

## THE MASTER CLASS

## Surgeons Respond to Pelvic Reconstruction Column

As editor of the Master Class columns on gynecology, I was very proud to have C.Y. Liu, M.D., present an excellent two-part discourse on pelvic floor prolapse in the October 1, 2004, and November 1, 2004, issues of OB.GYN. NEWS.

I subsequently received a letter to the editor from Marvin H. Terry Grody, M.D. In my mind, Dr. Grody has raised compelling issues, especially in regard to the importance of the perineal body in pelvic floor prolapse. Because of this, I have asked Dr. Liu and a panel of experts to discuss Dr. Grody's concerns.

I trust you will find this discussion both interesting and informative.



CHARLES E. MILLER, M.D.

CHARLES E. MILLER, M.D., a reproductive endocrinologist in private practice in Arlington Heights, Ill., and Naperville, Ill., is the medical editor of this column.

## Dear Editors:

In the Oct. 1, 2004, issue of Ob.Gyn. News, there appeared Part 1 of a two-part series entitled "Laparoscopic Pelvic Reconstructive Surgery." The author, C.Y. Liu, M.D., who is a well-reputed and skilled laparoscopic surgeon, acceptably covered the issues of defects of the pelvic supportive and suspensory mechanisms and their effects on associated organs. But from the viewpoint of a vaginal and pelvic reconstructive surgeon, he embodied a major misconception in his statement, "The perineal membrane and perineal body are not very crucial for pelvic organ support."

He is not only dead wrong, but he is giving misinformation that could be seriously destructive to surgery performed by a myriad of minimally experienced young surgeons whom experts in the field are trying tenaciously to convince otherwise.

Before I go further into this matter, I must first suppress my emotionally charged conviction (shared by many others) that the average gynecologic surgeon will not achieve anywhere near the degree of success working through a telescope that has been thrust through the abdominal wall as she or he could attain much more directly with less time and expense—and probably less risk—by using alternative approaches.

Contrary to Dr. Liu's disregard of any contributive importance of the perineal body (PB), pelvic reconstructive surgeons universally consider a disrupted PB to be a critical obstacle to the achievement of durably effective success in pelvic anatomical and functional restoration. Over a period of 4 decades starting in the 1960s, David H. Nichols, M.D.—whom most of us view as one of the most renowned vaginal surgeons—firmly and repeatedly established the mandatory requirements of restitution of the normal vaginal axis in the correction of the anatomically defective pelvic floor.

For reference, a full description of the normal vaginal axis and its vital role in good pelvic support can be found in my chapter on colpoperineorrhaphy in the ninth edition of TeLinde's Operative Gynecology (Philadelphia: Lippincott Williams & Wilkins, 2003, p. 966-85).

The PB is a key element in the structural composition of the normal vaginal axis. If significant defects in the PB are ignored and not completely repaired to natural configuration in this commonly co-existent lesion in pelvic floor anatomical failure, then no matter how wonderful the surgeon feels about his or her effort in correcting the other defects, the operation is almost certainly doomed to fail in time. Such inevitability relates to the interdependence of all the elements of the connective tissue network running through the pelvis. An ignored, significantly defective PB can become the weak link that will blow the entire chain of support.

Even if we uncover the rare gynecologic surgeon possessed of laparoscopic skill equivalent to that of Dr. Liu, if the patient does not undergo a full perineorrhaphy from the vaginal approach as the last part of the total operation, then that surgeon must be considered stupid.

Finally, I must question the wisdom of publishing this laparoscopy series that focuses on a surgical approach that will unquestionably be within the province of only a highly-specialized, well-trained, innately gifted few when other easier, safer, very effective, and far less costly and time-consuming procedures can be ably pursued by a significantly larger segment of qualified operating practitioners.

Given today's world of astounding technological feats, will such a truly perverse printed exposure stimulate adventurous young gynecologic surgeons who think they are much better than they really are into imprudent undertakings beyond their true capabilities, leading to serious injury to their patients? Goodness knows what difficulties we already find in our cluttered residency programs in getting basic maneuvers (like vaginal hysterectomy) across, let alone highly sophisticated, industry-driven, potentially dangerous operative challenges performed through a spyglass.

If there are critics abroad who think I am wrong, let them please tell me.

MARVIN H. TERRY GRODY, M.D., is a professor of obstetrics and gynecology and senior attending gynecology consultant, Robert Wood Johnson Medical School at Camden (N.J.).

Rather than repudiating Dr. Grody's opinion about laparoscopic surgery, I will only respond to his point about the importance of the perineal membrane and PB to pelvic organ support.

All defects should be repaired at the time of pelvic floor reconstructive surgery. Any tear or defect in the area of the perineal membrane or PB should be repaired concurrently with pelvic floor reconstruction. This point was emphasized in the final step outlined in Part 2 of my series: "Repair the rectocele and perform perineorrhaphy vaginally if necessary."

Based upon my understanding of the functional pelvic support anatomy as well as clinical observation, I maintain my position that "the perineal membrane and perineal body are not very crucial for pelvic organ support."

The perineal membrane is a single layer of fibromuscular tissue that spans the anterior triangle of the pelvic outlet. Laterally, it attaches to the ischiopubic ramus; medially, it fuses with the sidewalls of the vagina and perineal body. The anterior portion of the perineal membrane is fused with the muscles of the distal urethra. Rather than forming a supportive sheet as it does in the male, the perineal membrane in the female—because of the large opening of the vagina—provides only lateral attachment for the PB and some support for the lower urethra.

The PB is an ill-defined, bordered mass of dense connective tissue lying between the vagina and anus. Fused anteriorly to the posterior vaginal wall and attached laterally to the perineal membrane and bulbocavernosus and superficial transverse perineal muscles, a significant portion of what is clinically called the perineal body is actually the muscle of the external anal sphincter. The strong upward traction of the levator ani muscles is much more important in maintaining vaginal outlet support than are the bulbocavernosus and superficial transverse perineal muscle.

Contrary to Dr. Grody's assertion that the PB makes a substantial contribution to pelvic support, in actuality the support is minimal. Rather, restoration of the PB is important for sexual function and anal/fecal continence. I have examined several patients with no PB as the result of chronic unrepaired fourth-degree obstetric lacerations, yet none of them had prolapse. Similarly, women who have had a radical resection of the anus and rectum for cancer, including the entire removal of the PB, suffered no significant prolapse.

Because considerable descent (up to 1 inch) of the PB is possible during voluntary straining, the perineal membrane and PB cannot be the main supportive layer of the genital outlet. The fact that the PB can move backward 3-4 cm toward the sacrum when a weighted speculum is placed in the posterior vagina likewise indicates that the position of the PB is determined by the levator ani muscle rather than by any inherent importance of its own.

Advances in technology afford greater magnification, visualization, and accuracy—leading to a level of surgical precision heretofore impossible with the relatively "blind" vaginal approach. We must train young surgeons for these state-of-the-art advances.

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Although I have the utmost respect for both Dr. Grody and Dr. Liu and I believe that everyone is entitled to his or her own opinion, Dr. Liu's article is certainly not worthy of such admonishment.

Dr. Liu not only correctly addresses normal vaginal anatomy, clinical assessment, and one surgeon's approach to the anatomical correction of symptomatic prolapse, he does so in a concise, informative manner.

Dr. Grody's belief that the perineal membrane and PB are crucial for pelvic organ support is indeed just that: his belief. Using the PubMed search term "perineal body surgery," I found no scientific literature written in the past 40 years that supports the concept that either the perineal membrane or the PB is crucial in the support of any organs of the pelvis. I have yet to read or find an article that suggests that the cure rates of sacrospinous ligament suspension; sacral colpopexy; paravaginal repair; uterosacral ligament suspension; enterocele repair; or Burch, sling, or any other prolapse corrective surgery—including colpocleisis or Lefort procedures—are improved by repairing the PB.

Furthermore, there is no scientific literature that supports the concept that poor perineal support increases the incidence of prolapse. If this were a fact, patients with traumatic or congenital cloaca would also suffer a greater incidence of vaginal prolapse. I have not seen or read of any scientific literature or text that can directly show a cause-and-effect relationship between a damaged PB and vaginal prolapse.

Dr. Grody is a purist in his pursuit of vaginal anatomic correction, but this fine trait does not constitute scientific proof for his allegation. He has the right to theorize that the anatomical correction is essential to improve long-term cure rates of prolapse surgery. But a theory is belief unsupported by substantial fact, and will thus remain just a theory.

JOHN R. MIKLOS, M.D., is the director of the Atlanta Center for Laparoscopic Urogynecology.

After reading Dr. Liu's article on laparoscopic pelvic reconstructive surgery and Dr. Grody's response, I found myself perplexed. How is it that two experienced and respected surgeons can underappreciate each other's perspective on pelvic reconstructive surgery?

For the most part, I agree with most of what each has stated but disagree on the finer points. I must confess that being predominantly a laparoscopic or minimally invasive surgeon, I too did not completely comprehend the complexity and functional anatomy of the PB and membrane as an important element in pelvic floor support until more recently.

Thanks to cadaver sections and MRI studies reported by John O.L. Delancey, M.D., at the joint annual meeting of the American Urogynecologic Society and the Society of Gynecologic Surgeons in 2004, we realize that the perineal membrane is a complex 3-D structure composed of a dorsal and ventral portion rather than a trilaminar sheet as previously thought. His description of the anatomical relationship to the compressor urethra, urethra vaginal sphincter, arcus

tendineus, pubic bone, and levator muscles underscores the importance of this structure in pelvic support.

We now have level 1 evidence of the laparoscope's benefit in sacral colpopexies compared with an open procedure, as well as its inferiority in treating stress urinary incontinence when comparing a laparoscopic Burch with a transvaginal tape procedure. But the laparoscope is a tool that requires proper training to master. Thanks to the pioneering efforts of Dr. Liu and Dr. Miklos, the development of training centers, and the support of organizations like the American Association of Gynecologic Laparoscopists, it is no longer the gifted few who use this valuable instrument.

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The recent articles by Dr. C.Y. Liu in OB.GYN.NEWS on laparoscopic pelvic reconstructive surgery, Parts 1 and 2, are a must-read for any gynecologic surgeon performing reconstructive vaginal surgery. Although the article presents Dr. Liu's laparoscopic approach to problems of vaginal suspension and support, the anatomy presented and the surgical steps discussed are clearly applicable to the repair of any vaginal prolapse via any surgical approach, including vaginal and abdominal.

The anatomy of genital prolapse is up to date, well written, and clearly explained. Part 1 contains many pearls of insight from a master of this anatomy, and it summarizes our current concepts of vaginal suspension and support. The section on clinical assessment of prolapse is practical and very helpful.

The surgical techniques presented are anatomical and readily applicable. Dr. Liu explains how to safely dissect out and investigate the suspensory anatomy to clearly define the anatomical defects that caused the vaginal prolapse. Not only does Dr. Liu address and repair the specific breaks in the continuity of the visceral connective tissue suspensory network, but he presents an excellent dissection technique for safeguarding the ureters.

One point that should have been emphasized is the requirement for cystoscopic confirmation of bilateral ureteral functioning at the end of the case.

The article explains that one of the three supporting layers of the female pelvic organs is "the perineal membrane/external anal sphincter." What is not said is that the anal sphincter is an important component of the posterior part of the PB.

The lower third of the vagina and the anal canal/anal sphincter are fused with the PB. The PB is shaped roughly like a pyramid, with the base between the vaginal introitus and the anal sphincter. The apex is found at the junction of the lower third and the middle third of the vagina, and at the rectoanal junction. At the apex of the perineal body, the vagina slopes to a more horizontal orientation in the standing patient, whereas the anal canal forms a right angle with the lower rectum.

Portions of the pubococcygeus and puborectalis muscles insert into the apex of the PB. The rectovaginal fascia also inserts into the apex of the PB and helps in its proper anatomical orientation. The intact PB positions itself and the anus just above the level of the ischial tuberosities. The fusion of the anus and anal canal with the PB is important

for their anatomical positioning and physiologic functioning in fecal continence. The fusion of the lower third of the vagina with the PB is important for its anatomical positioning and physiologic functioning in pelvic organ support. The PB assists in closing off the genital hiatus at times of increased intrapelvic pressures, supporting the pelvic organs. Another support mechanism is the flap-valve action of the levator plate.

Many women with vaginal prolapse demonstrate abnormal descent of the perineum. Dr. Liu states, "The active support of the pelvic floor comes from the levator ani muscles (the iliococcygeus and pubococcygeus muscles). These muscles close off the

pelvic floor so the pelvic organs can rest upon them without tension." This statement is true.

Dr. Liu does not mention the important action of the levator plate or the action of the PB in this vaginal support mechanism. In fact, with a poorly supportive levator plate, as is frequently seen in vaginal prolapse patients, a well-reconstructed PB will substitute as a backstop against which the resuspended vagina can be compressed for support.

The reconstructed PB will help close off the genital hiatus at times of mechanical pelvic stress. The PB must be reconstructed in shape and bulk to support and orient the anal canal and lower third of the vagina, but

also to position itself and the anal canal at or above the level of the ischial tuberosities.

As Dr. Liu implies, we cannot repair or completely rehabilitate damaged and weakened pelvic floor muscles and their innervations. We should surgically reconstruct a disrupted PB. I do feel that Dr. Liu does indeed perform perineoplasty on many of his prolapse patients. He simply emphasized the reconstruction and proper placement of the pericervical ring in his excellent article.

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**INDICATIONS AND USAGE:** ORTHO TRI-CYCLEN® Lo Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

**CONTRAINDICATIONS:** Oral contraceptives should not be used in women who have any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders 2. A past history of deep vein thrombophlebitis or thromboembolic disorders 3. Cerebral vascular or coronary artery disease (current or history) 4. Valvular heart disease with complications 5. Severe hypertension 6. Diabetes with vascular involvement 7. Headaches with focal neurological symptoms 8. Major surgery with prolonged immobilization 9. Known or suspected carcinoma of the breast or personal history of breast cancer 10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia 11. Undiagnosed abnormal genital bleeding 12. Cholestatic jaundice of pregnancy or jaundice with prior pill use 13. Hepatic adenomas or carcinomas 14. Known or suspected pregnancy 15. 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 risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although 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 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 progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations 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 provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

**1. Thromboembolic Disorders and Other Vascular Problems**  
**a. Myocardial Infarction**  
 An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers and increases with the amount of smoking. 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 infarctions 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, especially in those 35 years of age and older and in 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 progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associated with an increase in the incidence of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY in full Prescribing Information), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater.

**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 nonusers 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 risk of thromboembolic disease associated with 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, and smoking interacted to increase the risk of hemorrhagic stroke. 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 non-smokers 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 non-smokers users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

**d. 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 activity of the progestogen used in the contraceptive. The activity and 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 an 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 9 years for women 40-49 years 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 (Table 3). 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. The study concluded that with the exception of oral contraceptives for women 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's. Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over.

The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also 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. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

**3. 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.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after discontinuation of combination oral contraceptives and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use combination oral contraceptives before age 20. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of developing intraepithelial neoplasia in some populations of women. However, the data continues to be controversial 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 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 the incidence of benign tumors 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 especially with oral contraceptives of higher dose. Rupture of benign, 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. 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**  
 Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.

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.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

**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 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 progestogens.

**8. Carbohydrate and Lipid Metabolic Effects**  
 Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users. This effect has been shown to be directly related to estrogen dose. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored 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 lipoproteins 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 extended duration of use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity and 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 elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.

**10. Headache**  
 The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

**11. Bleeding Irregularities**  
 Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

**12. Ectopic Pregnancy**  
 Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

**PRECAUTIONS**

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

**2. Physical Examination and Follow-Up**  
 It is good medical practice for all women to have annual history and physical examinations, 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, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate 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.

**3. 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 hyperlipidemias more difficult.

**4. Liver Function**  
 If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

**5. 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.

**6. Emotional Disorders**  
 Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

**7. Contact Lenses**  
 Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

**8. Drug Interactions**  
**Changes in contraceptive effectiveness associated with co-administration of other products:**

Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, antifungals, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, 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 antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.

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 oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors. Health care providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

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 ethinyl estradiol levels associated with co-administered drugs:**  
 Co-administration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Aspirin 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 oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of fentanyl, salicylic acid, morphine and clofibrate acid, due to induction of conjugation, have been noted when drugs were administered with oral contraceptives.

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

- a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin III; increased norepinephrine-induced platelet aggregability.
- b. 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.
- c. Other binding proteins may be elevated in serum.
- d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
- e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
- f. Glucose tolerance may be decreased.
- g. 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.

**10. Carcinogenesis**  
 See WARNINGS section.

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

**12. Nursing Mothers**  
 Small amounts of oral contraceptive steroids 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 combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

**13. Pediatric Use**  
 Safety and efficacy of ORTHO TRI-CYCLEN® Lo Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

**14. Geriatric Use**  
 This product has not been studied in women over 65 years of age and is not indicated in this population.

**INFORMATION FOR THE PATIENT**

See Patient Package Insert.

**ADVERSE REACTIONS**

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS section).

- Thrombophlebitis and venous thrombosis
- Cerebral hemorrhage with or without embolism
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral thrombosis
- Retinal thrombosis

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
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Erythema nodosum
- Cataracts
- Hemorrhagic eruption
- Changes in appetite
- Vaginitis
- Cystitis-like syndrome
- Porphyria
- Headache
- Impaired renal function
- Nervousness
- Hemolytic uremic syndrome
- Dizziness
- Acne
- Hirsutism
- Changes in libido
- Loss of scalp hair
- Colitis
- Erythema multiforme
- Budd-Chiari Syndrome

**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.

Ⓜ only



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