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The Journal of Applied Medicine for the Primary Care Physician

Postgraduate Medicine

Editorial
The rooter man taught me about charging for after-hours service

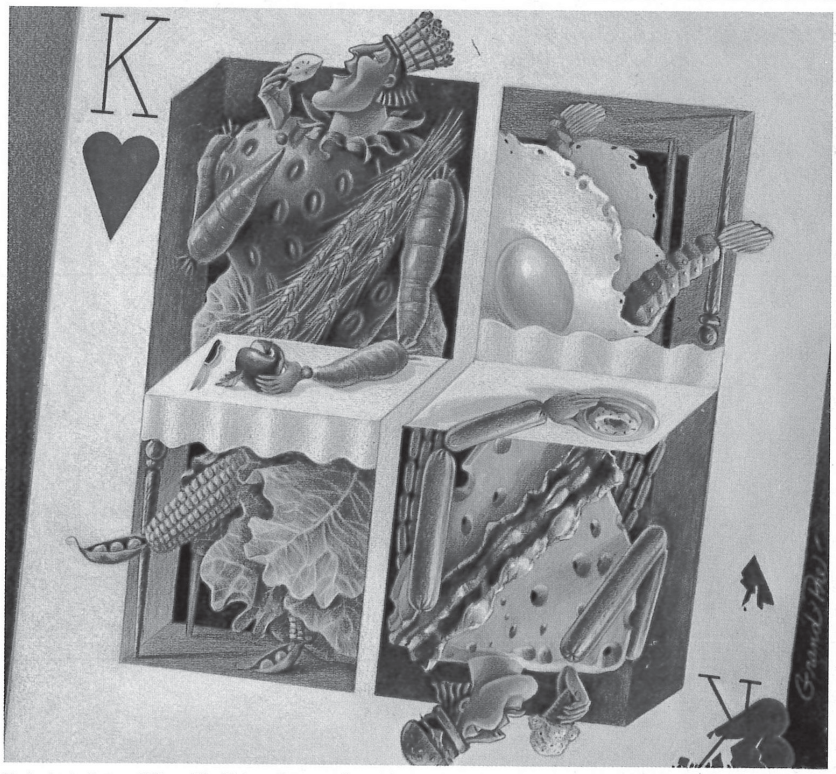
Renal disease 1947-1987
A PGM retrospective by H. E. de Wardener, MD, FRCP

Renal disease: Managing acute renal failure • When is hematuria a cause for alarm? • Renal disease resulting from too much uric acid

High-carbohydrate, high-fiber diet for treating hyperlipidemia • How to control persistent nosebleed • Oral contraceptives: Who, which, when, and why? • Loss of function in the frail elderly • Breast cancer presenting as periostitis • Sports-related CNS injuries in children

Complete contents beginning page 5

Coming in the next issue:
A PGM symposium on allergy



Carbohydrates and fiber: Modifying diet to reduce heart disease

CONTENTS

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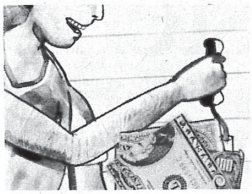
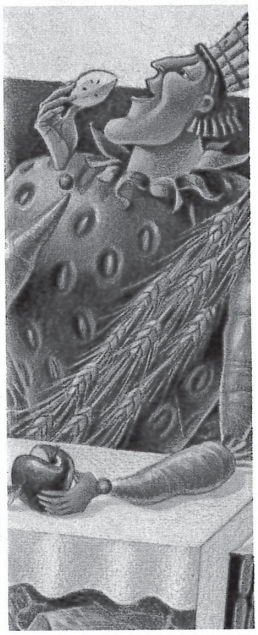


13



40

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continued on page 7

Oral contraceptives

Who, which, when, and why?

Edward L. Marut, MD

Preview

Who can safely use oral contraceptives? Which estrogen dose is best for most women? When does the estrogen and progestin content need to be adjusted? Why is "the pill" considered of non-contraceptive, as well as contraceptive, benefit? Dr Marut answers these questions with particular reference to the low-dose combination products now widely used.

The development of low-dose combination oral contraceptives in the 1970s has permitted oral contraceptives to be more acceptable and more available to women in the 1980s. Because oral contraceptives are the most effective nonsurgical method of contraception available[1] and have a number of desirable medical side effects, an increasing number of women in the United States are using them. The major risk attributed to "the pill" is cardiovascular disease, including myocardial infarction, cerebrovascular accident, and thromboembolism.[2,3] However, the risks are very small, and they cluster in a subset of women who use oral contraceptives.

Who can use them?

In general, the cardiovascular risks of oral contraceptives become highly significant after age 45 in nonsmoking women with no other risk factors and after age 35 in women who smoke but have no additional risk factors. Obviously, risk with use of the pill is least in the youngest age-groups, but apparently the major component of cardiovascular risk is smoking. Tobacco use and oral contraceptive use have been shown to be synergistic in regard to cardiovascular complications.[4,5]

Thus, age and smoking status constitute a major category of strong relative contraindications to use of oral contraceptives. Other contraindications (absolute, strong relative, and possible relative) are listed in table 1. (While this list shows the major categories, it is not all-inclusive.)

Which is best?

The best choices among the oral contraceptives are those with a low (< 50 µg) estrogen content, since many side effects correlate positively with estrogen dose. The dose should not be so low as to make compliance a problem because of nuisance side effects (breakthrough bleeding, amenorrhea) or to reduce effectiveness.

For the most part, this means that pills with 30 to 35 µg of estrogen (ethinyl estradiol) are appropriate. In general, their effectiveness is equivalent to that of products with 50 µg or more and there is no reason to start therapy with a higher dose. However, if breakthrough bleeding or amenorrhea is intractable with 30 to 35 µg of estrogen, the dose may need to be increased. Rarely is more than 50 µg necessary, but an apparent "pill failure" with a low-dose preparation would be one reason to use a higher dose. The effectiveness of oral contraceptives may be decreased by concurrent use of drugs that affect absorption and metabolism.

The progestin component of oral contraceptives should also be considered. Long-term use of progestins has the potential for causing cardiovascular effects because it reduces the level of high-density lipoprotein cholesterol.[6,7] The androgenic potency of progestin should be kept to a minimum. Table 2 shows the relative androgenic effect (which extends to skin and hair) of the various progestins at a similar dose.[8]

A major issue in gynecology in the 1980s concerns the desirability of "multiphasic" oral contraceptives. The amount of estrogen and/or progestin in these pills varies with the menstrual cycle so that the total dose of hormone is less than that of the fixed-dose parent product with 35 µg of ethinyl estradiol. Multiphasics,

according to their manufacturers, are physiologic or more natural than their fixed-dose counterparts. In my opinion, this is a fallacy, because the purpose of oral contraceptives is nonphysiologic, ie, to block ovulation and prevent conception.

What multiphasics should provide is a reduction in progestin-related side effects. However, the total hormone dose per cycle is lower for some fixed-dose products than for multiphasics. In everyday usage, the inflexibility of the preplanned dosage of multiphasics makes intracycle adjustments more difficult and proper use somewhat trickier than with fixed-dose oral contraceptives. Although the multiphasics are said to cause less breakthrough bleeding than the standard fixed-dose counterpart, this may not be the case.[8]

When should the pill cycle be started?

Considerable flexibility is allowed in starting oral contraceptive use. Manufacturers' directions range from starting on day 1 of the menstrual cycle to starting on the first Sunday of the cycle (to avoid subsequent weekend menses). The patient can generally begin taking the pills on any day up to the sixth day of her cycle, presuming a normal period and a cycle length of at least 28 days. If the usual cycle length is less than 28 days, use of the pills must be started earlier or a backup method of contraception must be used. Because the follicle destined to ovulate is selected seven days before ovulation, the pill cycle can be initiated up to day 6. If ovulation occurs before day 14, the dominant follicle may go on to ovulate unless the patient begins taking the pills before the selection process occurs.

When to start oral contraceptive therapy after early termination of pregnancy (elective or spontaneous), after delivery, or after nursing depends on when ovulation is likely to resume in each situation. After a first-trimester abortion or miscarriage, oral contraceptive therapy should be started within six days—just as in a regular menstrual cycle—since some women ovulate about two weeks after the termination of pregnancy. For a pregnancy loss in the second or third trimester when lactation is suppressed by bromocriptine (Parlodel), the pill should be started within two weeks, since ovulation may occur three to four weeks later. This is also true for a premature or full-term delivery when bromocriptine has been administered, since the reduction in prolactin levels results in a faster return to regular cyclicity.

A woman who breast-feeds should not use combination oral contraceptives until nursing is well established, since the milk supply may be decreased by immediate postpartum use. However, ovulation may resume in a mother who is breast-feeding but has reduced suckling episodes. Therefore, an alternative method of contraception should be used by all nursing mothers as soon as they resume sexual activity post partum. (Although small amounts of hormone are excreted in breast milk[9,10] and the absolute safety to the infant is not established, the American Academy of Pediatrics[11] approves use of oral contraceptives by breast-feeding mothers.)

When is worry justified?

Warning signs of potential major complications of oral contraceptives must be heeded. These complications are mostly cardiovascular: thromboembolism, cerebrovascular accidents, myocardial infarction, and hypertension.[2-5] A patient with symptoms referable to these complications (table 3) should seek medical advice immediately. Abdominal pain is included in table 3 because of the risk of hepatocellular adenoma associated with use of oral contraceptives. This disease is rare (3 to 4/100,000 long-term users) but potentially fatal.

The absolute risk in most women taking oral contracep-

continued

Side effects related to either progestin or estrogen in oral contraceptives may be alleviated by adjusting the appropriate component.

Table 1. Contraindications to use of oral contraceptives

Absolute contraindications
Cardiovascular or thromboembolic disease
Estrogen-dependent neoplasm
Liver neoplasm
Active liver disease
Persistent hypertension
Strong relative contraindications
Migraine or vascular headaches
Diabetes
Gallbladder disease
Hemoglobin S-S or S-C disease
Immobilization or leg injury
Age over 40 yr and second risk factor for cardiovascular disease
Age over 35 yr and history of heavy smoking
Possible relative contraindications
Family history of absolute or strong relative contraindications
Previous cholestatic disease or recent liver disease
Lactation
Psychiatric disease
Varices
Asthma
Seizure disorder
Leiomyomata uteri

Table 2. Relative effects of progestins at similar doses

Androgenic	
Norethynodrel	0
Ethynodiol diacetate	1.0
Norethindrone	1.6
Norethindrone acetate	2.5
Norgestrel	7.5
Levonorgestrel	15.0
Progestational	
Norethindrone	1.0
Norethynodrel	1.1
Norethindrone acetate	2.0
Ethynodiol diacetate	15.0
Norgestrel	30.0
Levonorgestrel	60.0

Table 3. Warning signs of major complications with oral contraceptive use

Abdominal pain
Chest pain or dyspnea
Headache or neurologic symptoms
Visual or speech problems
Leg pain or weakness

tives is low. A British study[1] established that the excess annual cardiovascular mortality for women taking the pill is 1/77,000 for nonsmokers under 35 years of age, 1/10,000 for smokers under 35, 1/6,700 for nonsmokers between 35 and 40, and 1/2,000 for smokers between 35 and 40.

When should the regimen be changed?

A woman who experiences breakthrough bleeding while taking low-dose combination oral contraceptives usually finds that it disappears after a few cycles. If the breakthrough bleeding persists, the first option is to add estrogen (10 to 20 μg of ethinyl estradiol or equivalent) for the remainder of the cycle. Often this is enough to stabilize the endometrium. If breakthrough bleeding recurs, changing to a 50-μg preparation for several cycles may be useful.

Amenorrhea with use of oral contraceptives is also caused by the effect of a low level of estrogen on the endometrium. This is unsettling but not dangerous. A woman who is amenorrheic while properly taking the pill can be reassured, but a pregnancy test may be necessary to relieve anxiety.

Estrogen may be added for breakthrough bleeding to obtain some endometrial proliferation, but increasing the estrogen content of the pill seems unwise for long-term use because of the increased likelihood of side effects. Manipulating the progestin-estrogen ratio by lowering the amount of progestin may be useful in breakthrough bleeding and amenorrhea, since both are caused by a relative insufficiency of estrogen.

Nuisance side effects related to progestin or estrogen may be alleviated by adjusting the appropriate component. With low-dose combination pills, these effects are fortunately uncommon. If side effects are androgenic (eg, acne, weight gain), the relative

Evidence supports a protective effect of oral contraceptives against endometrial and ovarian malignancy, benign breast disease, and infection of the upper genital tract.

Edward L. Marut
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androgenic effect of the progestins (table 2) should be considered so that appropriate adjustments can be made. If side effects are progestational (eg, headaches, depression), the relative progestational potency of the progestins (table 2) should likewise be considered. Estrogen side effects include fluid retention, nausea, and headache. Keeping the estrogen content below 50 µg should minimize these side effects. (Whether ethinyl estradiol and mestranol are equivalent in estrogenicity is still controversial. However, since all pills with less than 50 µg of estrogen contain ethinyl estradiol, this may not be a critical point.)

Why should women take the pill?

Besides the obvious contraceptive benefit of the combination pill—an effectiveness superior to that of all other nonsurgical forms of contraception—the many noncontraceptive benefits are good reasons to select oral contraceptives.

The mechanism by which oral contraceptives act (ie, suppression of gonadotropins and, thus, of the ovaries) results in menstrual regulation, decreased men-

continued

strual flow, and prevention of functional ovarian cysts.[12] Evidence also supports a protective effect of the pill against endometrial and ovarian malignancy, most likely by its progestational effect on the endometrial lining and its suppressive effect on the ovaries. The risk of these neoplasms is reduced by one half in women who have used oral contraceptives.[13]

Most studies indicate no increased risk of breast cancer in women taking oral contraceptives, and there is agreement that the pill has a protective effect against benign breast disease, again by eliminating the cyclicity of ovarian steroids. Similarly, suppression of androgen secretion by the ovaries can improve hirsutism and acne, if either is present. Premenstrual symptoms and dysmenorrhea, when functional, are often blunted by smoothing the usual hormonal cyclicity.

Interestingly, use of oral contraceptives may protect against infection of the upper genital tract (salpingitis, pelvic inflammatory disease).[14,15] The reasons for this protection include a decrease in menstrual effluent, which is a potential culture medium for bacteria, and thickening of cervical mucus, which may prevent microorganisms from ascending the genital tract.

Summary

The risks of oral contraceptives are very small, and they cluster in a subset of users, although warning signs of cardiovascular complications must be heeded. The best choice of an oral contraceptive is one with an estrogen content of 30 to 35 μg. A greater (50 μg) content may be necessary if breakthrough bleeding or amenorrhea persists beyond a few treatment cycles. The starting date for the pill can be up to the sixth day of the cycle.

Noncontraceptive benefits of the pill may include a protective effect against endometrial and ovarian malignancy, benign breast disease, and infection of the upper genital tract. Both the contraceptive and noncontraceptive benefits of low-dose combination oral contraceptives are desirable. They far outweigh the risks in women who require a high-efficacy, reversible contraceptive and who have no significant contraindication to use of the pill. PGM

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