

Ectopic Pregnancy During Coronavirus Disease 2019 (COVID-19)

To Operate, or Not to Operate

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CLINICAL VIGNETTE

A 37-year-old woman with type 2 diabetes mellitus and a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 42, diagnosed 2 days previously as positive for coronavirus disease 2019 (COVID-19) infection after exposure to her affected spouse, presents to the emergency department with vaginal bleeding. She is afebrile and has stable vital signs, normal pulmonary examination, and a nontender abdomen on examination. Pelvic ultrasound examination shows a 3.5-cm right ectopic pregnancy, with a serum human chorionic gonadotropin (hCG) level of 6,500 milli-international units/mL. You are consulted on treatment.

THE CONUNDRUM

Approximately 2% of pregnancies in the United States are ectopic and remain a cause of significant morbidity and mortality. Treatment options in the stable patient include surgery, medical therapy, and observation for a very select, limited number.¹

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly infectious, positive-sense, single-strand RNA virus currently at pandemic levels. Coronavirus disease 2019 infection has a spectrum of disease; mild cases are the most common, affecting

about 80% of patients, severe cases affect about 14% of patients, and critical disease occurs in 5% of patients, with an infection fatality ratio of 0.66% in China.^{2,3} The host immune system plays a vital role in recovery from COVID-19 infection, but, in severe infections, a dysregulated immune system may result in cytokine release syndrome. The treatment for COVID-19 infection is currently supportive, with ongoing investigations into antiviral and some antiinflammatory agents.⁴

In a stable, unruptured ectopic pregnancy with significant exposure or asymptomatic COVID-19 infection, should the patient be treated surgically, given limited personal protective equipment and potential exposure of surgical team members, or administered medical therapy with potential risk of immunodeficiency?

THE DATA

How Should the Patient be Evaluated?

All patients with a probable ectopic pregnancy should undergo a complete history and physical examination to determine whether the patient is hemodynamically stable and a candidate for medical or minimally invasive surgical management. The assessment should evaluate the patient for any contraindications to the use of methotrexate, including intrauterine pregnancy, immunodeficiency, moderate to severe anemia, leukopenia or thrombocytopenia, active pulmonary or peptic ulcer disease, allergy to methotrexate, and significant renal or hepatic dysfunction. To be eligible for medical therapy, the patient must have no severe pain or evidence of ruptured ectopic pregnancy, no contraindications, and normal liver and renal function and be willing to closely follow-up until the serum hCG level returns to non-pregnant levels.¹ Another consideration, specific to this pandemic, is evaluation for COVID-19 exposure or infection. The most common symptoms of COVID-19 infection include fever (in 99% of individuals), fatigue, dry cough, anorexia, myalgias, dyspnea, and sputum production; less common symptoms including anosmia,

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dysgeusia, nausea, and diarrhea. A thorough physical examination, including assessment for fever, and a pulmonary examination are critical.⁴

Laboratory tests before determining treatment method for an unruptured ectopic pregnancy include a complete blood count, liver function tests, serum creatinine level, blood type, and Rh. A chest X-ray is also suggested in a patient with pre-existing pulmonary disease.¹

In COVID-19 infection, chest computed tomography (CT) scan is the most sensitive and specific imaging test. The American College of Radiology recommends that chest CT scans be used sparingly for diagnosis in patients with COVID-19 infection, and not for screening. In one study, 71% (17/24) of patients with asymptomatic COVID-19 infection had significant findings on chest CT scan, 50% with ground-glass appearance and 21% with stripe shadowing of the lungs.^{5,6} Additional tests for patients with COVID-19 infection include a comprehensive metabolic panel and electrocardiogram. In patients with symptomatic COVID-19 infection, further tests, especially in those with more severe disease, include lactate dehydrogenase, inflammatory markers (c-reactive protein, ferritin), coagulation tests (D-dimer, fibrin degradation products, prothrombin time, activated partial thromboplastin time), and procalcitonin.⁴

Methotrexate is a folic acid antagonist that interferes with the enzyme dihydrofolate reductase, which converts dihydrofolate to tetrahydrofolate, essential to production of DNA and RNA precursors (thymidylate and purines). Methotrexate nonspecifically destroys any rapidly dividing cells, including chorionic epithelium, intestinal epithelium, and bone marrow, and this destruction of normal cells can result in adverse effects. Higher cumulative doses of methotrexate have the potential for more severe side effects.⁷ There are three dosing options of methotrexate for treatment of ectopic gestation: single-dose (50 mg/M²), dual-dose (50 mg/M² on day 1 and day 4), and multi-dose (methotrexate 1 mg/kg on days 1, 3, 5, and 7) with folinic acid (0.1 mg/kg on days 2, 4, 6, and 8) rescue. Methotrexate is most efficacious as a treatment for ectopic gestation when the quantitative serum hCG level is less than 5,000 milli-international units/mL, the ectopic pregnancy is less than 4 cm in size, and there is no fetal cardiac activity detected by ultrasonography.¹

However, methotrexate can cause myelosuppression, which increases the risk for or may worsen an infection. Previous case reports have described neutropenia, sometimes severe and accompanied by life-threatening infections, in patients treated with either single-dose or multi-dose regimens of methotrexate.^{8,9}

A previous report demonstrates a reduced immune response, more rapid disease progression, and a high mortality rate in immunosuppressed patients who have undergone kidney transplant (Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. *NEJM* 2020 Apr 24 [Epub ahead of print]). Another adverse effect of methotrexate that could affect patients with COVID-19 infection is a hypersensitivity-type pneumonitis, most commonly occurring in those with pre-existing interstitial lung disease.¹

Coronavirus disease 2019 infection is primarily transmitted by respiratory droplets, contaminated surfaces, and, theoretically, by aerosolized viral particles in surgical smoke plumes.^{4,10,11} Coronavirus disease 2019 has been detected in numerous organ systems, including respiratory organs, blood, and the gastrointestinal tract, increasing concern that abdominal surgery could disseminate the virus. Previous studies have demonstrated aerosolization of human papillomavirus, hepatitis B virus, and human immunodeficiency virus (HIV) within the surgical plume, but not COVID-19. Although viruses have been detected in surgical smoke, there have been only rare cases of transmission from this smoke, primarily with human papillomavirus.¹⁰

Aerosolization of viral particles by electrosurgical, harmonic, or laser surgery techniques may occur when employed during either laparotomy or laparoscopy. Compared with an open procedure, laparoscopy is more contained, which should decrease risk of viral transmission from surgical smoke to the operating room staff. However, because of the pneumoperitoneum, viral particles in the surgical plume could potentially escape into the operating theater from leakage around an imperfect trocar seal and during rapid venting through the trocars at the time of changing instruments, removing specimens, or desufflation at the conclusion of the operation.^{11,12}

What is a Reasonable Course of Action?

During the COVID-19 pandemic, it is first important to evaluate whether the planned surgery is urgent or emergent and whether there are safe, alternative, non-surgical therapies. In this patient who tested positive for COVID-19 infection who has an ectopic gestation, one must carefully balance the benefits and risks of medical and surgical therapies. With a quantitative hCG level of 6,500 milli-international units/mL, there is an increased probability of failed medical therapy and potential need for multiple doses of methotrexate to effectively treat the ectopic gestation. An increased cumulative dose of methotrexate would increase risk of adverse events, including myelosuppression. In this patient, the



potential for immunosuppression with methotrexate and the initial hCG level make surgery the preferred option. One must carefully balance the benefits and risks of different surgical approaches and select the safest route based on clinical findings for the patient. Whereas laparotomy may potentially reduce the risk of operating-room exposure to COVID-19 infection, laparoscopy, as a minimally invasive approach, has the advantage of reduced hospital stay, reduced need for analgesia, and quicker recovery.^{11,12}

There are a number of techniques to reduce the theoretical risk of viral transmission at the time of laparoscopy. First, operate at a lower pressure (10–12 mm Hg) pneumoperitoneum if possible, avoid leakage or blood spray from trocar sites, and avoid rapid venting from the trocars. The smoke plume should be evacuated to avoid rapid venting using a smoke-evacuation system with an ultra-low particulate air filtration system or laparoscopic suction with filter system before changing instruments, removing specimens, and removing trocars at the conclusion of surgery. One should also minimize smoke production by using lower power and shorter duration of energy from electrosurgical or harmonic instruments. The surgeon and operating-room personnel should also wear appropriate personal protective equipment.^{11,12}

THE BOTTOM LINE

In a patient who has tested positive for COVID-19 infection, one must carefully consider the benefits and potential adverse effects of medical or surgical therapy before treatment for an ectopic pregnancy. Methotrexate may potentially cause immunosuppression and exacerbate COVID-19 infection. Laparoscopy, with appropriate surgical techniques and personal protective equipment to reduce the theoretical risk of viral transmission from the surgical smoke plume, remains a reasonable minimally invasive approach for treating an ectopic pregnancy in a patient who has tested positive for COVID-19 infection.

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