom the use of COCs would be associated with an unacceptable level of cardiovascular risk. Additional introspection may be warranted when using COCs for reasons other than contraception in women with cardiovascular risk factors. Although the use of Framingham risk scores would not alleviate all uncertainty, it can provide an objective estimate of a patient's 10 year cardiovascular risk, which in conjunction with the current WHO and ACOG guidelines may help physicians and patients assess whether anticipated benefits of COCs outweigh the risks. ■

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