Chorioamnionitis May Not Mandate C-Section

BY SHERRY BOSCHERT
San Francisco Bureau

MONTEREY, CALIF. — By itself, chorioamnionitis does not justify an operative delivery even if the first stage of labor is prolonged, a retrospective study of 1,810 deliveries suggests.

Longer first-stage labor in pregnancies with chorioamnionitis was associated with a 60% increased risk for cesarean delivery and a 30% increased risk for meconium-stained amniotic fluid, a multivariate analysis found. The results showed no increase in risk for meconium aspiration syndrome with prolonged first-stage labor in pregnancies with chorioamnionitis, Dr. Natali Aziz said at the annual meeting of the Infectious Diseases Society for Obstetrics and Gynecology.

Chorioamnionitis in previous studies has been associated with significant adverse obstetric and neonatal outcomes including maternal blood loss and transfusions, endomyometritis, greater severity of lacerations, meconium aspiration syndrome, lower Apgar scores, neonatal sepsis, and other problems.

The current study found that the duration of first-stage labor in women with chorioamnionitis did not affect the risk of neonatal sequelae, "which was surprising to us," said Dr. Aziz of the University of California, San Francisco.

The timing of delivery for patients with chorioamnionitis is controversial, she said. Her institution does not deliver based solely on the diagnosis of chorioamnionitis, but some other institutions do.

The investigators analyzed outcomes by comparing women with chorioamnionitis whose first stage of labor lasted less than 12 hours (39% of cases), 12-24 hours (48%), or 24 hours or longer (13%). The results "support continued efforts to achieve a vaginal delivery if other obstetrical indications permit, even in the setting of a prolonged course of labor and intraamniotic infection," Dr. Aziz said. "Much of the maternal morbidity in our data was due to operative delivery in itself."

An initial univariate analysis found that a longer first-stage labor was associated with worse maternal and obstetric outcomes, but "not as much as we expected," she said. Risks for postpartum hemorrhage, C-section, endomyometritis, and operative vaginal delivery increased with longer labors.

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Postpartum hemorrhage and endomyometritis, however, can be associated with cesarean delivery, so the investigators conducted a multivariate analysis that controlled for the effects of potential confounders, including cesarean delivery. That analysis found associations only between longer labor and increased risks for cesarean delivery or meconium-stained amniotic fluid.

They then conducted a second multivariate analysis that did not control for the effects of cesarean delivery. Some researchers have speculated that cesarean delivery may be a causal pathway that leads from chorioamnionitis to adverse perinatal outcomes, and so controlling for cesarean delivery might mask any effects of prolonged labor on chorioamnionitis and neonatal outcomes, Dr. Aziz and her associates reasoned.

In the analysis that did not control for cesarean delivery, the only other significant association with increased duration of first-stage labor was a 20% increased risk for postpartum hemorrhage. There was a trend toward greater need for blood transfusion with prolonged first-stage labor in pregnancies with chorioamnionitis. "We've demonstrated that the increasing duration of first-stage labor was associated with increased maternal morbidity, and in turn with operative delivery and thereby postpartum hemorrhage, but not with neonatal morbidity," she said.

One physician in the audience commented, "I think these are very encouraging and reassuring data."

Prolonged first-stage labor in pregnancies with chorioamnionitis also was associated with a significantly decreased risk for an umbilical artery base excess greater than 12 mmol/L, which puzzled the investigators. This may be due to fetal indications causing the delivery, Dr. Aziz said. ■

MIRENA® (levonorgestrel-releasing intrauterine system)

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES

Rx only

INDICATIONS AND USAGE: **MIRENA**® is indicated for intrauterine contraception for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced. **RECOMMENDED PATIENT PROFILE:** **MIRENA**® is recommended for women who have had at least one child, are in a stable, mutually monogamous relationship, have no history of pelvic inflammatory disease, and have no history of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

CONTRAINDICATIONS: **MIRENA**® insertion is contraindicated when one or more of the following conditions exist: 1. Pregnancy or suspicion of pregnancy. 2. Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity. 3. Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy. 4. Postpartum endometritis or infected abortion in the past 3 months. 5. Known or suspected uterine or cervical neoplasia or unresolved, abnormal Pap smear. 6. Genital bleeding of unknown etiology. 7. Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled. 8. Acute liver disease or liver tumor (benign or malignant). 9. Woman or her partner has multiple sexual partners. 10. Conditions associated with increased susceptibility to infections with micro-organisms. Such conditions include, but are not limited to, leukemia, acquired immune deficiency syndrome (AIDS), and I.V. drug abuse. 11. Genital actinomycosis (See **WARNINGS**) 12. A previously inserted IUD that has not been removed. 13. Hypersensitivity to any component of this product. 14. Known or suspected carcinoma of the breast. 15. History of ectopic pregnancy or condition that would predispose to ectopic pregnancy.

WARNINGS: 1. Ectopic Pregnancy: In large clinical trials of **MIRENA**®, half of all pregnancies detected during the studies were ectopic. The per-year incidence of ectopic pregnancy in the clinical trials was approximately 1 ectopic pregnancy per 1000 users per year. The rate of ectopic pregnancies associated with **MIRENA**® use is not significantly different than the rate for sexually active women not using any contraception. Clinical trials of **MIRENA**® excluded women with a history of ectopic pregnancy. **MIRENA**® is not recommended for use in women with a history of ectopic pregnancy or conditions that increase the risk of ectopic pregnancy. Women who choose **MIRENA**® must be warned about the risks of ectopic pregnancy. They should be taught to recognize and report to their physician promptly any symptoms of ectopic pregnancy. Women should also be informed that ectopic pregnancy has been associated with complications leading to loss of fertility. **2. Intrauterine Pregnancy:** In the event of an intrauterine pregnancy with **MIRENA**®, the following should be considered. a) Septic abortion: In patients becoming pregnant with an IUD in place, septic abortion – with septicemia, septic shock, and death – may occur. If pregnancy should occur with a **MIRENA**® in place, **MIRENA**® should be removed. Removal or manipulation of **MIRENA**® may result in pregnancy loss. b) Continuation of pregnancy: If a woman becomes pregnant with **MIRENA**® in place and if **MIRENA**® cannot be removed or the woman chooses not to have it removed, she should be warned that failure to remove **MIRENA**® increases the risk of miscarriage, sepsis, premature labor and premature delivery. She should be followed closely and advised to report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid. c) Long-term effects and congenital anomalies: When pregnancy continues with **MIRENA**® in place, long-term effects on the offspring are unknown. Because of the intrauterine administration of levonorgestrel and local exposure to the hormone, the possibility of teratogenicity following exposure to **MIRENA**® cannot be completely excluded. Clinical experience with the outcomes of pregnancies is limited due to the small number of reported pregnancies following exposure to **MIRENA**®. Congenital anomalies have occurred infrequently when **MIRENA**® has been in place during pregnancy. In these cases the role of **MIRENA**® in the development of the congenital anomalies is unknown. As of September 1999, 32 live births following exposure to **MIRENA**® were reported retrospectively. All but 2 of the infants were healthy at birth. One infant had pulmonary artery hypoplasia and another infant had cystic hypoplastic kidneys. (A sibling of this infant had renal agenesis with no **MIRENA**® exposure.) **3. Sepsis:** As of 1999, four cases of Group A streptococcal sepsis (GAS) out of an estimated 1.3 million **MIRENA**® users were reported. All four women experienced the symptom of severe pain within hours of insertion, and this was followed by sepsis within a few days (of insertion). All recovered with treatment. Since death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during **MIRENA**® insertion is essential. (GAS sepsis can also occur postpartum, after minor surgery, in wounds and in association with other IUDs.) **4. Pelvic Inflammatory Disease (PID):** **MIRENA**® is contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy. Use of IUDs has been associated with an increased risk of PID. The highest risk of PID occurs shortly after insertion (usually within the first 20 days thereafter) (see **Insertion Precautions**). A decision to use **MIRENA**® must include consideration of the risks of PID. a) Women at increased risk for PID: PID is often associated with a sexually transmitted disease, and **MIRENA**® does not protect against sexually transmitted disease. The risk of PID is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have ever had PID are at increased risk for a recurrence or re-infection. b) PID warning to **MIRENA**® users: All women who choose **MIRENA**® must be informed prior to insertion about the possibility of PID and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or in infrequent cases can necessitate hysterectomy, or can cause death. Patients must be taught to recognize and report to their physician promptly any symptoms of pelvic inflammatory disease. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever. c) Asymptomatic PID: PID may be asymptomatic but still result in tubal damage and its sequelae. d) Treatment of PID: Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly. Removal of **MIRENA**® after initiation of antibiotic therapy is usually appropriate. Guidelines for PID treatment are available from the Center for Disease Control (CDC), Atlanta, Georgia. Adequate PID treatment requires the application of current standards of therapy prevailing at the time of occurrence of the infection with reference to prescription labeling. Actinomycosis has been associated with IUDs. Symptomatic women with IUDs should have the IUD removed and should receive antibiotics. However, the management of the asymptomatic carrier is controversial because actinomycetes can be found normally in the genital tract cultures in healthy women without IUDs. False positive findings of actinomycosis on Pap smears can be a problem. When possible, confirm the Pap smear diagnosis with cultures. **5. Irregular Bleeding and Amenorrhea:** **MIRENA**® can alter the bleeding pattern. During the first three to six months of **MIRENA**® use the number of bleeding and spotting days may be increased and bleeding patterns may be irregular. Thereafter the number of bleeding and spotting days usually decreases but bleeding may remain irregular. If bleeding irregularities develop during prolonged treatment appropriate diagnostic measures should be taken to rule out endometrial pathology. Amenorrhea develops in approximately 20% of **MIRENA**® users by one year. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are not necessary in amenorrheic subjects unless indicated by other signs of pregnancy or by pelvic pain. **6. Embedment:** Partial penetration or embedment of **MIRENA**® in the myometrium may decrease contraceptive effectiveness and can result in difficult removal. **7. Perforation:** An IUD may perforate the uterus or cervix, most often during insertion although the perforation may not be detected until some time later. If perforation occurs, the IUD must be removed and surgery may be required. Adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera have been reported with IUDs. It is recommended that postpartum **MIRENA**® insertion be delayed until uterine involution is complete to decrease perforation risk. There is an increased risk of perforation in women who are lactating. Inserting **MIRENA**® immediately after first trimester abortion is not known to increase the risk of perforation, but insertion after second trimester abortion should be delayed until uterine involution is complete. **8. Ovarian Cysts:** Since the contraceptive effect of **MIRENA**® is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age using **MIRENA**®. Sometimes atresia of the follicle is delayed and the follicle may continue to grow. Enlarged follicles have been diagnosed in about 12% of the subjects using **MIRENA**®. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases the enlarged follicles disappear spontaneously during two to three months observation. Surgical intervention is not usually required. **9. Breast Cancer:** Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer is a hormone-sensitive tumor. **10. Risks of Mortality:** The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death include the combined risk of the contraceptive method plus the risk of pregnancy or abortion in the event of method failure. The findings of the analysis are shown in the following table: **Annual Number of Birth-Related or Method-Related Deaths Associated with Control of Fertility per 100,000 Nonsterile Women, by Fertility Control Method According to Age**

	AGE GROUP					
METHODS	15–19	20–24	25–29	30–34	35–39	40–44
No Birth Control Method/Term	4.7	5.4	4.8	6.3	11.7	20.6
No Birth Control Method/AB	2.1	2.0	1.6	1.9	2.8	5.3
IUD	0.2	0.3	0.2	0.1	0.3	0.6
Periodic Abstinence	1.4	1.3	0.7	1.0	1.0	1.9
Withdrawal	0.9	1.7	0.9	1.3	0.8	1.5
Condom	0.5	1.2	0.6	0.9	0.5	1.0
Diaphragm/Cap	0.6	1.1	0.6	0.9	1.6	3.1
Sponge	0.8	1.5	0.8	1.1	2.2	4.1
Spermicides	1.6	1.9	1.4	1.9	1.5	2.7
Oral Contraceptives	0.8	1.3	1.1	1.8	1.0	1.9
Implants/Injectables	0.2	0.6	0.5	0.8	0.5	0.6
Tubal Sterilization	1.3	1.2	1.1	1.1	1.2	1.3
Vasectomy	0.1	0.1	0.1	0.1	0.1	0.2

Harlap S. et al., Preventing Pregnancy, protecting health: a new look at birth control choices in the US. The Alan Guttmacher Institute 1991: 1-129

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PRECAUTIONS

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

1. PATIENT COUNSELING: Prior to insertion, the physician, nurse, or other trained health professional must provide the patient with the Patient Package Insert. The patient should be given the opportunity to read the information and discuss fully any questions she may have concerning **MIRENA**® as well as other methods of contraception. Careful and objective counseling of the user prior to insertion regarding the expected bleeding pattern, the possible interindividual variation in changes in bleeding and the etiology of the changes may have an effect on the frequency of removal due to bleeding problems and amenorrhea. The patient should be told that some bleeding such as irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her health care provider. She should also be given instructions on what other symptoms require her to call her health care provider. She should be instructed on how to check after her menstrual period to make certain that the thread still protrudes from the cervix and cautioned not to pull on the thread and displace **MIRENA**®. She should be informed that there is no contraceptive protection if **MIRENA**® is displaced or expelled. **EVALUATION AND CLINICAL CONSIDERATIONS:** a) A complete medical and social history, including that of the partner, should be obtained to determine conditions that might influence the selection of an IUD for contraception (see **CONTRAINDICATIONS**). A physical examination should include a pelvic examination, a Pap smear, and appropriate tests for any other forms of genital disease, such as gonorrhea and chlamydia laboratory evaluations, if indicated. **Special attention must be given to ascertaining whether the woman is at increased risk of ectopic pregnancy or PID. MIRENA**® **is contraindicated in these women.** b) **The health care provider should determine that the patient is not pregnant.** The possibility of insertion of **MIRENA**® in the presence of an existing undetermined pregnancy is reduced if insertion is performed within 7 days of the onset of a menstrual period. **MIRENA**® can be replaced by a new system at any time in the cycle. **MIRENA**® can be inserted immediately after first trimester abortion. c) **MIRENA**® should not be inserted until 6 weeks postpartum or until involution of the uterus is complete in order to reduce the incidence of perforation and expulsion. d) Patients with certain types of valvular or congenital heart disease and surgically constructed systemic-pulmonary shunts are at increased risk of infective endocarditis. Use of **MIRENA**® in these patients may represent a potential source of septic emboli. Patients with known congenital heart disease who may be at increased risk should be treated with appropriate antibiotics at the time of insertion and removal. Patients requiring chronic corticosteroid therapy or insulin for diabetes should be monitored with special care for infection. e) **MIRENA**® should be used with caution in patients who have a coagulopathy or are receiving anticoagulants. f) Use of **MIRENA**® in patients with vaginitis or cervicitis should be postponed until proper treatment has eradicated the infection and until it has been shown that the cervicitis is not due to gonorrhea or chlamydia (see **CONTRAINDICATIONS**). **2. Insertion Precautions:** Because the presence of organisms capable of establishing PID cannot be determined by appearance, and because IUD insertion may be associated with introduction of vaginal bacteria into the uterus, strict asepsis should be observed at insertion. Administration of antibiotics may be considered, but the utility of this treatment is unknown. The uterus should be carefully sounded prior to **MIRENA**® insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance. Syncope, bradycardia, or other neurovascular episodes may occur during insertion or removal of **MIRENA**®, especially in patients with a predisposition to these conditions or cervical stenosis. If decreased pulse, perspiration, or pallor are observed, the patient should remain supine until these signs have disappeared. **3. Continuation and Removal:** **MIRENA**® must be replaced every 5 years because contraceptive effectiveness after 5 years has not been established. a) User complaints of pain, odorous discharge, bleeding, fever, genital lesions or sores should be promptly responded to and prompt examination recommended. (See **WARNINGS** regarding amenorrhea). b) If examination during visits subsequent to insertion reveals that the length of the threads has changed from the length at time of insertion, and the system is verified as displaced, it should be removed. A new system may be inserted at that time or during the next menses if it is certain that conception has not occurred. If the threads are not visible, location of the **MIRENA**® should be verified, for example with X-ray, ultrasound, or gentle probing of the uterine cavity. If the **MIRENA**® is in place with no evidence of perforation, no intervention is indicated. If expulsion has occurred, it may be replaced within 7 days of a menstrual period after pregnancy has been ruled out. c) Since **MIRENA**® may be displaced, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within 3 months after insertion. Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of **MIRENA**®. As menstrual flow usually decreases after the first 3 to 6 months of **MIRENA**® use, increase of menstrual flow may be indicative of an expulsion. d) In the event a pregnancy is confirmed during **MIRENA**® use, the following steps should be taken: • Determine whether pregnancy is ectopic and take appropriate measures if it is. • Inform patient of the risks of leaving **MIRENA**® in place or removing it during pregnancy and of the lack of data on long-term effects on the offspring of women who have had **MIRENA**® in place during conception or gestation (see **WARNINGS**). • If possible **MIRENA**® should be removed after the patient has been warned of the risks of removal. If removal is difficult, the patient should be counseled and offered pregnancy termination. • If **MIRENA**® is left in place, the patient's course should be followed closely. e) Should the patient's relationship cease to be mutually monogamous, or should her partner become HIV positive, or acquire a sexually transmitted disease, she should be instructed to report this change to her clinician immediately. The use of a barrier method as a partial protection against acquiring sexually transmitted diseases should be strongly recommended. Removal of **MIRENA**® should be considered. f) **MIRENA**® should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia; acquired immune deficiency syndrome (AIDS); sexually transmitted disease; pelvic infection; endometritis; symptomatic genital actinomycosis; intractable pelvic pain; severe dyspareunia; pregnancy; endometrial or cervical malignancy; uterine or cervical perforation. g) If the retrieval threads are not visible, they may have retracted into the uterus or have been broken, or **MIRENA**® may have been broken, perforated the uterus, or have been expelled. Location of **MIRENA**® may be determined by sonography, X-ray, or by gentle exploration of the uterine cavity with a probe. h) Removal of the system should also be considered if any of the following conditions arise for the first time: • migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia; • exceptionally severe headache; • jaundice; • marked increase of blood pressure; • severe arterial disease such as stroke or myocardial infarction. **4. Glucose Tolerance:** Levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of **MIRENA**®.

DRUG INTERACTIONS: The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes. The influence of these drugs on the contraceptive efficacy of **MIRENA**® has not been studied. **CARCINOGENESIS:** Long-term studies in animals to assess the carcinogenic potential of levonorgestrel releasing intrauterine system have not been performed. See 'WARNINGS' section. **PREGNANCY:** Pregnancy Category X. See 'WARNINGS' section. **NURSING MOTHERS:** Levonorgestrel has been identified in small quantities in the breast milk of lactating women using **MIRENA**®. In a study of 14 breastfeeding women using a **MIRENA**® prototype during lactation, mean infant serum levels of levonorgestrel were approximately 7% of maternal serum levels. Hormonal contraceptives are not recommended as the contraceptive method of first choice during lactation. **PEDIATRIC USE:** Safety and efficacy of **MIRENA**® have been established in women of reproductive age. Use of this product before menarche is not indicated. (See **RECOMMENDED PATIENT PROFILE**) **GERIATRIC USE:** **MIRENA**® has not been studied in women over age 65 and is not currently approved for use in this population. INFORMATION FOR THE PATIENT: See Patient Labeling. Patients should also be advised that the prescribing information is available to them at their request. It is recommended that potential users be fully informed about the risks and benefits associated with the use of **MIRENA**®, with other forms of contraception, and with no contraception at all. **Return to fertility:** About 80% of women wishing to become pregnant conceived within 12 months after removal of **MIRENA**®. **ADVERSE REACTIONS:** The most serious adverse reactions associated with the use of **MIRENA**® are discussed above in the Warnings section. Others are presented in the Precautions section. Other adverse events reported by 5% or more subjects include: Abdominal pain, Upper respiratory infection, Leukorrhea, Nausea, Headache, Nervousness, Vaginitis, Dysmenorrhea, Back pain, Weight increase, Breast pain, Skin disorder, Acne, Decreased libido, Depression, Abnormal Pap smear, Hypertension, Sinusitis. Other reported adverse reactions occurring in less than 3% of patients include: failed insertion, migraine, vomiting, anemia, cervicitis, dyspareunia, hair loss, eczema. **HOW SUPPLIED:** **MIRENA**® (levonorgestrel-releasing intrauterine system), containing a total of 52 mg levonorgestrel, is available in a carton of one sterile unit NDC# 50419-421-01. Each **MIRENA**® is packaged in a thermoformed blister package with a peelable lid, together with an insertion tube. **MIRENA**® is supplied sterile. **MIRENA**® is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

Mirena®
(levonorgestrel-releasing intrauterine system)

STORAGE AND HANDLING: Store at 25°C (77°F); with excursions permitted between 15°-30°C (59-86°F) [See USP Controlled Room Temperature]

DIRECTIONS FOR USE: NOTE: Health care providers are advised to become thoroughly familiar with the insertion instructions before attempting insertion of MIRENA®.

Manufactured for:
Berlex, Montville, NJ 07045 Manufactured in Finland (B) 6004703 9/04

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