asized the safety of low-dose oral contra-
ase-control study of 408 strokes from the
(edical Care Program found no increase in
or hemorrhagic stroke.[109] The identifiable
e were smoking, hypertension, diabetes,
socioeconomic status. The risk factors for
ıe plus greater body mass and heavy use of
oral contraceptives did not have an increased
troke compared with former users and with
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l contraceptive use and smoking, but the
result was not statistically significant). A
rol studies from U.S. concluded that there
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ıalyzed their data for ischemic stroke in a
hemic strokes in the United Kingdom,
and Austria.[111] Overall, there was a 3-fold
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were published as two separate reports, one
:r on hemorrhagic stroke.[113,114] In addition,
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containing desogestrel or gestodene with
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-control study from 21 centers in 17 coun-
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ference in risk with low-dose and higher
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of hypertension to be using oral contraceptives; however, this was not the case in developing countries. Duration of use and type of progestin had no impact, and past users did not have an increased risk, but smoking 10 or more cigarettes daily exerted a synergistic effect with oral contraceptives, increasing the risk of ischemic stroke, approximating the effect of hypertension and oral contraceptives. The risk was greater in women 35 years and older; however, this, too, was believed to be due to an effect of hypertension. *Thus, the conclusion of this study was that the risk of ischemic stroke is extremely low, concentrated in those who use higher dose products, smoke, or have hypertension.*

In the WHO study on hemorrhagic stroke, there were 1068 cases.[114] Current use of oral contraceptives was associated with a slightly increased risk of hemorrhagic stroke only in developing countries, not in Europe. This again reflects the lack of screening for hypertension, because the greatest increased risk (about 10- to 15-fold) was identified in current users of oral contraceptives who had a history of hypertension. Current cigarette smoking also increased the risk in oral contraceptive users, but not as dramatically as hypertension. For hemorrhagic stroke, the dose of estrogen had no effect on risk, and neither did duration of use or type of progestin. *This study concluded that the risk of hemorrhagic stroke due to oral contraceptives is increased only slightly in older women, probably occurring only in women with risk factors such as hypertension.*

A second Danish case-control study included thrombotic strokes and transitory cerebral ischemic attacks analyzed together as cerebral thromboembolic attacks.[97] In this study, the 219 cases during 1994 and 1995 included 146 cases of cerebral infarction and 73 cases of transient ischemic attacks. Only users of 2nd generation oral contraceptives (levonorgestrel, norgestrel, and norgestimate) had a statistically significant increased risk (about 2.5-fold). There was a dose-response relationship with estrogen in the dose ranges of 20, 30–40, and 50 µg ethinyl estradiol, although the number of 20 µg users (5 cases, 22 controls) was not sufficient to establish a lower risk at this lower dose. This analysis claimed a reduced risk associated with desogestrel and gestodene; however, the odds ratio did not achieve statistical significance. Risk was increased with smoking, treated hypertension, diabetes, heart diseases, frequent migraine, a family history of myocardial infarction, but not duration of use, or family history of venous thromboembolism.

Incidence of Stroke in Reproductive Age Women [105,109,113,114]

Incidence of ischemic stroke	5 per 100,000 per year
	1-3 per 100,000 per year in women under age 35
	10 per 100,000 per year in women over age 35
Incidence of hemorrhagic stroke	6 per 100,000 per year
Excess cases per year due to OCs, *including smokers and hypertensives*	2 per 100,000 per year in low-dose OC users
	1 per 100,000 per year in low-dose OC users under age 35
	8 per 100,000 per year in high-dose users

Arterial Thrombosis — Current Assessment

There has been no evidence with respectable statistical power that the new progestins have an appreciable difference in risk for arterial disease, an event that is *NOT* increased with low-dose older type progestin oral contraceptives. It is possible that as these studies continue and acquire greater statistical power, a difference will emerge, but even if this is the case, the difference in actual incidence will be minor and likely unmeasureable. Conclusions based on a limited number of cases are premature, and a critical attitude toward arterial thrombosis is appropriate just as such an approach finally revealed explanations for the initial findings with venous thrombosis.

Most importantly, the new studies fail to find any substantial risk of ischemic or hemorrhagic stroke with low-dose oral contraceptives in healthy, young women. The WHO study did find evidence for an adverse impact of smoking in women under age 35; the Kaiser study did not. This difference is explained by the confounding effect of hypertension, the major risk factor identified. In the WHO study, a history of hypertension was based on whether a patient reported ever having had high blood pressure (other than in pregnancy) and not validated by medical records. In the Kaiser study, women were classified as having hypertension if they reported using antihypertensive medication (less than 5% of oral contraceptive users had treated hypertension, and there were no users of higher dose products). In the WHO study, the effect of using oral contraceptives in the presence of a high-risk factor is apparent in the different odds ratios when European women who received good screening from clinicians were compared with

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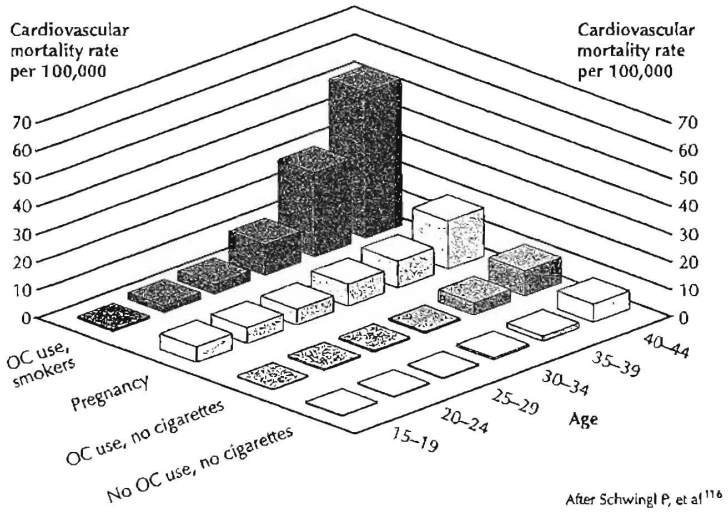
Over the years, there has been recurring discussion over whether to provide oral contraceptives over the counter on a non-prescription basis. The data in the WHO report make an impressive argument against such a move. The increased risk of myocardial infarction was most evident in developing countries where 70% of the cases received their oral contraceptives from a non-clinical source. Deprived of screening, women with cardiovascular risk factors in developing countries were exposed to a greater risk of arterial thrombosis.

Oral contraceptives containing less than 50 µg ethinyl estradiol do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age. The effect of smoking in women under age 35 is, as we have long recognized, not detectable in the absence of hypertension. After age 35, the subtle presence of hypertension makes analysis difficult, but the Kaiser study indicates that increasing age and smoking by themselves have little impact on the risk of stroke in low-dose oral contraceptive users. The screening of patients in the Kaiser program was excellent, resulting in few women with hypertension using oral contraceptives. *The new studies indicate that hypertension should be a major concern, especially in regards to the risk of stroke.* Certainly, women with uncontrolled hypertension should not use oral contraceptives. Generally, family planning experts have believed that well-treated hypertension should not be a contraindication for oral contraceptive use. The new data do not help us with this problem because it is impossible to accurately categorize hypertensive patients in the studies into groups representing successful and unsuccessful treatment. Nevertheless, the outstanding safety of low estrogen dose oral contraceptives in these studies supports the continued use of low-dose oral contraceptives in treated and well-controlled hypertensive women.

Estimated Annual Cardiovascular Mortality Rates Associated with Oral Contraceptive Use and Smoking Compared with Pregnancy



After Schwingl P, et al[116]

Smoking. Smoking continues to be a difficult problem, not only for patient management, but for analysis of data as well. In large U.S. surveys in 1982 and 1988, the decline in the prevalence of smoking was similar in users and nonusers of oral contraception; however, 24.3% of 35- to 45-year-old women who used oral contraceptives were smokers![117] In this group of smoking, oral contraceptive-using women, 85.3% smoked 15 or more cigarettes per day (heavy smoking). Despite the widespread teaching and publicity that smoking is a contraindication to oral contraceptive use over the age of 35, more older women who use oral contraceptives smoke and smoke heavily, compared with young women. This strongly implies that older smokers are less than honest with clinicians when requesting oral contraception, and further raises serious concern over how well this confounding variable can be controlled in case-control and cohort studies. *A former smoker must have stopped smoking for at least 12 consecutive months to be regarded as a nonsmoker. Women who have nicotine obtained from patches or gum in their bloodstreams should be regarded as smokers.*

Lipoproteins and Oral Contraception. The balance of estrogen and progestin potency in a given oral contraceptive formulation can potentially influence cardiovascular risk by its overall effect on lipoprotein levels. Oral

contraceptives with relatively high
today's low-dose formulations)
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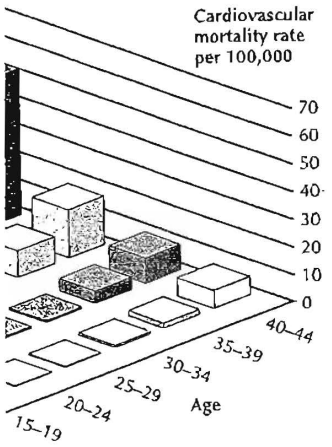

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contraceptives with relatively high doses of progestins (doses not used in today's low-dose formulations) do produce unfavorable lipoprotein changes.[118] The levonorgestrel triphasic exerts no significant changes on HDL-cholesterol, LDL-cholesterol, apoprotein B, and no change or an increase in apoprotein A, while the higher dose levonorgestrel monophasic combination has a tendency to increase LDL-cholesterol and apoprotein B, and to decrease HDL-cholesterol and apoprotein A. The monophasic desogestrel pills have a favorable effect on the lipoprotein profile, while the triphasic norgestimate and gestodene pills also produce beneficial alterations in the LDL:HDL and apoprotein B:apoprotein A ratios.[119-122] Like the triphasic levonorgestrel pills, norethindrone multiphasic pills have no significant impact on the lipoprotein profile over 6–12 months.[123] *In summary, studies of low-dose formulations indicate that the adverse effects of progestins are limited to the fixed-dose combination with a dose of levonorgestrel that exceeds that in the multiphasic formulation.* The formulation that contains 100 µg levonorgestrel and 20 µg ethinyl estradiol produces short-term changes in the lipid profile that are similar to those seen with other low-dose oral contraceptives, and with long-term use, the levels revert to those observed at baseline before treatment.[124]

An important study in monkeys indicated a protective action of estrogen against atherosclerosis, but by a mechanism independent of the cholesterol-lipoprotein profile. Oral administration of a combination of estrogen and progestin to monkeys fed a high-cholesterol, atherogenic diet decreased the extent of coronary atherosclerosis despite a reduction in HDL-cholesterol levels.[125-127] In somewhat similar experiments, estrogen treatment markedly prevented arterial lesion development in rabbits.[128-130] In considering the impact of progestational agents, lowering of HDL is not necessarily atherogenic if accompanied by a significant estrogen effect. These animal studies help explain why older, higher dose combinations, which had an adverse impact on the lipoprotein profile did not increase subsequent cardiovascular disease.[45,46] The estrogen component provided protection through a direct effect on vessel walls, especially favorably influencing vasomotor and platelet factors such as nitric oxide and prostacyclin.

This conclusion is reinforced by angiographic and autopsy studies. Young women with myocardial infarctions who have used oral contraceptives have less diffuse atherosclerosis than nonusers.[131,132] Indeed, a case-control study indicated that the risk of myocardial infarction in patients taking older, high-dose levonorgestrel-containing formulations is the same as that experienced with pills containing other progestins.[43]

In the past decade, we have been subjected to considerable marketing hype about the importance of the impact of oral contraceptives on the cholesterol-lipoprotein profile. If indeed certain oral contraceptives had a

negative impact on the lipoprotein profile, one would expect to find evidence of atherosclerosis as a cause of an increase in subsequent cardiovascular disease. There is no such evidence. Thus, the mechanism of the cardiovascular complications is undoubtedly a short-term acute mechanism—thrombosis (an estrogen-related effect).

Hypertension

Oral contraceptive-induced hypertension was observed in approximately 5% of users of higher dose pills. More recent evidence indicates that small increases in blood pressure can be observed even with 30 μg estrogen, monophasic pills, including those containing the new progestins. However, an increased incidence of clinically significant hypertension has not been reported.[135-136] The lack of clinical hypertension in most studies may be due to the rarity of its occurrence. The Nurses' Health Study observed an increased risk of clinical hypertension in current users of low-dose oral contraceptives, providing an incidence of 41.5 cases per 10,000 women per year.[137] Therefore, an annual assessment of blood pressure is still an important element of clinical surveillance, even when low-dose oral contraceptives are used. Postmenopausal women in the Rancho Bernardo Study who had previously used oral contraceptives (probably high-dose products) had slightly higher (2–4 mm Hg) diastolic blood pressures.[138] Because past users do not demonstrate differences in incidence or risk factors for cardiovascular disease, it is unlikely this blood pressure difference has an important clinical effect.

Variables such as previous preeclampsia of pregnancy or previous renal disease do not predict whether a woman will develop hypertension on oral contraception.[139] Likewise, women who have developed hypertension on oral contraception are not more predisposed to develop preeclampsia of pregnancy. Overall, there is no evidence that previous oral contraceptive users have an increased risk of hypertension during a subsequent pregnancy.[140-142] The Nurses Health Study has indicated that recent users for a long duration (8 or more years) have a 2-fold increased risk of preeclampsia, a finding based on a small number of cases.[142] These epidemiologic associations are hard to establish because of the role of underlying hypertension in pregnancy-induced hypertension and the difficulty in assessing the efficacy of hypertension screening in oral contraceptive users.

The mechanism for an effect on blood pressure during oral contraceptive use is thought to involve the renin angiotensin system. The most consistent finding is a marked increase in plasma angiotensinogen, the renin substrate, up to 8 times normal values (on higher dose pills). In nearly all women, excessive vasoconstriction is prevented by a compensatory decrease in plasma renin concentration. If hypertension does develop, the

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Cardiovascular Disease —

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One must also consider the effects of oral contraceptives in patients with preexisting hypertension or cardiac disease. In our view, with medical control of the blood pressure and close follow-up (at least every 3 months), the patient and her clinician may choose low-dose oral contraception. Close follow-up is also indicated in women with a history of preexisting renal disease or a strong family history of hypertension or cardiovascular disease. It seems prudent to suggest that patients with marginal cardiac reserve should utilize other means of contraception. Significant increases in cardiac output and plasma volume have been recorded with oral contraceptive use (higher dose pills), probably a result of fluid retention.

Cardiovascular Disease — Summary

The outpouring of epidemiologic data in the last few years allows the construction of a clinical formulation that is evidence-based. The following conclusions are consistent with the recent reports.

SUMMARY: Oral Contraceptives and Thrombosis

- Pharmacologic estrogen increases the production of clotting factors.
- Progestins have no significant impact on clotting factors.
- Past users of oral contraceptives do not have an increased incidence of cardiovascular disease.
- All low-dose oral contraceptives, regardless of progestin type, have an increased risk of venous thromboembolism, concentrated in the first 1–2 years of use. The actual risk of venous thrombosis with low-dose oral contraceptives is lower in the new studies compared with previous reports. Some have argued that this is due to preferential prescribing and the healthy user effect. However, it is also logical that the lower risk reflects better screening of patients and lower estrogen doses (although there are no apparent differences in risk associated with estrogen doses below 50 μg).
- Smoking has no effect on the risk of venous thrombosis.
- Smoking and estrogen have an additive effect on the risk of arterial thrombosis. Why is there a difference between venous and arterial clotting? The venous system has low flow with a state of high fibrinogen and low platelets, in contrast to the high-flow state of the arterial system with low fibrinogen and high platelets. Thus, it is understandable why these two different systems can respond in different ways.

- Hypertension is a very important additive risk factor for stroke in oral contraceptive users.
- Low-dose oral contraceptives (less than 50 µg ethinyl estradiol) do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age.
- Almost all myocardial infarctions and strokes in oral contraceptive users occur in users of high-dose products, or users with cardiovascular risk factors over the age of 35.
- Arterial thrombosis (myocardial infarction and stroke) has a dose-response relationship with estrogen, but there are insufficient data to determine whether there is a difference in risk with products that contain 20, 30 or 35 µg ethinyl estradiol.

The recent studies reinforce the belief that the risks of arterial and venous thrombosis are a consequence of the estrogen component of combination oral contraceptives. Current evidence does not support an advantage or disadvantage for any particular formulation, except for the greater safety associated with any product containing less than 50 µg ethinyl estradiol. Although it is logical to expect the greatest safety with the lowest dose of estrogen, the rare occurrence of arterial and venous thrombosis in healthy women makes it unlikely that there will be any measurable differences in the attributable incidence of clinical events among low-dose products.

The new studies emphasize the importance of good patient screening. The occurrence of arterial thrombosis is essentially limited to older women who smoke or have cardiovascular risk factors, especially hypertension. The impact of good screening is evident in the repeated failure to detect an increase in mortality due to myocardial infarction or stroke in several studies.[68,105] Although the risk of venous thromboembolism is slightly increased, the actual incidence is still relatively rare, and the mortality rate is about 1% (probably less with oral contraceptives, because most deaths from thromboembolism are associated with trauma, surgery, or a major illness). The minimal risk of venous thrombosis associated with oral contraceptive use does not justify the cost of routine screening for coagulation deficiencies. Nevertheless, the importance of this issue is illustrated by the increased risk of a very rare event, cerebral sinus thrombosis, in women who have an inherited predisposition for clotting and use oral contraceptives.[25,143]

If a patient has a close family history (parent or sibling) or a previous episode of idiopathic thromboembolism, an evaluation to search for an underlying abnormality in the coagulation system is warranted.[90] The following measurements are recommended, and abnormal results require consultation with a hematologist regarding prognosis and prophylaxis. The

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Antithrombin III defici
Protein C deficiency
Protein S deficiency
Factor V Leiden mutati
Prothrombin gene muta
Antiphospholipid syndr

Combination oral contraceptic
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list of laboratory tests is long, and because this is a dynamic and changing field, the best advice is to consult with a hematologist. *If a diagnosis of a congenital deficiency is made, screening should be offered to other family members.*

Hypercoaguable Conditions	Thrombophilia Screening
Antithrombin III deficiency	Antithrombin III
Protein C deficiency	Protein C
Protein S deficiency	Protein S
Factor V Leiden mutation	Activated protein C resistance ratio
Prothrombin gene mutation	Activated partial thromboplastin time
Antiphospholipid syndrome	Hexagonal activated partial thromboplastin time
	Anticardiolipin antibodies
	Lupus anticoagulant
	Fibrinogen
	Prothrombin G mutation (DNA test)
	Thrombin Time
	Homocysteine level
	Complete blood count

Combination oral contraception is contraindicated in women who have a history of idiopathic venous thromboembolism, and also in women who have a close family history (parent or sibling) of idiopathic venous thromboembolism. These women will have a higher incidence of congenital deficiencies in important clotting factors, especially antithrombin III, protein C, protein S, and resistance to activated protein C.[144] Such a patient who screens negatively for an inherited clotting deficiency might still consider the use of oral contraceptives, but this would be a difficult decision with unknown risks for both patient and clinician, and it seems more prudent to consider other contraceptive options. Other risk factors for thromboembolism that should be considered by clinicians include an acquired predisposition such as the presence of lupus anticoagulant or malignancy, and immobility or trauma. Varicose veins are not a risk factor unless they are very extensive.[58]

The conclusion once again is that low-dose oral contraceptives are very safe for healthy, young women. By effectively screening for the presence of smoking and cardiovascular risk factors, especially hypertension, in older women, we can limit, if not eliminate, any increased risk for arterial disease associated with low-dose oral contraceptives. And it is very important to emphasize that there is no increased risk of cardiovascular events associated with long-term use.

Carbohydrate Metabolism

With the older high-dose oral contraceptives, an impaired glucose tolerance test was present in many women. In these women, plasma levels of insulin as well as the blood sugar were elevated. Generally, the effect of oral contraception is to produce an increase in peripheral resistance to insulin action. Most women can meet this challenge by increasing insulin secretion, and there is no change in the glucose tolerance test, although 1-hour values may be slightly elevated.

Insulin sensitivity is affected mainly by the progestin component of the pill.[145] The derangement of carbohydrate metabolism may also be affected by estrogen influences on lipid metabolism, hepatic enzymes, and elevation of unbound cortisol. The glucose intolerance is dose-related, and effects are less with the low-dose formulations. ***Insulin and glucose changes with low-dose monophasic and multiphasic oral contraceptives are so minimal, that it is now believed they are of no clinical significance.***[136,146-148] This includes long-term evaluation with hemoglobin A1c.

The observed changes in studies of oral contraception and carbohydrate metabolism are in the nondiabetic range. In order to measure differences, investigators have resorted to analysis by measuring the area under the curve for glucose and insulin responses during glucose tolerance tests. A highly regarded cross-sectional study utilizing this technique reported that even lower dose formulations have detectable effects on insulin resistance.[145] The reason this is important is that it is now recognized that hyperinsulinemia due to insulin resistance is a contributor to cardiovascular disease.

Because long-term, follow-up studies of large populations have failed to detect any increase in the incidence of diabetes mellitus or impaired glucose tolerance (even in past and current users of high-dose pills),[138,149,150] the concern now appropriately focuses on the slight impairment as a potential risk for cardiovascular disease. If slight hyperinsulinemia were meaningful, wouldn't you expect to see evidence of an increase in cardiovascular disease in past users who took oral contraceptives when doses were higher? As we have emphasized before, there is no such evidence. The data strongly indicate that the changes in lipids and carbohydrate metabolism that have been measured are not clinically meaningful.

It can be stated definitively that oral contraceptive use does not produce an increase in diabetes mellitus.[149-152] The hyperglycemia associated with oral contraception is not deleterious and is completely reversible. Even women who have risk factors for diabetes in their history are not affected. In women with recent gestational diabetes, no significant impact on glucose

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The Liver

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:n. In these women, plasma levels of
: elevated. Generally, the effect of oral
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nulations. *Insulin and glucose changes*
ultiphasic oral contraceptives are so
are of no clinical significance.[136,146-148]
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tolerance could be demonstrated over 6–13 months comparing the use of low-dose monophasic and multiphasic oral contraceptives with a control group, and no increase in the risk of overt diabetes mellitus could be detected with long-term follow-up.[153,154] A high percentage of women with previous gestational diabetes develop overt diabetes and associated vascular complications. Until overt diabetes develops, it is appropriate for these patients to use low-dose oral contraception.

In clinical practice, it may, at times, be necessary to prescribe oral contraception for the overt diabetic. No effect on insulin requirement is expected with low-dose pills.[155] According to the older epidemiologic data, the use of oral contraceptives increases the risk of thrombosis in women with insulin-dependent diabetes mellitus; therefore, women with diabetes have been encouraged to use other forms of contraception. However, this effect in women under age 35 who are otherwise healthy is probably very minimal with low-dose oral contraception, and reliable protection against pregnancy is a benefit for these patients that outweighs the small risk. A case-control study could find no evidence that oral contraceptive use by young women with insulin-dependent diabetes mellitus increased the development of retinopathy or nephropathy.[156] In a 1-year study of women with insulin-dependent diabetes mellitus who were using a low-dose oral contraceptive, no deterioration could be documented in lipoprotein or hemostatic biochemical markers for cardiovascular risk.[157] And finally, no effect of oral contraceptives on cardiovascular mortality could be detected in a group of women with diabetes mellitus.[158]

The Liver

The liver is affected in more ways and with more regularity and intensity by the sex steroids than any other extragenital organ. Estrogen influences the synthesis of hepatic DNA and RNA, hepatic cell enzymes, serum enzymes formed in the liver, and plasma proteins. Estrogenic hormones also affect hepatic lipid and lipoprotein formation, the intermediary metabolism of carbohydrates, and intracellular enzyme activity. Nevertheless, an extensive analysis of the prospective cohorts of women in the Royal College of General Practitioners' Oral Contraception Study and the Oxford–Family Planning Association Contraceptive Study could detect no evidence of an increased incidence or risk of serious liver disease among oral contraceptive users.[159]

The active transport of biliary components is impaired by estrogens as well as some progestins. The mechanism is unclear, but cholestatic jaundice and pruritus were occasional complications of higher dose oral contraception, and are similar to the recurrent jaundice of pregnancy, i.e., benign and reversible. The incidence with lower dose oral contraception is unknown, but it must be a very rare occurrence.

The only absolute hepatic contraindication to oral contraceptive use is acute or chronic cholestatic liver disease. Cirrhosis and previous hepatitis are not aggravated. Once recovered from the acute phase of liver disease, a woman can use oral contraception.

Data from the Royal College of General Practitioners' prospective study indicated that an increase in the incidence of gallstones occurred in the first years of oral contraceptive use, apparently due to an acceleration of gallbladder disease in women already susceptible.[160] In other words, the overall risk of gallbladder disease was not increased, but in the first years of use, disease was activated or accelerated in women who were vulnerable because of asymptomatic disease or a tendency toward gallbladder disease. The mechanism appears to be induced alterations in the composition of gallbladder bile, specifically a rise in cholesterol saturation that is presumably an estrogen effect.[161] The Nurses' Health Study reported no significant increase in the risk of symptomatic gallstones among ever-users, but slightly elevated risks among current and long-term users.[162] Although oral contraceptive use has been linked to an increased risk of gallbladder disease, the epidemiologic evidence has been inconsistent. Indeed an Italian case-control study, a report from the Oxford–Family Planning Association cohort, and a French population survey found no increase in the risk of gallbladder disease in association with oral contraceptive use and no interaction with increasing age or body weight.[163-165] Keep in mind that even though some studies found a statistically significant modest increase in the relative risk of gallbladder disease, even if the effect were real, it is of little clinical importance because the actual incidence of this problem in young women is very low.

Other Effects

Nausea, breast discomfort, and weight gain continue to be disturbing effects, but their incidence is significantly less with low-dose oral contraception. Fortunately, these effects are most intense in the first few months of use and, in most cases, gradually disappear. Weight gain usually responds to dietary restriction, but for some patients, the weight gain may be an anabolic response to the sex steroids, and discontinuation of oral contraception is the only way that weight loss can be achieved. This must be rare with low-dose oral contraception because data in published studies fail to indicate a difference in body weight between users and nonusers.[166-170] Indeed, in a placebo-controlled randomized trial of low-dose oral contraceptives and acne, the incidence of weight gain and headaches was identical in both the treated and the placebo groups.[171]

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There is no association between oral contraception and peptic ulcer disease or inflammatory bowel disease.[172,173] Oral contraception is not recommended for patients with problems of gastrointestinal malabsorption because of the possibility of contraceptive failure.

Chloasma, a patchy increase in facial pigment, was, at one time, found to occur in approximately 5% of oral contraceptive users. It is now a rare problem due to the decrease in estrogen dose. Unfortunately, once chloasma appears, it fades only gradually following discontinuation of the pill and may never disappear completely. Skin-blanching medications may be useful.

Hematologic effects include an increased sedimentation rate, increased total iron-binding capacity due to the increase in globulins, and a decrease in prothrombin time. The use of oral contraceptives results in a decrease in iron deficiency anemia, probably the result of a reduction in menstrual bleeding.[174,175] Indeed, in anemic women, an increase in hemoglobin and ferritin levels accompanies the use of oral contraceptives.[176]

The continuous daily use of oral contraceptives may prevent the appearance of symptoms in porphyria precipitated by menses. Changes in vitamin metabolism have been noted: a small nonharmful increase in vitamin A and decreases in blood levels of pyridoxine (B_6) and the other B vitamins, folic acid, and ascorbic acid. Despite these changes, routine vitamin supplements are not necessary for women eating adequate, normal diets.[177]

Mental depression is very rarely associated with oral contraceptives. In studies with higher dose oral contraceptives, the effect was due to estrogen interference with the synthesis of tryptophan that could be reversed with pyridoxine treatment. It seems wiser, however, to discontinue oral contraception if depression is encountered. Though infrequent, a reduction in libido is occasionally a problem and may be a cause for seeking an alternative method of contraception.

Adverse androgenic voice changes were occasionally encountered with the use of the first very high-dose oral contraceptives. Vocal virilization can be a serious and devastating problem for some women, especially when vocal performance is important. Careful study of women on low-dose oral contraceptives indicates that this is no longer a side effect of concern.[178]

The Risk of Cancer

Endometrial Cancer

The use of oral contraception protects against endometrial cancer. Use for at least 12 months reduces the risk of developing endometrial cancer by *50%*, with the greatest protective effect gained by use for more than 3 years, reaching 80% after 10 years of use.[179-184] This protection persists for 20 or more years after discontinuation (the actual length of duration of protection is unknown) and is greatest in women at highest risk: nulliparous and low parity women.[164,185] This protection is equal for all 3 major histologic subtypes of endometrial cancer: adenocarcinoma, adenoacanthoma, and adenosquamous cancers. Finally, protection is seen with all monophasic formulations of oral contraceptives, including pills with less than 50 µg estrogen.[179,181,184,186] There are no data as yet with multiphasic preparations or the new progestin formulations, but because these products are still dominated by their progestational component, there is every reason to believe that they will be protective.

Ovarian Cancer

Protection against ovarian cancer, the most lethal of female reproductive tract cancers, is one of the most important benefits of oral contraception. Because this cancer is detected late and prognosis is poor, the impact of this protection is very significant. Indeed, a decline in mortality from ovarian cancer has been observed in several countries since the early 1970s, perhaps an effect of oral contraceptive use.[187] Cohorts of women with increased exposure to oral contraceptives have demonstrated a marked decrease in the incidence of ovarian cancer.[188-190] Epidemiologic studies indicate that the risk of developing epithelial ovarian cancer of any histologic subtype in users of oral contraception is reduced by *40%* compared with that of nonusers.[181,188,191-194] This protective effect increases with duration of use and continues for 20 or more years after stopping the medication. This protection is seen in women who use oral contraception for as little as 3 to 6 months (although at least 3 years of use are required for a notable impact), reaches an 80% reduction in risk with more than 10 years of use, and is a benefit associated with all monophasic formulations, including the low-dose products.[195] The protective effect of oral contraceptives is especially prominent in women at high risk of ovarian cancer (nulliparous women and women with a positive family history).[196] Continuous use of oral contraception for 10 years by women with a positive family history for ovarian cancer can reduce the risk of epithelial ovarian cancer to a level equal to or less than that experienced by women with a negative family history.[196] The multiphasic and new progestin products have not been in use long enough to yield any data on this issue, but because ovulation is effectively inhibited by these formulations, protection against ovarian cancer should be exerted. The sar observed in a case-control study of tions.[197]

Cancer of the Cervix

Studies have indicated that the risk the uterine cervix increases with the one year.[198-203] Invasive cervical canc reaching a two-fold increase after 1 that the number of partners a wom most important risk factors for c factors include exposure to human p ception (protective), and smoking. and, therefore, the conclusions rega An excellent study from the Cente (CDC) concluded there is no incr users of oral contraception, and an situ is due to enhanced detection of have more frequent Pap smears).[201] I of Neoplasia and Steroid Contrace identified, nevertheless the eviden cervical carcinoma in situ with long

A case-control study of patients ir Mexico concluded that there was a adenocarcinoma.[204] Similar results v Los Angeles and in the World Study.[205,206] In Los Angeles, the relat increased from 2.1 with ever use contraceptive use.[205] Because the inc (10% of all cervical cancers) has i 20 years, there is concern that this ception.[207] Oral contraceptives incr increases the risk of cervical adeno

This concern obviously is an impor lance. Fortunately, steroid contrace changes, and the necessity for pres for improved screening for cervical smears every 6 months in women years who are also at higher risk be partners, history of sexually transm appropriate for women with a hist (CIN), including those who have b

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Cancer of the Cervix

Studies have indicated that the risk for dysplasia and carcinoma in situ of the uterine cervix increases with the use of oral contraception for more than one year.[198-203] Invasive cervical cancer may be increased after 5 years of use, reaching a two-fold increase after 10 years. It is well recognized, however, that the number of partners a woman has had and age at first coitus are the most important risk factors for cervical neoplasia. Other confounding factors include exposure to human papillomavirus, the use of barrier contraception (protective), and smoking. These are difficult factors to control, and, therefore, the conclusions regarding cervical cancer are not definitive. An excellent study from the Centers for Disease Control and Prevention (CDC) concluded there is no increased risk of invasive cervical cancer in users of oral contraception, and an apparent increased risk of carcinoma in situ is due to enhanced detection of disease (because oral contraceptive users have more frequent Pap smears).[201] In the World Health Organization Study of Neoplasia and Steroid Contraceptives, a Pap smear screening bias was identified, nevertheless the evidence still suggested an increased risk of cervical carcinoma in situ with long-term oral contraceptive use.[202]

A case-control study of patients in Panama, Costa Rica, Colombia, and Mexico concluded that there was a significantly increased risk for invasive adenocarcinoma.[204] Similar results were obtained in a case-control study in Los Angeles and in the World Health Organization Collaborative Study.[203,205] In Los Angeles, the relative risk of adenocarcinoma of the cervix increased from 2.1 with ever use to 4.4 with 12 or more years of oral contraceptive use.[205] Because the incidence of adenocarcinoma of the cervix (10% of all cervical cancers) has increased in young women over the last 20 years, there is concern that this increase reflects the use of oral contraception.[207] Oral contraceptives increase cervical ectropion, but whether this increases the risk of cervical adenocarcinoma is unclear.

This concern obviously is an important reason for annual Pap smear surveillance. Fortunately, steroid contraception does not mask abnormal cervical changes, and the necessity for prescription renewals offers the opportunity for improved screening for cervical disease. It is reasonable to perform Pap smears every 6 months in women using oral contraception for 5 or more years who are also at higher risk because of their sexual behavior (multiple partners, history of sexually transmitted diseases). Oral contraceptive use is appropriate for women with a history of cervical intraepithelial neoplasia (CIN), including those who have been surgically treated.

Liver Adenomas

Hepatocellular adenomas can be produced by steroids of both the estrogen and androgen families. Actually, there are several different lesions, peliosis, focal nodular hyperplasia, and adenomas. Peliosis is characterized by dilated vascular spaces without endothelial lining, and may occur in the absence of adenomatous changes. The adenomas are not malignant; their significance lies in the potential for hemorrhage. The most common presentation is acute right upper quadrant or epigastric pain. The tumors may be asymptomatic, or they may present suddenly with hematoperitoneum. There is some evidence that the tumors and focal nodular hyperplasia regress when oral contraception is stopped.[208,269] Epidemiologic data have not supported the contention that mestranol increased the risk more than ethinyl estradiol.

The risk appears to be related to duration of oral contraceptive use and to the steroid dose in the pills. This is reinforced by the rarity of the condition ever since low-dose oral contraception became available. The ongoing prospective studies have accumulated many woman-years of use and have not identified an increased incidence of such tumors.[159] In a collaborative study of 15 German liver centers, no increase in risk for liver adenomas in contemporary oral contraceptive users could be detected.[210] In our view, the risk of liver disease does not merit mentioning during the informed consent (choice) process.

No reliable screening test or procedure is currently available. Routine liver function tests are normal. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) is the best means of diagnosis; angiography and ultrasonography are not reliable. Palpation of the liver should be part of the periodic evaluation in oral contraceptive users. If an enlarged liver is found, oral contraception should be stopped, and regression should be evaluated and followed by imaging.

Liver Cancer

Oral contraception has been linked to the development of hepatocellular carcinoma.[211,212] However, the very small number of cases, and, thus, the limited statistical power, requires great caution in interpretation. The largest study on this question, the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, found no association between oral contraception and liver cancer.[213] Even case-control analysis of oral contraceptives containing cyproterone acetate (known to be toxic to the liver in high doses) could detect no evidence of an increased risk of liver cancer.[214] In the United States, Sweden, England, and Wales, the death rates from liver cancer did not change during the time period that reflects the introduction and use of oral contraception.[215,216] An increase in liver cancer incidence

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Breast Cancer

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and mortality in the U.S. has occurred over the last 2 decades, believed to be due to infection with hepatitis C and hepatitis B.[217]

Breast Cancer

Because of its prevalence and its long latent phase, concern over the relationship between oral contraception and breast cancer continues to be an issue in the minds of both patients and clinicians. Unfortunately, the issue is not totally resolved and probably will not be until another decade passes, allowing data to emerge from the modern era of lower dose oral contraception.

Some early studies, reflecting the use of higher dose pills, indicated a protective effect of oral contraception on benign breast disease, an effect that was limited to current and recent users;[218-220] however, one case-control study did not find this effect.[221] It is still uncertain whether any protection is provided by the lower dose products. A French case-control study indicated a reduction of nonproliferative benign breast disease associated with low-dose oral contraceptives used before a first full-term pregnancy, but no effect on proliferative disease or with use after a pregnancy.[222] A Canadian cohort study that almost certainly reflected the use of modern low-dose oral contraceptives concluded that oral contraceptives do protect against proliferative benign disease, with an increasing reduction in risk with increasing duration of use.[223]

The Royal College of General Practitioners,[224] Oxford–Family Planning Association,[225,226] and Walnut Creek[227] cohort studies (and more recently, the Nurses' Health Study)[228] indicated no significant differences in breast cancer rates between users and nonusers. However, patients were enrolled in these studies at a time when oral contraception was used primarily by married couples spacing out their children. Beginning in the 1980s, oral contraception was primarily being used by women early in life, for longer durations, and to delay an initial pregnancy (remember, a full-term pregnancy early in life protects against breast cancer).

Over the last decade, case-control studies have focused on the use of oral contraception early in life, for long duration, and to delay a first, full-term pregnancy. Because the cohort of women who have used oral contraception in this fashion is just now beginning to reach the ages of postmenopausal breast cancer, the studies have had to focus on the risk of breast cancer diagnosed before age 45 (only 13% of all breast cancer). The results of these studies have not been clear-cut. Some studies have indicated an overall increased relative risk of early, premenopausal breast cancer,[229-237] while others indicated no increase in overall risk.[238-240] The most impressive finding indicates a link in most studies,[241-246] but not all,[247-251] of

early breast cancer (before age 40) with women who used oral contraception for long durations of time.

A collaborative group composed of an enormous number of epidemiologists and cancer investigators from around the world re-analyzed data from 54 studies in 26 countries, a total of 53,297 women with breast cancer and 100,239 without breast cancer, in order to assess the relationship between the risk of breast cancer and the use of oral contraceptives.[252,253] Oral contraceptives were grouped into 3 categories: low, medium, and high dose (which correlated with <50 µg, 50 µg, and >50 µg of estrogen). At the time of diagnosis, 9% of the women with breast cancer were under age 35, 25% were 35–44, 33% were 45–54, and 33% were age 55 and older. A similar percentage of women with breast cancer (41%) and women without breast cancer (40%) had used combined oral contraceptives at some time in their lives. Overall, the relative risk (RR) of breast cancer in ever users of oral contraceptives was very slightly elevated and statistically significant: RR = 1.07; CI = 1.03–1.10.

The relative risk analyzed by duration of use was barely elevated and not statistically significant (even when long-term virtually continuous use, was analyzed). Women who had begun use as teenagers had about a 20% statistically significant increased relative risk. In other words, recent users who began use before age 20 had a higher relative risk compared with recent users who began at later ages. The evidence was strong for a relationship with time since last use, an elevated risk being significant for current users and in women who had stopped use 1–4 years before (recent use). No influence on this risk was observed with the following: a family history of breast cancer, age of menarche, country of origin, ethnic groups, body weight, alcohol use, years of education, and the design of the study. There was no variation according to specific type of estrogen or progestin in the various products. Importantly, there was no statistically significant effect of low, medium, or high dose preparations. Ten or more years after stopping use, there was no increased risk of breast cancer; indeed, the risk of metastatic disease compared with localized tumors was reduced: Relative Risk = 0.88; CI = 0.81–0.95.

Oral Contraceptives and
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Oral Contraceptives and the Risk of Breast Cancer Re-analysis of the World's Data[252]

Current users	RR = 1.24, 95% CI 1.15-1.33
1-4 years after stopping	RR = 1.16, 95% CI 1.08-1.23
5-9 years after stopping	RR = 1.07, 95% CI 1.02-1.13

Data were limited for progestin-only methods. The re-analysis indicated that the results were similar to those with combined oral contraceptives, but a close look at the numbers reveals that not one relative risk reached statistical significance.

Overall, this massive statistical exercise yielded good news. No major adverse impact of oral contraceptives emerged. *Even though the data indicated that young women who begin use before age 20 have higher relative risks of breast cancer during current use and in the 5 years after stopping, this is a time period when breast cancer is very rare; and, thus, there would be little impact on the actual number of breast cancers.* The difference between localized disease and metastatic disease was statistically greater and should be observable. Thus many years after stopping oral contraceptive use, the main effect may be protection against metastatic disease. Breast cancer is more common in older years, and 10 or more years after stopping, the risk was not increased.

What other explanation could account for an increased risk associated only with current or recent use, no increase with duration of use, and a return to normal 10 years after exposure? The slightly increased risk could be influenced by detection/surveillance bias (more interaction with the health care system by oral contraceptive users). It is also possible that this situation is analogous to that of pregnancy. Recent studies indicate that pregnancy transiently increases the risk of breast cancer (for a period of several years) after a woman's first childbirth, and this is followed by a lifetime reduction in risk.[254] And some have found that a concurrent or recent pregnancy adversely affects survival.[255,256] It is argued that breast cells that have already begun malignant transformation are adversely affected by the hormones of pregnancy, while normal stem cells become more resistant because of a pregnancy. It is possible that early and recent use of oral contraceptives also accelerates the growth of a pre-existing malignancy, explaining the limitation of the finding to current and recent use and the increase in localized disease. With the accumulation of greater numbers of older women previously exposed to oral contraceptives, a protective effect

may become evident. In a case-control study of women in Toronto, Canada, aged 40–69 years, those women who had used oral contraceptives for 5 or more years, 15 or more years previously, had a 50% reduced risk of breast cancer.[257] However, a case-control study from Sweden could detect neither a beneficial nor an adverse effect of previous use of oral contraceptives (mainly 50 μg estrogen products) on the risk of breast cancer in women aged 50–74 years.[258]

One case-control study of women with breast cancer who were positive for the BRCA gene found an increased risk associated with the use of oral contraceptives; however, the numbers were small and the conclusions were not statistically significant with broad confidence limits.[259]

Conclusion. Adding up the benefits of oral contraception, the possible slight increase in risk of breast cancer is far outweighed by positive effects on our public health. But the impact on public health is of little concern during the private clinician–patient interchange in the office. Here personal risk receives highest priority; fear of cancer is a motivating force, and compliance with effective contraception requires accurate information. For these reasons, we provide the following summary of our assessment of the impact of oral contraceptives on the risk of breast cancer.

SUMMARY: Oral Contraceptives and the Risk of Breast Cancer

- Current and recent use of oral contraceptives may be associated with about a 20% increased risk of early premenopausal breast cancer, essentially limited to localized disease and a very small increase in the actual number of cases (so small, there would be no major impact on incidence figures). This finding may be due to detection/surveillance bias and accelerated growth of already present malignancies, a situation similar to the effects of pregnancy and postmenopausal hormone therapy on the risk of breast cancer. Further comfort can be derived from the fact that the increased incidence in breast cancer in American women occurred in older women from 1973 to 1996, those who did not have the opportunity to use oral contraception.[260] In women under 40 years of age, the incidence of breast cancer has actually declined since 1985.
- There is no effect of past use or duration of oral contraceptive use (up to 15 years of continuous use) on the risk of breast cancer, and there is no evidence indicating that higher dose oral contraceptives increased the risk of breast cancer.
- Previous oral contraceptiv
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possibly with a reduced
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- The clinician should not
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Other Cancers

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Endocrine Effects

Adrenal Gland

Estrogen increases cortisol-bindi
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of oral contraceptives may be associ- increased risk of early premenopausal ly limited to localized disease and a he actual number of cases (so small, ɔr impact on incidence figures). This detection/surveillance bias and accel- dy present malignancies, a situation of pregnancy and postmenopausal the risk of breast cancer. Further from the fact that the increased inci- r in American women occurred in 73 to 1996, those who did not have se oral contraception.[260] In women , the incidence of breast cancer has 1985.

ıst use or duration of oral contracep- rs of continuous use) on the risk of ere is no evidence indicating that aceptives increased the risk of breast

- Previous oral contraceptive use may be associated with a reduced risk of metastatic breast cancer later in life, and possibly with a reduced risk of postmenopausal breast cancer.
- Oral contraceptive use does not further increase the risk of breast cancer in women with positive family histories of breast cancer or in women with proven benign breast disease.
- The clinician should not fail to take every opportunity to direct attention to all factors that affect breast cancer. Breastfeeding and control of alcohol intake are good examples, and are also components of preventive health care. Especially important is this added motivation to encourage breastfeeding. The protective effect (although it is probably a small one) of breastfeeding is exerted on premenopausal breast cancer, the cancer of concern to younger women using oral contraception.

Other Cancers

The Walnut Creek study suggested that melanoma was linked to oral contraception; however, the major risk factor for melanoma is exposure to sunlight. Later and more accurate evaluation utilizing both the Royal College General Practitioners and Oxford–Family Planning Association prospective cohorts and accounting for exposure to sunlight did not indicate a significant difference in the risk of melanoma comparing users with nonusers.[261,262] There is no evidence linking oral contraceptive use to kidney cancer, gallbladder cancer, or pituitary tumors.[263] Long-term oral contraceptive use may be associated with a slightly increased risk of molar pregnancy, but there is no convincing evidence of a cause-and-effect association.[264] A case-control study concluded that oral contraceptives reduce the risk of salivary gland cancer.[265] Although previous studies have not been in agreement, the Nurses' Health Study reports about a 40% reduced risk of colorectal cancer associated with 8 years of previous use of oral contraceptives (most likely higher dose products).[266] A review of the literature found that 3 of 4 cohort studies and 5 of 11 case-control studies indicated a reduced risk of colorectal cancer in oral contraceptive ever users.[267]

Endocrine Effects

Adrenal Gland

Estrogen increases cortisol-binding globulin. It had been thought that the increase in plasma cortisol while on oral contraception was due to increased binding by this globulin and not an increase in free active cortisol. Now it is apparent that free and active cortisol levels are also elevated.

Estrogen decreases the ability of the liver to metabolize cortisol, and in addition, progesterone and related compounds can displace cortisol from transcortin, and thus contribute to the elevation of unbound cortisol. The effects of these elevated levels over prolonged periods of time are unknown, but no obvious impact has been observed. To put this into perspective, the increase is not as great as that which occurs in pregnancy, and, in fact, it is within the normal range for nonpregnant women.

The adrenal gland responds to adrenocorticotropic hormone (ACTH) normally in women on oral contraceptives; therefore, there is no suppression of the adrenal gland itself. Initial studies indicated that the response to metyrapone (an 11β-hydroxylase blocker) was abnormal, suggesting that the pituitary was suppressed. However, estrogen accelerates the conjugation of metyrapone by the liver; and, therefore, the drug has less effect, thus explaining the subnormal responses initially reported. The pituitary-adrenal reaction to stress is normal in women on oral contraceptive pills.

Thyroid

Estrogen increases the synthesis and circulating levels of thyroxine-binding globulin, Prior to the introduction of new methods for measuring free thyroxine levels, evaluation of thyroid function was a problem. Measurements of TSH (thyroid-stimulating hormone) and the free thyroxine level in a woman on oral contraception provide an accurate assessment of a patient's thyroid state. Oral contraception affects the total thyroxine level in the blood by increasing the amount of binding globulin, but the free thyroxine level is unchanged.

Oral Contraception and Reproduction

The impact of oral contraceptives on the reproductive system is less than initially thought. Early studies that indicated adverse effects have not stood the test of time and the scrutiny of multiple, careful studies. There are two major areas that deserve review: (1). Inadvertent use of oral contraceptives during the cycle of conception and during early pregnancy, and (2). Reproduction after discontinuing oral contraception.

Inadvertent Use During the Cycle of Conception and During Early Pregnancy

One of the reasons, if not the major reason, why a lack of withdrawal bleeding while using oral contraceptives is such a problem is the anxiety produced in both patient and clinician. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the concerns stemming from the retrospective studies that indicated an increased risk of congenital malformations among the offspring of women who were pregnant and using oral contraception.

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Initial positive reports linking the use of contraceptive steroids to congenital malformations have not been substantiated. Many suspect a strong component of recall bias in the few positive studies due to a tendency of patients with malformed infants to recall details better than those with normal children. Other confounding problems have included a failure to consider the reasons for the administration of hormones (e.g., bleeding in an already abnormal pregnancy), and a failure to delineate the exact timing of the treatment (e.g., treatment was sometimes confined to a period of time during which the heart could not have been affected). Organogenesis does not occur in the first 2 embryonic weeks (first 4 weeks since last menstrual period); however, teratogenic effects are possible between the third and eighth embryonic weeks (5 to 10 weeks since LMP).

An association with cardiac anomalies was first claimed in the 1970s.[268,269] This association received considerable support with a report from the U.S. Collaborative Perinatal Project; however, subsequent analysis of these data uncovered several methodologic shortcomings.[270] Simpson, in a very thorough and critical review in 1990, concluded that there was no reliable evidence implicating sex steroids as cardiac teratogens.[271] In fact, in his review, Simpson found no relationship between oral contraception and the following problems: hypospadias, limb reduction anomalies, neural tube defects, and mutagenic effects which would be responsible for chromosomally abnormal fetuses. Even virilization is not a practical consideration today because the doses required (e.g., 20–40 mg norethindrone per day) are in excess of anything currently used. These conclusions reflect use of combined oral contraceptives as well as progestins alone.

In the past there was a concern regarding the VACTERL complex. VACTERL refers to a complex of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies. While case-control studies indicated a relationship with oral contraception, prospective studies have failed to observe any connection between sex steroids and the VACTERL complex.[272] Meta-analyses of studies of the risk of birth defects with oral contraceptive ingestion during pregnancy have concluded that there is no increase in risk for major malformations, congenital heart defects, or limb reduction defects.[273,274]

Women who become pregnant while taking oral contraceptives or women who inadvertently take birth control pills early in pregnancy should be advised that the risk of a significant congenital anomaly is no greater than the general rate of 2–3%. This recommendation can be extended to those pregnant woman who have been exposed to a progestational agent such as medroxyprogesterone acetate or 17-hydroxyprogesterone caproate.[275,276]

Reproduction After Discontinuing Oral Contraception

Fertility. The early reports from the British prospective studies indicated that former users of oral contraception had a delay in achieving pregnancy. In the Oxford Family Planning Association study, former use had an effect on fertility for up to 42 months in nulligravid women and for up to 30 months in multigravid women.[277] Presumably, the delay is due to lingering suppression of the hypothalamic-pituitary reproductive system.

A later analysis of the Oxford data indicated that the delay was concentrated in women age 30–34 who had never given birth.[278] At 48 months, 82% of these women had given birth compared with 89% of users of other contraceptive methods, not a big difference. No effect was observed in women younger than 30 or in women who had previously given birth. Childless women age 25–29 experienced some delay in return to fertility, but by 48 months, 91% had given birth compared with 92% in users of other methods. It should be noted that after 72 months the proportions of women who remained undelivered were the same in both groups of women.

This delay has been observed in the United States as well. In the Boston area, the interval from cessation of contraception to conception was 13 months or greater for 24.8% of prior oral contraceptive users compared with 10.6% for former users of all other methods (12.4% for intrauterine device users, 8.5% for diaphragm uses, and 11.9% for other methods).[279] Oral contraceptive users had a lower monthly percentage of conceptions for the first 3 months, and somewhat lower percentage from 4 to 10 months. It took 24 months for 90% of previous oral contraceptive users to become pregnant, 14 months for IUD users, and 10 months for diaphragm users. Similar findings in Connecticut indicate that this delay lasts at least a year, and the effect is greater with higher dose preparations.[280] Despite this delay, there is no evidence that infertility is increased by the use of oral contraception. In fact, in young women, previous oral contraceptive use is associated with a lower risk of primary infertility.[281]

Spontaneous Miscarriage. There is no increase in the incidence of spontaneous miscarriage in pregnancies after the cessation of oral contraception. Indeed, the rate of spontaneous miscarriages and stillbirths is slightly less in former pill users, about 1% less for spontaneous miscarriages and 0.3% less for stillbirths.[282] A protective effect of previous oral contraceptive use against spontaneous miscarriage has been observed to be more apparent in women who become pregnant after age 30.[283]

Pregnancy Outcome. There is no evidence that oral contraceptives cause changes in individual germ cells that would yield an abnormal child at a later time.[271] There is no increase in the number of abnormal children born to former oral contraceptive u
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Breastfeeding

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ıere is no evidence that oral contraceptives germ cells that would yield an abnormal child increase in the number of abnormal children born to former oral contraceptive users, and there is no change in the sex ratio (a sign of sex-linked recessive mutations).[282,284] These observations are not altered when analyzed for duration of use. Initial observations that women who had previously used oral contraception had an increase in chromosomally abnormal fetuses have not been confirmed. Furthermore, as noted above, there is no increase in the miscarriage rate after discontinuation, something one would expect if oral contraceptives induce chromosomal abnormalities because these are the principal cause of spontaneous miscarriage.

In a 3-year follow-up of children whose mothers used oral contraceptives prior to conception, no differences could be detected in weight, anemia, intelligence, or development.[285] Former pill users have no increased risks for perinatal morbidity or mortality, prematurity, or low birth weight.[286,287] Dizygous twinning has been observed to be nearly two-fold (1.6% versus 1.0%) increased in women who conceive soon after cessation of oral contraception.[282] This effect was greater with longer duration of use.

The only reason (and it is a good one) to recommend that women defer attempts to conceive for a month or two after stopping the pill is to improve the accuracy of gestational dating by allowing accurate identification of the last menstrual period.

Breastfeeding

Oral contraception has been demonstrated to diminish the quantity and quality of lactation in postpartum women. Women who use oral contraception have a lower incidence of breastfeeding after the 6th postpartum month, regardless of whether oral contraception is started at the first, second, or third postpartum month.[288-290] Also of concern is the potential hazard of transfer of contraceptive steroids to the infant (a significant amount of the progestational component is transferred into breast milk);[291] however, no adverse effects have thus far been identified.

In adequately nourished breastfeeding women, no impairment of infant growth can be detected; presumably, compensation is achieved either through supplementary feedings or increased suckling.[292] In an 8-year follow-up study of children breastfed by mothers using oral contraceptives, no effect could be detected on diseases, intelligence, or psychological behavior.[293] This study also found that mothers on birth control pills lactated a significantly shorter period of time than controls, a mean of 3.7 months versus 4.6 months in controls.

Because the above considerations indicate that oral contraception shortens the duration of breastfeeding, it is worthwhile to consider the contraceptive

effectiveness of lactation. The contraceptive effectiveness of lactation, i.e., the length of the interval between births, depends on the level of nutrition of the mother (if low, the longer the contraceptive interval), the intensity of suckling, and the extent to which supplemental food is added to the infant diet. If suckling intensity and/or frequency is diminished, contraceptive effect is reduced. Only amenorrheic women who exclusively breastfeed (full breastfeeding) at regular intervals, including nighttime, during the first 6 months have the contraceptive protection equivalent to that provided by oral contraception (98% efficacy); with menstruation or after 6 months, the chance of ovulation increases.[294,295] With full or nearly full breastfeeding, approximately 70% of women remain amenorrheic through 6 months and only 37% through one year; nevertheless with exclusive breastfeeding, the contraceptive efficacy at one year is high, at 92%.[295] Fully breastfeeding women commonly have some vaginal bleeding or spotting in the first 8 postpartum weeks, but this bleeding is not due to ovulation.[296]

Supplemental feeding increases the chance of ovulation (and pregnancy) even in amenorrheic women.[297] Total protection is achieved by the exclusively breastfeeding woman for a duration of only 10 weeks.[296] Half of women studied who are not fully breastfeeding ovulate before the 6th week, the time of the traditional postpartum visit; a visit during the 3rd postpartum week is strongly recommended for contraceptive counseling.

It is apparent that although lactation provides a contraceptive effect, it is variable and not reliable for every woman. Furthermore, because frequent suckling is required to maintain full milk production, women who use oral contraception and also breastfeed less frequently (e.g., because they work outside their homes) have two reasons for decreased milk volume. This combination can make it especially difficult to continue nursing.

Initiation of Oral Contraception in the Postpartum Period

Women need contraception early in the postpartum period. In a careful study of 22 postpartum, nonbreastfeeding women, the mean time from delivery to the first menses was 45 ± 10.1 days, and no woman ovulated before 25 days after delivery.[298] A high proportion of the first cycles (81.8%) and the subsequent cycles (37%) were not normal; however, this is certainly not predictable in individual women. Others have documented a mean delay of 7 weeks before resumption of ovulation, but half of the women studied ovulated before the 6th week, the time of the traditional postpartum visit. *The obstetrical tradition of scheduling the postpartum visit at 6 weeks should be changed. A 3-week visit would be more productive in avoiding postpartum surprises.*

The Rule of 3's:

In the presence of FULL breastfe
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method should begin during the 3

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Other Considerations

Prolactin-Secreting Adenoma

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A 3-week visit would be more productive in

The Rule of 3's:

In the presence of FULL breastfeeding, a contraceptive method should be used beginning in the *3rd postpartum month.*

With PARTIAL breastfeeding or NO breastfeeding, a contraceptive method should begin during the *3rd postpartum week.*

After the termination of a pregnancy of less than 12 weeks, oral contraception can be started immediately. After a pregnancy of 12 or more weeks, oral contraception has traditionally been started 2 weeks after delivery to avoid an increased risk of thrombosis during the initial postpartum period. We believe that oral contraception can be started immediately after a second-trimester abortion or premature delivery.

Because of the concerns regarding the impact of oral contraceptives on breastfeeding, a useful alternative is to combine the contraceptive effect of lactation with the progestin-only minipill. This low dose of progestin has no negative impact on breast milk, and some studies document an increase in milk quantity and nutritional quality.[299] Highly effective (near total) protection can be achieved with the combination of lactation and the minipill. Because of the slight positive impact on lactation, the minipill can be started soon after delivery, but at least a 3-day postpartum delay is recommended to allow the decline in pregnancy levels of estrogen and progesterone and the establishment of lactation.[300] In addition, use of the progestin-only minipill has been reported to be associated with a 3-fold increased risk of diabetes mellitus in lactating women with recent gestational diabetes.[154] This special group of women should consider other methods of contraception.

Other Considerations

Prolactin-Secreting Adenomas

Because estrogen is known to stimulate prolactin secretion and to cause hypertrophy of the pituitary lactotrophs, it is appropriate to be concerned over a possible relationship between oral contraception and prolactin-secreting adenomas. Case-control studies have uniformly concluded that no such relationship exists.[301,302] Data from both the Royal College of General Practitioners and the Oxford–Family Planning Association studies indicated no increase in the incidence of pituitary adenomas.[263,303] Previous use of oral contraceptives is not related to the size of prolactinomas at presentation and diagnosis.[303,304] Oral contraception can be prescribed to patients with pituitary microadenomas without fear of subsequent tumor growth.[305,306] *We have routinely prescribed oral contraception to patients with pituitary microadenomas and have never observed evidence of tumor growth.*

Postpill Amenorrhea

The approximate incidence of "postpill amenorrhea" is 0.7–0.8%, which is equal to the incidence of spontaneous secondary amenorrhea,[257,307,308] and there is no evidence to support the idea that oral contraception causes secondary amenorrhea. If a cause-and-effect relationship exists between oral contraception and subsequent amenorrhea, one would expect the incidence of infertility to be increased after a given population discontinues use of oral contraception. In those women who discontinue oral contraception in order to get pregnant, 50% conceive by 3 months, and after 2 years, a maximum of 15% of nulliparous women and 7% of parous women fail to conceive.[287] rates comparable with those quoted for the prevalence of spontaneous infertility. Attempts to document a cause-and-effect relationship between oral contraceptive use and secondary amenorrhea have failed.[309] Although patients with this problem come more quickly to our attention because of previous oral contraceptive use and follow-up, there is no cause-and-effect relationship. Women who have not resumed menstrual function within 12 months should be evaluated as any other patient with secondary amenorrhea.

Use During Puberty

Should oral contraception be advised for a young woman with irregular menses and oligoovulation or anovulation? The fear of subsequent infertility should not be a deterrent to providing appropriate contraception. Women who have irregular menstrual periods are more likely to develop secondary amenorrhea whether they use oral contraception or not. The possibility of subsequent secondary amenorrhea is less of a risk and a less urgent problem for a young woman than leaving her unprotected. The need for contraception takes precedence

There is no evidence that the use of oral contraceptives in the pubertal, sexually active girl impairs growth and development of the reproductive system.[281] Again, the most important concern is and should be the prevention of an unwanted pregnancy. For most teenagers, oral contraception, dispensed in the 28-day package for better compliance, is the contraceptive method of choice.

Eye Diseases

In the 1960s and 1970s, there were numerous anecdotal reports of eye disorders in women using oral contraception. An analysis of the two large British cohort studies (the Royal College of General Practitioners' Study and the Oxford Family Planning Association Study) could find no increase in risk for the following conditions: conjunctivitis, keratitis, iritis, lacrimal disease, strabismus, cataract, glaucoma, and retinal detachment.[310] Retinal vascular lesions were slightly more common in recent users of oral contraception, but this finding did not reach statistica
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Multiple Sclerosis

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Infections and Oral Contraceptior

Viral STDs

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Bacterial STDs

Sexually transmitted diseases (STD
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: "postpill amenorrhea" is 0.7–0.8%, which
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ause-and-effect relationship exists between
ient amenorrhea, one would expect the inci-
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those women who discontinue oral contra-
nt, 50% conceive by 3 months, and after 2
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tes comparable with those quoted for the
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this finding did not reach statistical significance. Contact lens may be less well tolerated, requiring more frequent use of wetting solutions.

Multiple Sclerosis

There is no evidence in two cohort studies (the Oxford-Family Planning Association Study and the Royal College of General Practitioners' Oral Contraceptive Study) that there is any effect of oral contraceptive use on the risk or course of multiple sclerosis.[311,312]

Infections and Oral Contraception

Viral STDs

The viral STDs include human immunodeficiency virus (HIV), human papillomavirus (HPV), herpes simplex virus (HSV), and hepatitis B (HBV). At the present time, no known associations exist between oral contraception and the viral STDs. Thus far, most studies have found no association between oral contraceptive use and HIV seropositivity, and some have indicated a protective effect.[313-316] The studies are handicapped by great variation and often do not reach statistical significance. *For women not in a stable, monogamous relationship, a dual approach is recommended, combining the contraceptive efficacy and protection against PID offered by oral contraception with the use of a barrier method (and spermicide) for prevention of viral STDs.*

Bacterial STDs

Sexually transmitted diseases (STDs) are one of the most common public health problems in the United States. It was estimated in 1995, that 7.6% of reproductive age U.S. women had been treated for pelvic inflammatory disease (PID).[317] This upper genital tract infection is usually a consequence of STDs. The best estimate of subsequent tubal infertility is derived from an excellent Swedish report; approximately 12% after one episode of PID, 23% after 2 episodes, and 54% after 3 episodes.[318] Because pelvic infection is the single greatest threat to the reproductive future of a young woman, the now recognized protection offered by oral contraception against pelvic inflammatory disease is highly important.[319-321] *The risk of hospitalization for PID is reduced by approximately 50–60%, but at least 12 months of use are necessary, and the protection is limited to current users.*[319,322] Furthermore, if a patient does get a pelvic infection, the severity of the salpingitis found at laparoscopy is decreased.[323,324] The mechanism of this protection remains unknown. Speculation includes thickening of the cervical mucus to prevent movement of pathogens and bacteria-laden sperm into the uterus and tubes, and decreased menstrual bleeding, reducing movement of pathogens into the tubes as well as a reduction in "culture medium."

The argument has been made that this protection is limited to gonococcal disease, and chlamydial infections may even be enhanced. Fifteen of 17 published studies by 1985 reported a positive association of oral contraceptives with lower genital tract chlamydial cervicitis.[325] Because lower genital tract infections caused by chlamydia are on the rise (now the most prevalent bacterial STD in the U.S.) and the rate of hospitalization for PID is also increased, it is worthwhile for both patients and clinicians to be alert for symptoms of cervicitis or salpingitis in women on oral contraception who are at high risk of sexually transmitted disease (multiple sexual partners, a history of STD, or cervical discharge). The mechanism for the association between chlamydial cervicitis and oral contraceptives may be the well recognized extension of the columnar epithelium from the endocervix out over the cervix (ectropion) that occurs with oral contraceptive use.[326] This ectropion may allow a more effective collection of cervical specimens for culture, thus introducing detection bias into the epidemiologic studies.

Despite this potential relationship between oral contraception and chlamydial infections, we emphasize that there is no evidence for oral contraceptives increasing the incidence of tubal infertility.[327] In fact, a case-control study indicated that oral contraceptive users with chlamydia infection are protected against symptomatic PID.[328] A case-control study has suggested that oral contraceptive users are more likely to harbor unrecognized endometritis, and that this would explain the discrepancy between the observed rates of lower and upper tract infection.[329] However, this would not explain the lack of an association between oral contraceptive use and tubal infertility. Thus, the influence of oral contraception on the upper reproductive tract may be different than on the lower tract. These observations on fertility are derived mostly, if not totally, from women using oral contraceptives containing 50 μg of estrogen. The continued progestin dominance of the lower dose formulations, however, should produce the same protective effect, and evidence indicates that this is so.[322]

Other Infections

In the British prospective studies of high-dose oral contraceptives, urinary tract infections were increased in users of oral contraception by 20%, and a correlation was noted with estrogen dose. An increased incidence of cervicitis was also reported, an effect related to the progestin dose. The incidence of cervicitis increased with the length of time the pill was used, from no higher after 6 months to 3 times higher by the 6th year of use. A significant increase in a variety of viral diseases, e.g., chickenpox, was observed, suggesting steroid effects on the immune system. The prevalence of these effects with low-dose oral contraception is unknown.

Oral contraception appears to protect against bacterial vaginosis and infections with *Trichomonas*.[330,331] Evidence is lacking to convincingly implicate

oral contraception with vagina
however, clinical experience is son
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Patient Management

Absolute Contraindications to th

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6. Smokers over the age of
7. Elevated blood pressure.

Relative Contraindications Requ
Informed Consent

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oral contraception is unknown.

protect against bacterial vaginosis and infec-
Evidence is lacking to convincingly implicate

oral contraception with vaginal infections with *Candida* species;[330] however, clinical experience is sometimes impressive when recurrence and cure repeatedly follow use and discontinuation of oral contraception.

Patient Management

Absolute Contraindications to the Use of Oral Contraception

1. Thrombophlebitis, thromboembolic disorders (including a close family history, parent or sibling, suggestive of an inherited susceptibility for venous thrombosis), cerebral vascular disease, coronary occlusion, or a past history of these conditions, or conditions predisposing to these problems.
2. Markedly impaired liver function. Steroid hormones are contraindicated in patients with hepatitis until liver function tests return to normal.
3. Known or suspected breast cancer.
4. Undiagnosed abnormal vaginal bleeding.
5. Known or suspected pregnancy.
6. Smokers over the age of 35.
7. Elevated blood pressure.

Relative Contraindications Requiring Clinical Judgment and Informed Consent

1. Migraine headaches. In retrospective studies of low-dose pills, it is not clear whether migraine headaches are associated with an increased risk of stroke. Some women report an improvement in their headaches, and in our view, a trial of the lowest dose oral contraceptives is warranted. Oral contraceptives should be avoided in women who have migraine with aura, or if additional stroke factors are present (older age, smoking, hypertension).[332]
2. Hypertension. A woman under 35 who is otherwise healthy and whose blood pressure is well controlled by medication can elect to use oral contraception. We recommend the use of the lowest estrogen dose products.
3. Uterine leiomyoma. Uterine fibroids are not a contraindication with low-dose oral contraceptives. There is evidence that the risk of leiomyomas was decreased by 31% in women who used higher dose oral contraception for 10 years.[333] Case-control studies with lower dose oral contraceptives have found neither a decrease nor an increase in risk, although the Nurses' Health Study reported a slightly increased risk when oral contraceptives were first used in early teenage years.[334-336] However, one case-control study indicated a decreasing risk of uterine fibroids with increasing

duration of oral contraceptive use.[337] The administration of low-dose oral contraceptives to women with leiomyomata does not stimulate fibroid growth, and is associated with a reduction in menstrual bleeding.[338]

4. Gestational diabetes. Low-dose formulations do not produce a diabetic glucose tolerance response in women with previous gestational diabetes, and there is no evidence that combined oral contraceptives increase the incidence of overt diabetes mellitus.[153,154] We believe that women with previous gestational diabetes can use combined oral contraceptives with annual assessment of the fasting glucose level.
5. Elective surgery. The recommendation that oral contraception should be discontinued 4 weeks before elective major surgery to avoid an increased risk of postoperative thrombosis is based on data derived from high-dose pills. If possible, it is safer to follow this recommendation when a period of immobilization is to be expected. With major surgery and immobilization, prophylactic treatment should be considered for a current or recent user of oral contraceptives. It is prudent to maintain contraception right up to the performance of a sterilization procedure or other brief surgical procedures as these short, outpatient operations carry very little, if any, risk.
6. Epilepsy. Oral contraceptives do not exacerbate epilepsy, and in some women, improvement in seizure control has occurred.[339] Antiepileptic drugs, however, may decrease the effectiveness of oral contraception.
7. Obstructive jaundice in pregnancy. Not all patients with this history will develop jaundice on oral contraception, especially with the low-dose formulations.
8. Sickle cell disease or sickle C disease. Patients with sickle cell trait can use oral contraception. The risk of thrombosis in women with sickle cell disease or sickle C disease is theoretical (and medicolegal). We believe effective protection against pregnancy in these patients warrants the use of low-dose oral contraception.
9. Diabetes mellitus. Effective prevention of pregnancy outweighs the small risk of complicating vascular disease in diabetic women who are under age 35 and otherwise healthy.
10. Gallbladder disease. Oral contraceptives do not cause gallstones, but may accelerate the emergence of symptoms when gallstones are already present.

Clinical Decisions

Surveillance

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Diabetic women.

Choice of Pill

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Clinical Decisions

Surveillance

In view of the increased safety of low-dose preparations for healthy young women with no risk factors, such patients need be seen only every 12 months for exclusion of problems by history, measurement of the blood pressure, urinalysis, breast examination, palpation of the liver, and pelvic examination with Pap smear. Women with risk factors should be seen every 6 months by appropriately trained personnel for screening of problems by history and blood pressure measurement. Breast and pelvic examinations are necessary only yearly. It is worth emphasizing that better continuation is achieved by reassessing new users within 1–2 months. It is at this time that subtle fears and unvoiced concerns need to be confronted and resolved.

Oral contraception is safer than most people think it is, and the low-dose preparations are extremely safe. Health care providers should make a significant effort to get this message to our patients (and our colleagues). We must make sure our patients receive adequate counseling, either from ourselves or our professional staff. The major reason why patients discontinue oral contraception is fear of side effects.[340] Let's take time to put the risks into proper perspective, and to emphasize the benefits as well as the risks.

Laboratory surveillance should be used only when indicated. Routine biochemical measurements fail to yield sufficient information to warrant the expense. Assessing the cholesterol-lipoprotein profile and carbohydrate metabolism should follow the same guidelines applied to all patients, users and nonusers of contraception. The following is a useful guide as to who should receive blood screening tests for glucose, lipids, and lipoproteins:

Young women, at least once.
Women 35 years or older.
Women with a strong family history of heart disease, diabetes mellitus, or hypertension.
Women with gestational diabetes mellitus.
Women with xanthomatosis.
Obese women.
Diabetic women.

Choice of Pill

The therapeutic principle remains: utilize the formulations that give effective contraception and the greatest margin of safety. You and your patients are urged to choose a low-dose preparation containing less than 50 μg of estrogen, combined with low doses of new or old progestins. Current data support the view that there is greater safety with preparations containing less than 50 μg of estrogen. The arguments in this chapter indicate that all

patients should begin oral contraception with low-dose products, and that patients on higher dose oral contraception should be changed to the low-dose preparations. Stepping down to a lower dose can be accomplished immediately with no adverse reactions such as increased bleeding or failure of contraception.

The pharmacologic effects in animals of various formulations have been used as a basis for therapeutic recommendations in selecting the optimal oral contraceptive pill. *These recommendations (tailor-making the pill to the patient) have not been supported by appropriately controlled clinical trials. All too often this leads to the prescribing of a pill of excessive dosage with its attendant increased risk of serious side effects.* It is worth repeating our earlier comments on potency. Oral contraceptive potency (specifically progestin potency) is no longer a consideration when it comes to prescribing birth control pills. The potency of the various progestins has been accounted for by appropriate adjustments of dose. Clinical advice based on potency is an artificial exercise that has not stood the test of time. The biologic effect of the various progestational components in current low-dose oral contraceptives is approximately the same. Our progress in lowering the doses of the steroids contained in oral contraceptives has yielded products with little serious differences.

Pill Taking

Effective contraception is present during the first cycle of pill use, provided the pills are started no later than the 5th day of the cycle, and no pills are missed. Thus, starting oral contraception on the first day of menses ensures immediate protection. In the United States, most clinicians and patients prefer the Sunday start packages, beginning on the first Sunday following menstruation. This can be easier to remember, and it usually avoids menstrual bleeding on weekends. It is probable, but not totally certain, that even if a dominant follicle should emerge in occasional patients after a Sunday start, an LH surge and ovulation would still be prevented.[41] Some clinicians prefer to advise patients to use added protection in the first week of use.

Occasionally patients would like to postpone a menstrual period; e.g., for a wedding, holiday, or vacation. This can be easily achieved by omitting the 7-day hormone-free interval. Simply start a new package of pills the next day after finishing the series of 21 pills in the previous package. Remember, when using a 28-pill package, the patient would start a new package after using the 21 *active* pills.

There is no rationale for recommending a pill-free interval "to rest." The serious side effects are not eliminated by pill-free intervals. This practice all too often results in unwanted pregnancies.

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What To Do When Pills Are M
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How important is it to take the oral contraceptive at the same time every day? Although not well studied, there is reason to believe precise pill taking minimizes breakthrough bleeding. In addition, compliance is improved by a fixed schedule that is habit-forming.

What To Do When Pills Are Missed. Irregular pill taking is a common occurrence. Using an electronic monitoring device to measure compliance, it was apparent that consistency of pill taking is even worse than patients report; only 33% of women were documented to have missed no pills in cycle 1, and by cycle 3, about one-third of the women missed 3 or more pills per package with many episodes of consecutive days of missed pills.[342] These data indicate that women become less careful over time, emphasizing the importance of repeatedly reviewing with patients what to do when pills are missed.

If a woman misses 1 pill, she should take that pill as soon as she remembers and take the next pill as usual. No backup is needed.

If she misses 2 pills in the first two weeks, she should take two pills on each of the next two days; it is unlikely that a back-up method is needed, but the official consensus is to recommend backup for the next 7 days.

If 2 pills are missed in the third week, or if more than 2 active pills are missed at any time, another form of contraception should be used as backup immediately and for 7 days; if a Sunday starter, keep taking a pill every day until Sunday, and on Sunday start a new package; if a non-Sunday starter, start a new package the same day.