Chapter 7

The Young Woman with Headaches, Seeking the "Pill"

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Case History

A 22-year-old woman noted worsening of her migraine after being started on combination oral contraceptive (COC) to help control her acne. The migraines increased from once a month to once or twice weekly. The headaches required medication and were interfering with her work performance and the quality of her life. She had always considered herself healthy and fit, and the headaches were cramping her style. Her mother, who also suffered from migraines, encouraged her daughter to see a specialist.

She presented in the office as a healthy looking young woman. She indicated that she would like to stay on the pill, both for contraception and because it was helping with the facial acne. However, she was distressed by the headache and concerned about the risk of deep vein thrombosis (DVT) and stroke.

By history, she was not a smoker and was on no medication other than a COC. Her headaches were not associated with aura or focal neurologic changes. There was no family history of blood clots or stroke.

Her body mass index (BMI) was 25 and her blood pressure low (normal). Her physical examination was normal.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author's discussion.

- What are the risks of COC use in young women and in particular in women with migraine?
- Is there any benefit in switching to a COC with a lower dose of estradiol if there is increased frequency and/or severity of migraine on a higher dose COC?
- When would you suggest "progestin only" contraception in a woman with migraine?

Management Strategies

Before considering whether she should stay on the "pill," there are a series of questions that all physicians have to ask of the patient and themselves, which are as follows:

- How old is she?
- Does she have migraine without aura or with aura?
- Is the migraine associated with menses?
- Does she smoke?
- Does she have risk factors for stroke?
- Is there a personal or family history of a coagulation disorder or venous thrombosis?
- How long would she like contraception (months or years)?
- Does she prefer regular cyclic menses or no menses?

Also, on examination, there are observations to make, which are as follows:

- Is she overweight?
- Is she hypertensive?
- Is there evidence of vascular disease?
- Is there evidence of a neurologic disorder?

Finally, there are some decisions to make depending on the information gathered from the history and physical examination, and in different clinical scenarios, such as the following:

- What if she is 22 years old, normotensive, of healthy weight, with a negative family history, and suffers from migraine without aura?
- What if she has severe menstrual migraine?

- What if her migraine becomes more frequent on an oral contraceptive?
- What if she develops aura while on an oral contraceptive?
- Would your choice of contraception differ if she were overweight or hypertensive?
- What would you do if she developed a DVT?
- What would you do if she had a transient ischemic attack (TIA)?
- What would you recommend if she had preexisting migraine with aura or smoked 20 cigarettes a day?

General Discussion

Hormonal contraception provides the most effective (99.9%) reversible form of contraception for women. Migraine is associated with normal fertility. Most young women with or without migraine will choose hormonal contraception over other methods of birth control. This is usually in the form of COC pills that contain a synthetic estrogen, such as ethinyl estradiol (EE), and a variety of second- and third-generation progestins. "Low-dose" COCs are those with 35 μg or less of EE.

The pattern of migraine may be changed with the use of COCs. Cupini and colleagues found that migraine headaches worsened in 39% of cases and remained unchanged in another 39%. Migraines began with initiation of a COC in 18% of migraine patients.

Use of COCs involves an increase in the risk of both venous and arterial events, including venous thromboembolism (VTE), DVT, pulmonary embolism (PE), and ischemic stroke. Although migraine with aura confers an increased risk for ischemic stroke, it does not confer an increased risk for venous events such as DVT.

The risk of VTE among current COC users is increased within the first year of use, with higher dose of estrogen, with third-generation progestins, with a BMI > 30, and with a family history of VTE and a personal history of a coagulation disorder.

The risk of ischemic stroke in premenopausal women is increased by use of COCs, smoking, hypertension, and a history of migraine with aura.

Case-controlled studies in women aged 15 to 44 years have demonstrated a 3- to 4-fold increase in the risk of stroke in women with migraine.

In women aged 20 to 24 years with migraine with aura, Petitti and colleagues described the risk of ischemic stroke to be 8 of 100,000/yr for those not on a COC compared to 16 of 100,000/yr for those on a COC. The overall risk of ischemic stroke in women without migraine was 1.8 of 100,000/yr at ages 20 to 24 years, 3.3 of 100,000/yr at ages 30 to 34 years, and 16 of 100,000/yr at ages 40 to 44 years. In women who had migraine with aura, the risk of stroke on a COC was 29 of 100,000 at ages 30 to 34 years and 41 of 100,000 at ages 35 to 39 years.

Even low-dose COCs produce measurable changes in hemostasis (eg, increased fibrinogen, decreased protein S). They are also associated with an increased risk of ischemic stroke, although lower than the risk with EE 50 μg COCs.

Depending on the other risk factors, the risk may be either higher (eg, with smoking or hypertension) or lower (healthy women) than indicated. The risk factors are likely to be multiplicative or, in the least, additive.

Tzourio and colleagues found that the odds ratio for ischemic stroke was 3.7 for patients with migraine and 3.5 for COC use. Based on a small number of patients, if the woman had both risk factors, the odds ratio for ischemic stroke became 13.9.

Because of the risk of stroke, COCs should be discontinued in women who have prolonged (> 60 min) migraine auras or symptoms such as dysphasia or hemiparesis, or in women who develop TIAs or ischemic vascular disease. If there is aggravation of a preexisting migraine with or without typical visual aura, then consider switching to a lower dose estradiol COC, such as 20 or 30 μg EE versus 35 μg EE.

The second-generation testosterone-derived synthetic progestins include levonorgestrel (combined with EE 20 μg or 30 μg), norethindrone acetate (combined with EE 20 μg or 30 μg), ethynodiol diacetate (combined with EE 30 μg or 50 μg), and norethindrone (combined with EE 35 μg).

There is only one oral contraceptive that uses a natural progesterone-related progestin, cyproterone acetate, which is also a potent antiandrogen. The risk of DVT appears to be greater with cyproterone acetate than with the second-generation progestins. A preparation that contains EE 35 μg and cyproterone acetate 2 mg is marketed in Canada for the treatment of hyperandrogenic manifestations such as acne and hirsutism.

The newer progestins (third generation)—norgestimate, gestodene, and desogestrel—are all derivatives of levonorgestrel. All three share the high potency of levonorgestrel, but lack the androgenicity of the parent compound. Because norgestimate is partly metabolized to levonorgestrel, some investigators believe that it should be considered as a second-generation progestin rather than the third generation. In terms of DVT, norgestimate acts more like the second-generation progestins, but it is less androgenic than the parent levonogestrel. Norgestimate or desogestrel is combined with EE 35μg in a variety of COCs. Gestodene is not available in Canada.

Lidegaard and colleagues reported the risk of VTE with COC use to be 7.0 (5.1 to 9.6) in the first year of use, compared with 3.1 (2.5 to 3.8) after 5 years of use. The overall risk of VTE with 50 μg EE COCs was 4.2 (2.4 to 7.1), whereas that with 30 to 40 μg EE was 3.4 (2.8 to 4.2) and

for 20 μg EE was 4.3 (2.9 to 6.2). The risk of VTE was 2.9 (2.2 to 3.8) with second-generation progestins, 3.3 for cyproterone acetate, and 4.0 (3.2 to 4) for third-generation progestins. The authors considered norgestimate to be a second-generation progestin in their analysis. Women with a BMI > 30 had a 5-fold increased risk of VTE. A family history of VTE increased the risk 3 times and women with coagulation disorders had an adjusted risk of VTE of 37.4 (19.3 to 72.6). Smoking less than 10 cigarettes a day did not increase the risk of VTE. Smoking more than 20 cigarettes a day increased the risk by 94%.

The risk of VTE in non-COC users is about 5 of 100,000/yr compared with 60 of 100,000/yr during pregnancy. The risk with COC containing a second-generation progestin is about 15 of 100,000/yr and COC containing a third-generation progestin is 25 of 100,000/year. COCs with low-dose EE and a second-generation progestin would be preferred in women with a high BMI or genetic predisposition to VTE.

Although VTE is more common than ischemic stroke in young women, VTE has a lower disability and mortality than stroke. About 5% of women with VTE have a significant disability after the event, compared with 30% of women with stroke.

Lidegaard and Kreiner, and the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, have suggested that the risk of ischemic stroke is 40 to 50% lower in third-generation progestins versus second-generation progestins. The third-generation progestins may have less detrimental effects on metabolic parameters, including insulin resistance, which is thought to play a role in increasing cardiovascular risk. If indeed there is a lower risk of ischemic stroke with the third-generation progestins, then a low-dose COC with a third-generation progestin would be the COC of choice for the woman with migraine.

Women with migraine will experience the same non-contraceptive benefits of COCs as women who do not have migraine. These include improved cycle control with less dysmenorrhea and decreased blood loss with a lower risk of iron deficiency. In women on COCs, there is a decreased risk of ovarian cancer, endometrial cancer, pelvic infection, ectopic pregnancy, and therapeutic abortion. There are fewer benign ovarian cysts and there is decreased manifestation of ovarian hyperandrogenism of acne and hirsutism.

Women who have migraine without aura can probably use COCs with relative safety, although consideration should be given to the presence of any stroke risk factors. Simple aggravation of a preexisting migraine without aura or typical visual aura may respond to switching to a lower dose estrogen COC formulation. If migraine only occurs in the pill-free week, then a transdermal estradiol patch can be added during this interval. The migraine preventive dose (50 to 100 μg EE for 1 week) does not prevent the usual withdrawal bleeding. Nonsteroidal anti-inflammatory drugs and other migraine prophylactics may also be used during this vulnerable time for women with menstrual migraine.

Migraine with focal neurologic symptoms is a contraindication to the use of COCs. New onset aura or an unusual or persistent aura or the development of focal neurologic symptoms requires evaluation and possible/probable cessation of the COC.

In COCs, the dose of EE is consistent throughout the 21-day pill cycle. In the monophasic COCs, the dose of progestin is also constant. The biphasic COCs contain two different doses of progestins. Triphasic COCs have three different doses of progestin.

If a COC is used consecutively, one 21-day pack after another, then a monophasic COC is chosen over a biphasic or triphasic COC to help prevent breakthrough bleeding. If such bleeding occurs, then the COC is stopped for 5 to 7 days to allow shedding of the endometrium. In women with menstrual migraine, the migraine will occur at this time. The long-term safety of continuous COC use is unknown.

Progestin-only pills (POPs) have a lower contraceptive efficacy (90 to 99%) than COCs. The only one available in Canada contains the second-generation progestin norethindrone. The progestin levonorgestrel is employed as an emergency postcoital contraceptive medication. Levonorgestrel is also used as an implant for long-term (5-year) contraception. Depo-medroxyprogesterone acetate (DMPA), a progesterone-derived progestin, is used as a 3-month intramuscular injection to provide reliable contraception. There does not appear to be any increase in the risk of ischemic stroke or VTE with the POPs, implants, or injections. Side effects include menstrual irregularities with the POPs and with the injections and implants until amenorrhea has been achieved. The menstrual irregularities of POPs and in going on and coming off the progestin depots or implants may aggravate headache disorders. However, while amenorrhea occurs with the depots or implants, the woman with menstrual migraine is expected to be migraine free.

In women with severe menstrual migraine without aura, COCs may be used continuously, or progestin-only depots or implants may be used for contraception and amenorrhea.

Discussion with the Patient

The risk of DVT is low in a healthy, physically active, of normal weight, and nonsmoking individual, such as this patient. The risk of DVT is not increased by migraine, but may be increased by the use of a COC that contains 35 μg EE and 2 mg cyproterone acetate. This risk is greater in the first year of use. The risk of DVT, although low, could be reduced further by using a COC with a second-generation progesterone, such as levonorgestrel or norethindrone acetate, or a progestin contraceptive only.

The risk of ischemic stroke in this patient is also very low, considering that she is 22 years old, does not have migraine with aura, is not a smoker, and does not have hypertension. Use of a COC with a second-generation progestin may increase the risk of stroke, whereas the third-generation progestins such as desogestrel do not. There is no increase in ischemic stroke with a progestin-only contraception.

The increased frequency and severity of this patient's migraines may be related to the dose of estradiol in her COC. Since COCs with 20, 30, or 35 μg EE appear to provide similar contraceptive efficacy, it would be reasonable to try a low-dose COC. Typically, we would choose a COC with 20 μg EE. If there is spotting or inadequate cycle control with the 20 μg COC, then a 30 μg preparation could be tried, perhaps in combination with a third-generation progestin. The progestin-only oral contraceptive is a less desirable choice for this patient since it may increase her acne.

In most patients like the present case, a lower dose COC will restore the usual migraine frequency and severity. If this patient continues to have frequent migraines on the lower dose COCs, then a progestin-only injectable or implantable contraception could be considered. Keep in mind that headaches may worsen until amenorrhea occurs with the depots or implants, and that bone loss (largely reversible) may occur with DMPA.

Case Summary

In summary, a variety of hormonal contraceptives are available to women.

- Migraine alone does not confer an increased risk of VTE.
- Women starting a COC, or who are heavy (BMI > 30) or have a family history of VTE or a coagulation disorder are at a greater risk for VTE, DVT, or PE.
- Hormonal contraception with higher doses of estrogen or a third-generation progestin increases the risk of venous events.
- The currently available progestin-only contraception does not increase the risk of VTE or ischemic stroke.
- Migraine with aura confers an increased risk of ischemic stroke. This risk is greater in older women (ages 35 to 44 years), in women who smoke or have hypertension, or who use a COC with a second-generation progestin or a higher dose (50 μg) of EE.
- A low-dose (30 μg) estrogen COC containing a third-generation progestin may be preferred for attenuation of the stroke risk in women with migraine.
- A lower dose (20 μg) estrogen COC may help to prevent menstrual migraine in the week off the COC.
- For severe menstrual migraine, continuous use of a monophasic COC or progestin depots or implants can be considered.

Selected Readings

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Editorial Comments

No two cases are alike, even when the clinical diagnosis and circumstances around management are the same. Each case requires a balance of good clinical acumen, experience, and the most up-to-date evidence-based knowledge. Only with these factors in mind and by way of individual consideration can practical solutions be reached in the clinic and office for the majority of patients. Dr. Fettes analyzes the complexities of what should really be an easy call, "Should this patient be on COC?" The answer in this case is yes, but in other cases, the patient after being informed may elect another route, or there may be other factors that would dictate another course. Nowhere is it so important as to have excellent communication with the patient as in cases such as this one—the risks of serious untoward events is extremely low, but never zero, so it pays to get this right, and this chapter helps us a lot in that regard. (It should be noted that some of the medications noted in this chapter are not available in all countries.)

Final diagnosis:

Migraine without aura, on combined oral contraceptive for acne