

MASTER CLASS

The Changing Approach to Preterm Labor



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Preterm delivery accounts for a significant component of infant mortality in the world. In this, the United States has not been spared; in fact, our country ranks a dismal 21st internationally in infant mortality, with prematurity as a major contributor.

Historically, obstetrics has approached this problem from a therapeutic perspective: If you see a contraction, try to stop it. In large measure, we have been unsuccessful, staving off delivery by a mean of approximately 2 days despite our best efforts. Although this window can allow for the stabilization of patients, arranging for their transfer to

appropriate delivery sites, and initiating required medications, it does not solve the problem of prematurity.

By focusing on the symptoms of premature labor, we have not paused sufficiently to ask basic questions about potential causes and triggers that could help us to develop preventive strategies and targeted treatments for what is clearly a multifactorial syndrome.

This is all changing. The National Institutes of Health saw this as such a priority that it formed a Perinatology Research Branch within the National Institute of Child Health and Development and chose international authority Dr. Roberto Romero to lead it. The Centers for Disease Control and Prevention and the March of Dimes have similarly launched research initiatives and made the prevention of prematurity a priority.

Much progress has been made, with Dr. Romero's team taking a role in the forefront. I am very pleased to welcome Dr. Romero, professor of ob.gyn. at Wayne State University in Detroit and chief of the Perinatology Research Branch at NIH, as this month's guest professor. We will review advances in our understanding of the biology of prematurity as a syndrome and offer potential treatment implications, beginning with a focus on infection.

In September, we will similarly review the other contributors to the prematurity syndrome. ■

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The Role of Infection

Dr. E. Albert Reece: How important is infection as a mechanism of disease in premature labor?

Dr. Roberto Romero: Intrauterine and systemic infections are a leading cause of spontaneous preterm labor and delivery. Indeed, infections and inflammation are the only mechanisms of disease for which a clear causal link with prematurity has been established. Moreover, a clear molecular pathophysiology has been described.

EAR: How frequent is intrauterine infection in spontaneous preterm birth?

RR: It has been estimated that one of every four preterm births occurs to mothers with intraamniotic infection (defined as a positive amniotic fluid culture for microorganisms). Under normal circumstances, the amniotic cavity does not contain bacteria, just as cerebrospinal fluid does not. However, approximately 12% of women presenting with an episode of preterm labor will have a positive amniotic fluid culture for microorganisms.

The organisms most frequently isolated are genital mycoplasmas, particularly *Ureaplasma urealyticum*. Among women with preterm premature rupture of membranes (PROM), one of every three will have a positive amniotic fluid culture for microorganisms at the time of presentation. *U. urealyticum* is the most common microorganism isolated from the amniotic cavity.

EAR: Is there a particular subgroup of women in whom intrauterine infection is more prevalent?

RR: The earlier the gestational age at which a patient presents with preterm labor and intact membranes or preterm PROM, the higher the likelihood of a positive amniotic fluid culture. For example, infection and/or inflammation is present in close to 70% of women presenting around 24 weeks of gestation, but is much rarer in patients presenting after 34 weeks.

EAR: Among women who present with a clinical picture of acute cervical insufficiency, also known as an "incompetent

cervix," how common are infections?

RR: Studies by our group and others indicate that approximately 50% of women presenting with a dilated cervix and bulging membranes before 24 weeks of gestation will have a positive amniotic fluid culture for microorganisms. It is important to realize that rupture of membranes after a cervical cerclage may be the result of a subclinical infectious process, rather than the consequence of cerclage placement.

EAR: What proportion of intrauterine infections manifest themselves with clinical chorioamnionitis?



ROBERTO ROMERO, M.D.

RR: Most intrauterine infections are subclinical in nature. Our work indicates that among women with intraamniotic infection and preterm labor with intact membranes, only 12% will have a positive amniotic fluid culture. Among women with preterm PROM, only 20% will have clinical signs of chorioamnionitis when a positive amniotic fluid culture is present.

EAR: If most infections are subclinical in nature, how can they be detected?

RR: The most accurate method to detect the presence of intraamniotic infection is analysis of amniotic fluid. Amniotic fluid is normally sterile for bacteria. It is possible to isolate some viruses from amniotic fluid, but generally, cultures for viruses are not performed in patients with preterm labor and preterm PROM. Amniotic fluid should be cultured for aerobic and anaerobic bacteria, as well as for *Mycoplasma* species. Detection of mycoplasmas is important, because they are the most common organisms found in the amniotic fluid. Commercially available systems exist that can be implemented in U.S. laboratories.

EAR: The results of cultures take several days to become available. Thus, rapid tests are required to assess the likelihood of infection or inflammation. What tests would you recommend for this purpose?

RR: A positive Gram stain has 99% specificity, but 20% sensitivity in the detection of

intraamniotic infection. The low sensitivity is because the Gram stain cannot detect mycoplasmas since these organisms are too small to be seen with light microscopy. However, the take-home message is that a positive Gram stain is virtually always associated with a positive culture and that false positives are rare. The current approach to the detection of infection and/or inflammation in the amniotic fluid includes other tests that are routinely performed for the analysis of cerebrospinal fluid in all hospitals in the United States. Such tests include a white blood cell (WBC) count of amniotic fluid, and a glucose determination.

EAR: How can the clinician interpret the results of an amniotic fluid WBC and an amniotic fluid glucose determination?

RR: White blood cells—such as neutrophils, monocytes, or eosinophils—are not normally present in the amniotic fluid. Therefore, a high count of white blood cells is an indicator that intraamniotic inflammation is present. We recommend that an amniotic fluid sample be sent to the clinical hematology laboratory, that a WBC count be performed in the standard hemacytometer chamber, and that this be followed by a differential count. When the WBC count is greater than 50 cells/L in patients with intact membranes—or greater than 30 in patients with preterm PROM—the likelihood of a positive amniotic fluid culture is high.

In terms of the amniotic fluid glucose concentration, under normal circumstances glucose is present in the amniotic fluid. The lower the amniotic fluid glucose value, the higher the likelihood of intraamniotic infection or inflammation. For example, glucose values less than 14 mg/dL in women with intact membranes—or less than 10 mg/dL in women with preterm PROM—suggest that intraamniotic infection and/or inflammation is present.

EAR: Are there other tests, such as measurements of cytokines or other proteins, that can be used to detect inflammation in the amniotic fluid?

RR: The concentrations of a cytokine, such as interleukin-6, can be used to detect inflammation. Similarly, we have developed a rapid test that can be used at the

bedside to detect inflammation by detecting the concentration of an enzyme produced by neutrophils. This enzyme is MMP-8 (matrix metalloproteinase-8).

These tests can be valuable in the context of midtrimester amniocentesis. The rate of pregnancy loss after a midtrimester amniocentesis has been estimated to be 0.5%-1%; such losses have mistakenly been thought to be always procedure related. However, we have found that among women who have midtrimester amniocenteses, those who have an elevated IL-6 or MMP-8 concentration are more likely to lose their pregnancy or have a spontaneous abortion shortly after the procedure. In these circumstances, determination of IL-6 or MMP-8 in the amniotic fluid stored by the genetic laboratories may be helpful for the patient and physician to identify that intraamniotic inflammation was a cause of the pregnancy loss. This may also have medicolegal implications.

EAR: How common is intraamniotic infection and/or inflammation in women having genetic amniocenteses in the midtrimester of pregnancy?

RR: The frequency of intraamniotic infection has been estimated to be 0.9%; the frequency of intraamniotic inflammation is about 1.2%. The most common organism found in the amniotic fluid is *U. urealyticum*. Intraamniotic infection and/or inflammation is more common in women who have discolored amniotic fluid at the time of genetic amniocentesis. It is important to realize that these infections are subclinical and that sometimes, patients with these infections rupture their membranes within hours or days of the procedure.

EAR: Can treatment be offered to these patients with midtrimester intraamniotic infections?

RR: Recent evidence from Dr. Sonia Hassan in our group indicates that the administration of antibiotics to the mother can eradicate intraamniotic infection in the midtrimester. Women with a short cervix detected by ultrasound were found to have microorganisms in 9% of cases. Patients were offered treatment with antibiotics and a repeat amniocentesis was performed

Continued on following page

Continued from previous page

to be sure that the infections were eradicated. Most women treated in this fashion had eradication of their intraamniotic infection and their pregnancy went to term.

EAR: How frequently are intrauterine infections confined to the amniotic fluid, and how often is the fetus involved?

RR: A study conducted in the United Kingdom in women with preterm PROM indicated that approximately 30% of patients had microorganisms in the amniotic fluid. Of these, 30% had positive fetal blood cultures. This means that 10% of all fetuses with preterm PROM will have fetal bacteremia. Clearly, this represents a minimum estimate of the frequency of fetal infection, a result of the limitations of standard techniques and the difficulties in isolating relevant microorganisms from fetal blood.

EAR: What is the importance of congenital neonatal infections?

RR: Sepsis is a more serious disease in neonates than in adults. Neonates have been generally considered immunosuppressed hosts, and the lethality of sepsis in neonates is high. There is now accumulating evidence that neonates with sepsis are more likely to develop cerebral palsy and bronchopulmonary dysplasia or chronic lung disease.

EAR: How important is intrauterine infection as a cause for cerebral palsy?

RR: It has been estimated that as many as 20% of all cases of cerebral palsy result from infection. Moreover, this applies to term neonates as well as to preterm neonates. Therefore, the traditional paradigm—that intrapartum asphyxia was the leading cause of cerebral palsy—is probably not correct. Obstetricians need to be aware that undiagnosed infections can be a cause for cerebral palsy because this has medicolegal implications.

EAR: What is the link between infection and the brain injury associated with cerebral palsy?

RR: Microorganisms involved in cases of intraamniotic infection can invade the human fetus. When the fetus breathes or swallows infected amniotic fluid, microorganisms may be entering the fetal compartment. Once microorganisms invade the fetus, they elicit a fetal inflammatory response syndrome (FIRS), which is the counterpart of the systemic inflammatory response syndrome (SIRS) in the adult. In FIRS one of the most critical organs affected is the brain. Microorganisms or their products that gain access to the fetal brain can induce damage of neurons or white matter in utero. Damage to the white matter in utero is also known as periventricular leukomalacia (PVL) and is the most important predictor of cerebral palsy. There is evidence that cytokines, chemokines, and other inflammatory products—such as reactive oxygen metabolites—can cause damage to the glia or to neurons, which is responsible for the cognitive abnormalities, including mental retardation.

EAR: If most intrauterine infections are subclinical, how can an obstetrician determine whether or not a neonate had intrauterine infection after birth?

RR: One possibility is to look at the placenta. Inflammation in the placenta can be of maternal origin or of fetal origin. Histologic chorioamnionitis is inflammation of the chorioamnion membranes caused by maternal cells and is, therefore, a maternal inflammatory response. By contrast, funisitis—inflammation of the umbilical cord—is a fetal inflammatory response. Therefore, the presence of funisitis, diagnosed by examination of the placenta, indicates that the fetus was exposed to microorganisms before birth, or that the fetus mounted a FIRS. This is the reason why we call funisitis the hallmark of FIRS. The practical implication of this

is that the examination of the placenta may be helpful in understanding what happened before birth. This is particularly important, given that funisitis has been associated with the subsequent development of cerebral palsy. The medicolegal implications of this are apparent. Because there is no known treatment for funisitis, there is no evidence that any intervention by obstetricians can prevent cerebral palsy associated with or induced by intrauterine infection.

EAR: Do systemic infections cause preterm labor?

RR: Systemic clinical infections—such as

pyelonephritis, pneumonia, malaria, and appendicitis—have been associated with premature labor and delivery. However, there is recent evidence that subclinical distant infections may also be a cause of premature labor and delivery. Specifically, periodontal disease, which is a chronic inflammatory process, has been associated with the subsequent development of preterm labor as well as with small-for-gestational-age infants.

In September's Master Class: Dr. Reece will query Dr. Romero about the other important causes of preterm parturition, rounding out our exploration of the syndrome.



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 neoplasias • 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, and 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 progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses of both estrogens and progestogens 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 not provide information on the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems: Use of Seasonale[®] provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (an additional 9 weeks per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic disease, studies to date with Seasonale have not suggested an increased risk of these disorders.

a. **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, and 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.

b. **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 2 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.

c. **Cerebrovascular Diseases:** Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive 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 nonmestopausal users to 14 for users with severe hypertension. The relative risk of hemorrhagic strokes has been shown to range from 1.2 for nonusers to 2.6 for users who do not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for nonmestopausal 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.

d. **Dose-Related Risk of Vascular Disease from Oral Contraceptives:** A positive association has been observed between the amount of estrogen and progestin in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoprotein (HDL) has been reported with many progestational agents. A decline in serum high-density lipoprotein 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.

e. **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 6 years for women 40 to 49 years old 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.

2. 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 contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. This 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 childbearing. The overall mortality rate from all causes of mortality with the use of oral contraceptive users is based on data gathered in the 1970's—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 these 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.

3. Carcinoma of the Reproductive Organs and Breast: 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 the breast cancer risk is so rare at these young ages, the absolute 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 never-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.

4. 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.

5. 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.

6. Oral contraceptive Use Before or During Early Pregnancy: Because women using Seasonale[®] will likely have withdrawal bleeding only 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.

7. 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 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 progestogens.

8. 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 hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance. This effect varies 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.

9. Elevated Blood Pressure: Women with significant hypertension should not be started on hormonal contraception. 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 progestogens. 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 ever- and never-users.

10. 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.)

11. 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 (SEA 301) 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 regular, cyclic 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 (7.7% [Seasonale[®]] vs. 1.8% [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.

Days of intermenstrual bleeding and/or spotting	Percentage of Subjects*	
	Cycle 1 (N=385)	Cycle 4 (N=261)
Seasonale [®]		
≥ 7 days	65%	42%
≥ 20 days	35%	15%
28-day regimen	Cycles 1-4 (N=194)	Cycles 10-13 (N=158)
≥ 7 days	38%	39%
≥ 20 days	6%	4%

*Based on spotting and/or bleeding on days 1-84 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.

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 may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

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 use of oral contraceptives may make it more difficult to perform a physical examination. However, a periodic physical examination should be performed by the physician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.
- Lipid Disorders:** Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemia 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 advised 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, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of oral contraceptives with such antiparasitic and antifungal agents. However, epidemiological 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 or bleeding. **Increase in plasma levels of estradiol associated with co-administered drugs:** Co-administration of atrovastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Acoic 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 metoprolol, salicylic acid, morphine and diazepam, 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 globulin 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:** 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 • Cerebral 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 headache • Rash (allergic) • Mood changes, including depression • Vaginitis, including candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • Anaphylactoid/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 • Otic neuritis which may lead to partial or complete loss of vision • Oestitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis • 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.

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