

MASTER CLASS

Multiples and Mortality

Infant mortality is a problem of major concern to the industrialized world, and it continues to be an important marker for assessing the health and welfare of countries. Despite the fact that the United States spends 15% of its gross national product on health care, it ranks 21st in the world in its infant mortality rate, below countries that spend much less.



BY E. ALBERT REECE, M.D., PH.D.

The causes of our high infant mortality rate are complex and multifaceted, and we will not attempt in Master Class to address them all. We will, however, address one component: the rising

rate of multiple gestations.

Between 1996 and 2002, multiple births in the United States increased more than 22%, from 2.7% to 3.3% of all live births. In 2002, the preterm birth rate among multiple deliveries was approximately 60%, six times higher than the preterm birth rate among singleton births, according to the National Center for Health Statistics. In its preliminary report on births for 2004, the NCHS said that increases in multiple births "have strongly influenced recent upswings" in preterm and low-birth-weight births.

Assisted reproduction plays a role. There is evidence that the percentage of higher-order pregnancies resulting from assisted reproductive technology has been decreasing, but multiple pregnancies with ART remain a problem.

One has to ask whether, with greater care and improved protocols in assisted reproduction, we wouldn't be able to address the continuing effect that infertility treatment has on the rate of multiple pregnancies.

It is a subject that has caught national attention and has been addressed in many quarters. The Society for Assisted Reproductive Technology, an affiliate of the American Society for Reproductive Medicine has examined the issue and made recommendations for improved practice (see sidebar).

My guest professor this month is Dr. Aida Shanti, who is the director of the division of reproductive endocrinology and infertility at the University of Arkansas, Little Rock. She will address these contemporary recommendations and explore how such guidance can potentially have a real impact. ■

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The Art of Controlling Multiples

The most common complication of assisted reproductive technologies is multiple gestation, particularly triplet and higher-order pregnancy. As we all know, multiple gestation leads to an increased risk of complications in both the fetuses and the mother.

Ovulation induction results in a 20% increase in multiples, the majority of which are twins. In vitro fertilization (IVF) results in a 40% increase in multiples; 32% of these are twins. Unfortunately, we're not making progress in decreasing these rates. Knowing that most patients look at two things—pregnancy rates and cost—when they choose an infertility clinic, many competitive clinics are implanting more than the recommended number of embryos in order to achieve the highest pregnancy rates.

At any opportunity along the spectrum of general to specialized ob.gyn. care, we need to educate and encourage patients to look beyond the pregnancy rates and instead focus on the numbers of embryos transferred and the implantation rates. If we are successful, we could probably make some progress in decreasing the multiple pregnancies associated with assisted reproductive technology (ART). At a basic level, we can ensure that infertility evaluations and treatments are timely, thorough, individualized, and well explained to our patients. In doing so, we will provide good care, and perhaps we can keep the patients' feelings of desperation, which are valid and understandable, somewhat in check.

Infertility Diagnosis, Work-Up

A diagnosis of infertility is usually made when couples have been trying for more than 1 year to become pregnant. Fecundity drops after the age of 27 years, more significantly after the age of 35 years, and dramatically after 40 years. I recommend that, for women older than age 35, we not wait until a year is up, but rather begin a basic infertility work-up after 6 months. These women deserve a more aggressive approach.

After 6 months in a patient who is older than 35, or after 1 year in younger patients, we should provide the basics: blood testing to check ovarian reserve, a hysterosalpingogram to ensure that the uterus is normal and that tubes are patent, and a semen analysis. It is important to use an infertility laboratory for the semen analysis. Regular laboratories usually do not check for Kruger morphology, which is critical.

Examinations should include a check on thyroid function. Approximately 2% of women in the reproductive age group have hypothyroidism or subclinical hypothyroidism, which can affect fertility but is treatable. It's also important to know if a woman has had endometriosis

or previous pelvic surgeries. Diagnostic operative laparoscopies can be performed by general ob.gyns. to rule out or treat endometriosis if they feel comfortable doing the procedure.

When you take the patient's history, certain questions—such as "When did your mother enter menopause?"—are critical because they may lead to an early diagnosis and, appropriately, to a more aggressive treatment approach. Perimenopause—during which time ovarian reserve is compromised—usually begins 5-10 years earlier than menopause. If I know that a patient's mother went into menopause at age 40, I will work through infertility treatment more quickly, as I would with older patients. Testing for ovarian reserve in women younger than 35 is too often dismissed. It shouldn't be.

It's well known that smoking and exposure to secondhand smoke decrease fecundity. They increase rates of abnormal ovarian reserve, oocyte atresia, and miscarriage. In IVF patients, they increase IVF failure and the number of IVF cycles needed to conceive. One prospective study showed that for each year of active smoking, there is a 9% decrease in the success of ART. Smoking also affects the sperm cell. Even if sperm

look normal, smoking has been shown to lead to damage of the genetic material, causing abnormalities in sperm count, motility, morphology, and function. The good news is that many of the effects of smoking are reversible. The duration of smoking may affect the degree of reversibility, but certainly we have the opportunity to improve fecundity and the success of fertility treatment if we identify smokers and help them with cessation.

Starting Treatment

If all of these basic work-ups are normal and the patient is younger than 32 years of age we can proceed with a trial of Clomid (clomiphene citrate). I recommend treatment with Clomid for 3-4 months, because most patients who will achieve pregnancy will do so within the first three to four cycles. After several months, the chances of a pregnancy are significantly decreased, and other treatment options need to be considered. Treatment with Clomid alone for longer than 6 months really isn't fair to the patient, and neither is the use of Clomid in patients older than age 37.

Keep in mind that even in small doses, Clomid can have a negative effect on

the endometrium. I recommend ultrasonography to check for normal follicular development and to check the lining. If the lining is thin, the implantation rate will be low.

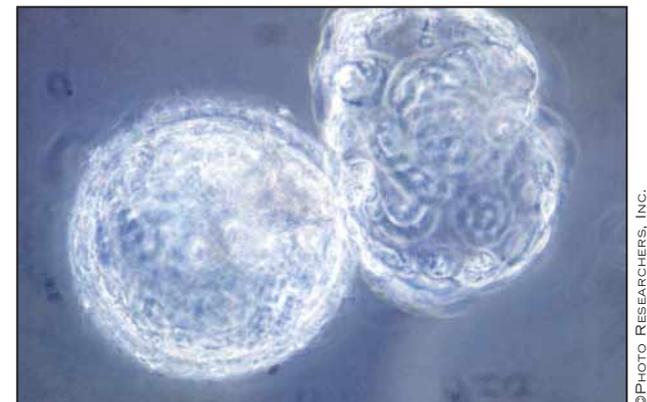
You may decide, after 2 months of Clomid treatment, to try another two to three cycles along with intrauterine insemination. You may also decide that ovulation induction or IVF is more appropriate.

If you are a general ob.gyn. who is performing superovulation induction with hormones, my advice is to judge your comfort level with hormonal stimulation, and to establish and maintain a good relationship with an infertility clinic.

Controlling Multiples

With both ovulation induction/enhancement and IVF, there are ways to control the rate of multiple gestations. Your degree of control is less with ovarian stimulation and intrauterine insemination, but you do have some control and it is important to proceed cautiously. If you see that a patient has more than two or three mature follicles and that her estradiol is elevated above the appropriate level at day 3, it's often best to cancel that cycle. The patient may prefer to proceed knowing the risks, but at least she is being counseled.

The guidelines of the Society for Assisted Reproductive Technology and the American Society for Reproductive Med-



A hatching blastocyst shown 6 days after fertilization, ready to begin implanting into the endometrium.

icine are age based, and are meant to help determine the appropriate number of cleavage-stage embryos to transfer.

According to the guidelines, no more than two good-quality embryos should be transferred in patients under age 35. If the embryos are not necessarily of good quality as judged by morphologic criteria, I believe a third embryo can be considered; but in no case should more than three be transferred.

The guidelines also say that for patients with a favorable prognosis, such as those with good-quality embryos or previous successes with IVF, consideration should be given to transferring only a single embryo. I do believe that if embryos are of excellent quality and the patient is young, and especially if the embryos can be cultured to the blastocyst stage and

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then transferred, it is worth pushing for a single embryo transfer, which dramatically decreases the risk of multiple births.

For patients aged 35-37, the guidelines are that no more than two good-quality embryos—and no more than three in any other case—should be transferred. Patients who are 38-40 years old should receive no more than three good-quality embryos, and no more than four in any other case.

For patients under age 40, the guidelines state that no more than five embryos should be transferred. And I would recommend that no more than four be transferred in many cases. All these numbers should be decreased, of course, when embryos are transferred as blastocysts.

European specialists routinely transfer no more than two embryos. They usually transfer embryos at the more advanced blastocyst stage, and because they work in systems of socialized medicine, it doesn't matter whether the patient gets pregnant after just one cycle or more. In the United

States, a cycle costs \$10,000-\$15,000, and patients want to get pregnant the first time.

I encourage my patients who have come for ART consultations to visit the neonatal ICU. The visits give them some perspective on the complications associated with higher-order births. I will often raise the issue of selective fetal reduction—posing it as theoretical—when I see a patient for an IVF consultation. Asking patients how they would feel about this possibility prompts them to think and be prepared for it. It also impresses upon patients that the risk of multiples is real if too many embryos are implanted. Selective fetal reduction is an option, but it has its own

complications and risks. We always prefer not to reach that point.

One of the most important things we can do to reduce the rate of multiple gestations is to ensure that we work with an experienced laboratory staffed with excellent embryologists and an excellent director. Certain elements of the visual inspection of embryos are standard and reliably consistent, whereas other elements are more subjective. To some extent, each laboratory director has his or her own way of grading embryos, so our attentiveness to outcomes is critical.

Preimplantation genetic diagnosis (PGD) is typically not performed unless a patient

requests it. It is recommended for patients who are older or who have certain chromosomal or genetic abnormalities. It is also recommended in some patients with repeat pregnancy wastage. Single cells can be sent out on day 3 of embryo culture and results can be obtained within 24 hours, in time for embryo transfer at day 5.

The other step we can routinely take is to encourage our patients to thoroughly examine the Society for Assisted Reproductive Technology's clinic-specific IVF data. Asking patients to step back and look at more than pregnancy rates could be the biggest key to reducing multiple gestations with IVF.

Age-Based Embryo Transfer Guidelines

► In patients under the age of 35, no more than two embryos should be transferred in the absence of extraordinary circumstances. For patients with the most favorable prognosis, consideration should be given to transferring only a single embryo. Patients having the most favorable prognosis include those who are undergoing their first cycle of IVF, have good-quality embryos as judged by morphologic criteria, and have excess of embryos of sufficient quality to warrant cryopreservation. Patients who have had previous success with IVF should also be considered in the most favorable prognostic category.

► For patients between 35 and 37 years of age having a more favorable prognosis, no more than two embryos should be transferred. All others in this age group should have no more than three embryos transferred.

► For patients between 38 and 40 years of age, no more than four embryos should be transferred. For patients in this age group having a more favorable prognosis, consideration should be given to transfer of no more than three embryos.

► For most patients greater than 40 years of age, no more than five embryos should be transferred.

► For patients with two or more previous failed IVF cycles and those having a less favorable prognosis, additional embryos may be transferred according to individual circumstances after appropriate consultation.

► In donor egg cycles, the donor's age should determine the appropriate number of embryos to transfer.

Since all oocytes may not fertilize when GIFT is performed, one more oocyte than embryo may be transferred for each prognostic category.



Brief Summary. See full package brochure for complete prescribing information.

Patients should be counseled that this product does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.

CONTRAINDICATIONS: Oral contraceptives should not be used in women who currently have the following conditions: • Thrombophlebitis or thromboembolic disorders • A past history of deep vein thrombophlebitis or thromboembolic disorders • Cerebrovascular or coronary artery disease (current or history) • Valvular heart disease with thrombotic complications • Uncontrolled hypertension • Diabetes with vascular involvement • Headaches with focal neurological symptoms • Major surgery with prolonged immobilization • Known or suspected carcinoma of the breast or personal history of breast cancer • Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia • Undiagnosed abnormal genital bleeding • Cholestatic jaundice of pregnancy or jaundice with prior pill use • Hepatic adenomas or carcinomas, or active liver disease • Known or suspected pregnancy • Hypersensitivity to any component of this product.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension. The risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as certain inherited thrombophilias, hypertension, hyperlipidemias, obesity and diabetes. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks. The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestagens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestagens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

- Thromboembolic Disorders and Other Vascular Problems:** Use of Seasonale® provides women with hormonal exposure on a yearly basis that compares favorably with that of women who do not use oral contraceptives. However, the relative risk of venous thrombosis in women who use oral contraceptives is increased (see **WARNINGS**). The severity and number of risk factors increase heart disease risk. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.
 - Myocardial Infarction:** An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30. Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestagens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hypercoagulability. Oral contraceptives have been shown to increase blood pressure in some users (see section on **WARNINGS**). The severity and number of risk factors increase heart disease risk. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.
 - Thromboembolism:** An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep vein thrombosis and pulmonary embolism in users of low dose (<50 µg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5-3 per 10,000 woman-years for non-users. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped. A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast-feed.
 - Cerebrovascular Diseases:** Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and embolic), although, in general, the risks are greatest among smokers. The risks are also increased in women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.
 - Dose-Related Risk of Vascular Disease from Oral Contraceptives:** A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which is judged appropriate for the individual patient.
- Persistence of Risk of Vascular Disease:** There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40 to 49 years of age who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.
- Estimates of Mortality from Contraceptive Use:** One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraceptive use. These estimates include the mortality rates associated with the use of oral contraceptives, as well as methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s—but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling. Because of changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.
- Carcinoma of the Reproductive Organs and Breasts:** Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. Although the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combined oral contraceptives (RR=1.24), this excess risk decreases over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use and no consistent relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in non-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between oral contraceptive use and breast cancer and cervical cancers, a cause-and-effect relationship has not been established.
- Hepatic Neoplasia:** Benign hepatic adenomas are associated with oral contraceptive use, although their occurrence is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.
- Ocular Lesions:** There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.
- Oral contraceptive Use Before or During Early Pregnancy:** Because women using Seasonale® will likely have withdrawal bleeding 4 times per year, pregnancy should be ruled out at the time of any missed menstrual period. Oral contraceptive use should be discontinued if pregnancy is confirmed. Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy (see **CONTRAINDICATIONS** section). The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should

- not be used during pregnancy to treat threatened or habitual abortion.
- Gallbladder Disease:** Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestagens.
- Carbohydrate and Lipid Metabolic Effects:** Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hypertriglyceridemia, while lower doses of estrogen cause less glucose intolerance. Progestagens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives. A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS** 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.
- Elevated Blood Pressure:** Women with significant hypertension should not be started on hormonal contraceptive. An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestagens. Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section). For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among past and present users.
- Headache:** The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See **WARNINGS**, 1c.)
- Bleeding Irregularities:** When prescribing Seasonale®, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased intermenstrual bleeding and/or spotting. The clinical trial (SEA301) that compared the efficacy of Seasonale® (91-day cycles) to an equivalent dosage 28-day cycle regimen also assessed intermenstrual bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding (spotting) ≥ 10 consecutive days on oral contraceptives were excluded from the study. More Seasonale® subjects, compared to subjects on the 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.1.8% vs 2.0% for 28-day cycle regimen). Table 4 shows the percentages of women with ≥ 7 days and ≥ 20 days of intermenstrual spotting and/or bleeding in the Seasonale® and the 28-day cycle treatment groups. Total days of bleeding and/or spotting (withdrawal plus intermenstrual) were similar over one year of treatment for Seasonale® subjects and subjects on the 28-day cycle regimen. As in any case of bleeding irregularities, nonhormonal causes should always be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy. In the event of amenorrhea, pregnancy should be ruled out. Some women encounter postpill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

Table 4. Percentage of Subjects with Intermenstrual Bleeding and/or Spotting

Days of intermenstrual bleeding and/or spotting	Percentage of Subjects*	
	Seasonale®	28-day regimen
≥ 7 days	65%	42%
≥ 20 days	35%	15%
≥ 7 days	38%	39%
≥ 20 days	6%	4%

* Based on spotting and/or bleeding on days 1-94 of a 91 day cycle in the Seasonale subjects and days 1-21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.

- PRECAUTIONS**
- Sexually Transmitted Diseases:** Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
 - Physical Examination and Follow-up:** A periodic history and physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs. Some women encounter postpill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.
 - Lipid Disorders:** Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestagens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See **WARNINGS** 1d.) In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.
 - Liver Function:** If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.
 - Fluid Retention:** Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.
 - Emotional Disorders:** Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related.
 - Contact Lenses:** Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.
 - Drug Interactions: Changes in contraceptive effectiveness associated with co-administration of other products**
 - Anti-infective agents and anticonvulsants:** Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.
 - Anti-HIV protease inhibitors:** Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.
 - Herbal products:** Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma levels of estradiol associated with co-administered drugs: Co-administration of atovaquone and certain combination oral contraceptives containing ethinyl estradiol increases AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs: Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of lamazepam, salicylic acid, morphine and clofibrate acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

Interactions with Laboratory Tests: Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:

- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability
- Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay, Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
- Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

Carcinogenesis: See **WARNINGS** section.

Pregnancy: Pregnancy Category X. See **CONTRAINDICATIONS** and **WARNINGS** sections.

Nursing Mothers: Small amounts of oral contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatric Use: Safety and efficacy of Seasonale® tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 and users 16 and older. Use of Seasonale® before menarche is not indicated.

Geriatric Use: Seasonale® tablets have not been studied in women who have reached menopause.

INFORMATION FOR THE PATIENT: See Patient Labeling in the full prescribing information.

ADVERSE REACTIONS: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **WARNINGS** section): • Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Coronial thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas or benign liver tumors. There is evidence of an association between the following conditions and the use of oral contraceptives: • Mesenteric thrombosis • Retinal thrombosis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: • Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema/fluid retention • Melasma/chloasma which may persist • Breast changes: tenderness, enlargement, and secretion • Change in weight or appetite (increase or decrease) • Change in cervical ectropion and secretion • Possible diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine headaches • Rash (allergic) • Mood changes, including depression • Vaginitis, including candidiasis • Change in corneal curvature (contacting) • Intolerance to contact lenses • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms. The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted: • Premenstrual Syndrome • Cataracts • Optic neuritis which may lead to partial or complete loss of vision • Oystis-like syndrome • Headache • Nervousness • Dizziness • Headaches • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Impaired renal function • Hemolytic uremic syndrome • Sudden Chorioid Syndrome • Acne • Ocular changes in blood • Ocular Pancreatitis • Dysmenorrhea.

OVERDOSAGE: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

