

Ovarian and Intrauterine Heterotopic Pregnancy Following Clomiphene Ovulation Induction: Report of a Healthy Live Birth

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Heterotopic pregnancy, or simultaneous intrauterine and ectopic gestation, has been reported since the early 18th century as a rare and curious obstetric event.¹⁻⁷ Although the generally accepted incidence of primary heterotopic pregnancy is 1 in 30,000 pregnancies,⁷ there is some indication that techniques of ovulation induction in the past 15 years may have made the occurrence of heterotopic pregnancy more common.¹

Heterotopic pregnancy is believed to result from the implantation of dizygotic twins at widely separated sites.^{1,5,8} Several cases have been reported following the use of clomiphene citrate for ovulation induction.^{1,4,6,9} Inasmuch as the incidence of twinning in clomiphene-induced pregnancy is raised to 12 percent, it has been suggested that the uncommon heterotopic variation may likewise be seen more frequently in pregnancies following clomiphene therapy.^{1,4}

The majority of heterotopic pregnancies reported after clomiphene induction of ovulation have involved ectopic implantation in the fallopian tube.^{1,4,6,9} The occurrence of the ovary as the ectopic site in clomiphene-induced combined pregnancies is distinctly less common than the tubal location,⁷ just as ovarian implantation occurs less often in primary ectopic gestation¹⁰ and in heterotopic pregnancy unrelated to ovulation induction.²

This report describes the presentation and management in a family practice of a patient with the rare combination of simultaneous ovarian and intrauterine pregnancies following clomiphene treatment for ovulatory failure. In this patient the ectopic gestation was responsible for the first symptoms, and following treat-

ment, the intrauterine pregnancy was able to continue satisfactorily to term.

The case is of interest in two respects. First, this is the second report of simultaneous ovarian and intrauterine pregnancy following clomiphene administration. Second, this is the first report of the viable delivery of a healthy infant following heterotopic pregnancy where the ovary is the ectopic site.

CASE REPORT

A 29-year-old, gravida 1, para 1, married woman presented with a 2¹/₂-year history of inability to conceive with regular exposure and no contraceptive use. Her menstrual pattern was unpredictable (25- to 50-day cycles) but with fairly discrete, mildly crampy menses lasting two to five days. This irregular pattern had occurred off and on through her menstrual life. Other significant past history was a laparotomy 2¹/₂ years previously for ovarian cystectomy, at which time multicystic ovaries with thickened capsules were found and confirmed pathologically. At the time of her consultation for inability to conceive, her pelvic examination indicated a normal-sized uterus. The right ovary was felt to be enlarged, but not cystic.

A semen analysis was obtained, which was within normal limits. The clinical impression was secondary infertility because of oligo-ovulation with multicystic ovaries, and ovulation induction with clomiphene, 50 mg days 5 through 9, was prescribed.

The patient apparently conceived during her first clomiphene cycle, as she had no further menses following the period that preceded clomiphene administration. She had a positive anti-human chorionic gonadotropin agglutination inhibition urine pregnancy test six weeks following the last menstrual period and had noted some mild fatigue and breast tenderness.

Seven weeks following her last menstrual period,

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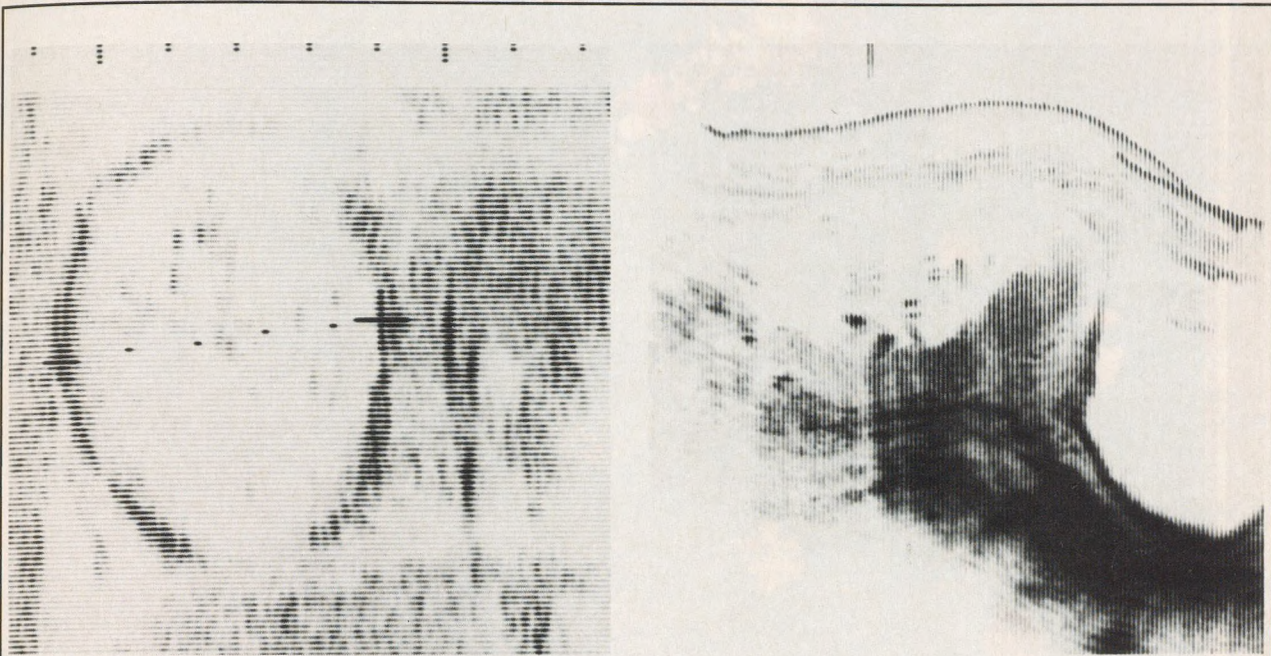


Figure 1. Ultrasound of the fetus obtained at 20 weeks' gestation. Biparietal diameter of 4.7 cm corresponds to 20.4 weeks \pm 1.6 (left). Bladder, fetal head, and placenta can be seen in transverse view of abdomen (right)

the patient experienced sharp, sudden pelvic pain. When examined, she was found to have marked uterine and left adnexal tenderness with guarding and rebound tenderness suggesting pelvic peritoneal irritation. There was no vaginal bleeding. She was normotensive. At this time her white blood count was $11.5 \times 10^3/\mu\text{L}$ with a mild left shift. Hemoglobin and hematocrit levels were normal. Pregnancy test was positive. Culdocentesis yielded nonclotting blood from the cul-de-sac, and the patient underwent laparotomy for ectopic pregnancy. Hematoperitoneum was found at surgery, and an actively bleeding tissue was present on the surface of the left ovary. The fallopian tubes were normal. The uterus was enlarged, compatible with a six-week gestation. Excision of the bleeding tissue was accomplished by a wedge resection of the left ovary. The pathologic report contained tissue evidence of an ectopic ovarian pregnancy with an associated corpus luteum.

The patient failed to have withdrawal bleeding post-operatively and failed to resume any kind of normal menstrual pattern subsequent to her surgery. When she was examined 13 weeks after her surgery, it was found that her uterus had grown to a size compatible with continuing intrauterine pregnancy. Ultrasound examination using fetal biparietal diameter measurements confirmed a single 20-week intrauterine gestation at 20 weeks from the last menstrual period (Figure 1). Uncomplicated prenatal care continued, and 41 weeks from her last menstrual period the patient spon-

taneously delivered a healthy 7-lb 13-oz female infant whose subsequent neonatal and infant course has been normal to 9 months of age.

DISCUSSION

The increasing use of ovulation-inducing drugs for infertility makes it likely that the prevalence of heterotopic pregnancy may increase. The diagnosis of combined pregnancy requires that the physician have a high level of suspicion and that appropriate use be made of generally available diagnostic aids to confirm the physical findings and the clinical impression. Especially suspect is the scenario of an ectopic pregnancy presenting after induction of ovulation in which vaginal bleeding is not present either before or after treatment.² Spontaneous abortion of an intrauterine pregnancy after ovulation induction should also prompt a search for an accompanying ectopic implantation. With the use of the beta human chorionic gonadotropin pregnancy test, the physician may determine the presence of continuing intrauterine or ectopic trophoblastic activity. In addition, Powell-Phillips⁷ has emphasized the precision with which the contents of the uterus or the presence of an adnexal mass may be revealed by pelvic ultrasonography. Any abnormality found on ultrasound might then be investigated by examination through a laparoscope, and

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ERYC® (erythromycin capsules, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: ERYC is indicated in children and adults for the treatment of the following conditions:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes* (group A beta hemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since not all strains of *H. influenzae* are susceptible at the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* (group A beta hemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); Respiratory tract infections due to *Mycoplasma pneumoniae* (Eaton's agent).

Pertussis (whooping cough) caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria—As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae*, to prevent establishment of carriers and to eradicate the organism in carriers.

Erythromycin—in the treatment of infections due to *Corynebacterium minutissimum*. Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Infections due to *Listeria monocytogenes*. Skin and soft tissue infections of mild to moderate severity caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy. The use of erythromycin for the treatment of *in utero* syphilis is not recommended. (See CLINICAL PHARMACOLOGY in full prescribing information.)

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, urogenital infections during pregnancy. When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of uncomplicated urethral, endocervical, or rectal infections in adults due to *Chlamydia trachomatis*.

Legionnaires' disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' disease.

Therapy with erythromycin should be monitored by bacteriological studies and by clinical response (See CLINICAL PHARMACOLOGY—Microbiology in full prescribing information).

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever. When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

Although no controlled clinical efficacy trials have been conducted, erythromycin has been suggested by the American Heart Association and the American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients allergic to penicillin who have congenital and/or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract. (Erythromycin is not suitable prior to genitourinary surgery where the organisms likely to lead to bacteremia are gram-negative bacilli or the enterococcal group of streptococci.)

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint 1984 statement of the American Heart Association and the American Dental Association.

CONTRAINDICATION: ERYC is contraindicated in patients with known hypersensitivity to this antibiotic. **WARNING:** There have been a few reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin ethylsuccinate, base, and stearate products.

PRECAUTIONS: Caution should be exercised when erythromycin is administered to patients with impaired hepatic function (See CLINICAL PHARMACOLOGY in full prescribing information, and WARNING).

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Erythromycin interferes with the fluorometric determination of urinary catecholamines. Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Pregnancy Category B—Reproduction studies have been performed in rats, mice and rabbits using erythromycin and its various salts and esters, at doses which were several times multiples of the usual human dose. No evidence of impaired fertility or harm to the fetus that appeared related to erythromycin was reported in these studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery—The effect of ERYC on labor and delivery is unknown. **Nursing Mothers**—Erythromycin is excreted in milk (see CLINICAL PHARMACOLOGY, in full prescribing information).

Pediatric Use—See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION. **ADVERSE REACTIONS:** The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatic dysfunction and/or abnormal liver function test results may occur (see WARNING).

Mild allergic reactions such as rashes with or without pruritus, urticaria, bullous fixed eruptions, and eczema have been reported with erythromycin. Serious allergic reactions, including anaphylaxis have been reported.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

DOSAGE AND ADMINISTRATION: Administration of a dose of ERYC in the presence of food lowers the blood levels of systemically available erythromycin. Although the blood levels obtained upon administration of enteric-coated erythromycin products in the presence of food are still above minimum inhibitory concentrations (MICs) of most organisms for which erythromycin is indicated, optimum blood levels are obtained on a fasting stomach (administration at least ½ hour and preferably two hours before or after a meal).

ADULTS: The usual dose is 250 mg every 6 hours taken one hour before meals. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 grams per day, according to the severity of infection. Twice-a-day dosing is not recommended when doses larger than 1 gram daily are administered.

CHILDREN: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30 to 50 mg/kg/day in divided doses. For the treatment of more severe infections, this dose may be doubled.

Streptococcal infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

For the prevention of bacterial endocarditis in penicillin-allergic patients with valvular heart disease who are to undergo dental procedures or surgical procedures of the upper respiratory tract, the adult dose is 10 gram orally (20 mg/kg for children) one hour prior to the procedure and then 500 mg (10 mg/kg for children) orally 6 hours later. (See INDICATIONS AND USAGE.)

Primary syphilis: 30-40 grams given in divided doses over a period of 10-15 days. **Intestinal amebiasis:** 250 mg four times daily for 10 to 14 days for adults; 30 to 50 mg/kg/day in divided doses for 10 to 14 days for children.

Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1 to 4 grams daily in divided doses).

Urogenital infections during pregnancy due to *Chlamydia trachomatis*: Although the optimal dose and duration of therapy have not been established, the suggested treatment is erythromycin 500 mg, by mouth, 4 times a day on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of 250 mg, by mouth, 4 times a day should be used for at least 14 days.

For adults with uncomplicated urethral, endocervical, or rectal infections caused by *Chlamydia trachomatis* in whom tetracyclines are contraindicated or not tolerated: 500 mg, by mouth, 4 times a day for at least 7 days.

Pertussis: Although optimum dosage and duration of therapy have not been established, doses of erythromycin utilized in reported clinical studies were 40-50 mg/kg/day, given in divided doses for 5 to 14 days.

Caution—Federal law prohibits dispensing without prescription. 0696G013

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those results may help to define indications for full laparotomy and definitive treatment.

Koroly and Belsky⁴ and others³ have observed that through the use of modern diagnostic techniques and aggressive management of these unusual combined pregnancies, better than 50 percent of the intrauterine gestations should survive if they are undisturbed by maternal hypotension or surgical trauma during the diagnosis and treatment of the ectopic implantation.

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