**GENERAL GYNECOLOGY**

**Outcome following high-dose methotrexate in pregnancies misdiagnosed as ectopic**

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**OBJECTIVE:** The objective of this study was to report the outcomes of intrauterine pregnancies misdiagnosed as ectopic and exposed to methotrexate, a major teratogen.

**STUDY DESIGN:** We report the outcomes of all subjects who sought consultation after exposure to high-dose methotrexate to induce abortion in presumed ectopic pregnancies, which were later identified as viable intrauterine pregnancies by 3 North American Teratology Information Services between 2002 and 2010.

**RESULTS:** Eight women with normal, desired pregnancies were administered high-dose methotrexate in the first trimester because of presumed, misdiagnosed ectopic pregnancies. All pregnancies resulted in catastrophic outcomes. Two pregnancies resulted in severely malformed newborns with methotrexate embryopathy; 3 women miscarried shortly after exposure, and in 3 the erroneous diagnosis led the physicians to advise and perform surgical termination.

**CONCLUSION:** Erroneous diagnosis of intrauterine pregnancies as ectopic with subsequent first-trimester exposure to methotrexate may result in the birth of severely malformed babies or fetal demise.

Key words: ectopic pregnancy, embryopathy, methotrexate, misdiagnosis, teratogen

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Ectopic pregnancies, accounting for about 2% of all pregnancies (over 125,000 pregnancies/year in the United States alone), are the leading cause of first-trimester maternal death. Medical termination of ectopic pregnancies with methotrexate has more than tripled in the United States during the last decade (from 11% in 2002 to 35% in 2007), as it minimizes the risks, complications, and costs associated with surgical terminations. The latter has declined from 73.9% in 2002 to 64.9% in 2007 (with 21.5% laparotomies and 43.5% laparoscopies). Methotrexate, a folic acid antagonist, is a major human teratogen which induces a well-defined malformation pattern, first described nearly 50 years ago. Affected newborns typically demonstrate intrauterine growth retardation, cardiac malformations, craniofacial, and skeletal abnormalities. In early ectopic pregnancies (5-10 weeks’ gestation), methotrexate is administered intramuscularly (50 mg/m²/dose to 1 mg/kg/dose in a single or repeated doses) to induce fetal death. This regimen typically delivers a high dose (60-90 mg) of methotrexate to the patient, constituting the only medical scenario, where a potent teratogen is intentionally administered to pregnant women to cause fetal death.

Diagnosing an early ectopic pregnancy remains difficult despite advances in imaging. The process may be long, distressing, and expensive, and about half of suspected cases require 4 visits or more to confirm or exclude this diagnosis. In about 40% of cases, the initial diagnosis of ectopic pregnancy is erroneous and a nonviable intrauterine pregnancy is later found. Because a proportion of presumed ectopic pregnancies, based on early ultrasound, may be subsequently identified as viable intrauterine pregnancies on follow-up exam, healthy and desired intrauterine pregnancies may be exposed to methotrexate during critical stages of em-
bryogenesis. The objective of the present report was to study this tenuous situation by reporting the experience of 3 North American Teratology Information Services.

**Methods**

We collected cases among callers (both physicians and patients), who sought consultation by one of 3 Teratology Information Service Centers: The Motherisk Program, The Hospital for Sick Children, Toronto; The California Teratogen Information Service, University of California, San Diego; and the Connecticut Pregnancy Exposure Information Service, West Hartford, between January 1, 2002 and April 30, 2010. All of the callers who were seeking advice in regards to first-trimester exposure to high-dose methotrexate to induce abortion, in intrauterine pregnancies misdiagnosed as ectopic, were captured. Information regarding patient age, indication, dose, route, timing, and effectiveness of methotrexate administration was recorded by each center. For cases in which the initial contact occurred before the outcome was known (n = 6) a subsequent follow-up call was made to the patient or physician, to obtain pregnancy outcome information.

**Results**

We identified 8 presumed ectopic pregnancies, for which high-dose methotrexate was administered, with subsequent confirmation of viable intrauterine pregnancies. Four of these were initially diagnosed by hospital emergency department physicians and the remainder by Obstetricians/Gynecologists.

None of the 8 pregnancies resulted in the birth of a healthy newborn (Table). Two pregnancies continued to delivery. The first resulted in a term, severely malformed newborn, with features consistent with the methotrexate embryopathy, including cyanotic cardiac disease (tetralogy of Fallot), pulmonary atresia, a single kidney and skeletal malformations, requiring multiple surgeries. The infant suffered a cardiac arrest requiring a prolonged resuscitation shortly after delivery, with subsequent severe brain injury. The second pregnancy resulted in a stillbirth at 30 weeks of gestation; the fetus had tetralogy of Fallot and a malformed kidney on autopsy. None of the 6 other pregnancies were continued to term. Three women miscarried between 7 to 14 days after methotrexate administration. In the 3 remaining cases, the women were advised by their physicians to terminate their pregnancies, and they all subsequently underwent surgical abortion. In 2 of these cases, the physicians reported that their advice was based on concerns of potential medicolegal repercussions ensuing from adverse fetal outcome. All 8 women reported significant emotional suffering as a result of the misdiagnosis and dire outcomes.

**Discussion**

The misdiagnosis of desired, intrauterine pregnancies as ectopic with subsequent exposure to high-dose methotrexate during embryogenesis may result in the birth of severely malformed babies, miscarriage, or induced abortion.

In recent years, the diagnosis of an ectopic pregnancy has often been made in the emergency department setting, by personnel who may be less experienced in prenatal ultrasound imaging, as part of lower abdominal pain or vaginal bleeding work-up in young women, as in half of our cases. The 2009 American College of Emergency Physicians (ACEP) guidelines define the assessment and identification of intrauterine pregnancies by emergency physicians as a “core application.”

A recent meta-analysis of 2057 pregnancies (of which

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**Table:** Pregnancy management and outcome in 8 intrauterine pregnancies misdiagnosed as ectopic

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient age, y</th>
<th>Gestational age at time of diagnosis and methotrexate administration, wks</th>
<th>Method of diagnosis of presumed ectopic pregnancy</th>
<th>Methotrexate dose</th>
<th>Outcome</th>
<th>Gestational age at outcome, wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>5</td>
<td>Ultrasound</td>
<td>50 mg IM</td>
<td>Liveborn; Tetralogy of Fallot, pulmonary atresia, congenital scoliosis, 7 ribs on left side and 11 ribs on right side, single kidney</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>6</td>
<td>Ultrasound</td>
<td>50 mg IM ×2 doses</td>
<td>Stillbirth; Tetralogy of Fallot, horseshoe kidney, single umbilical artery</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>5</td>
<td>Ultrasound</td>
<td>83 mg IM</td>
<td>Miscarriage</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>4</td>
<td>Ultrasound</td>
<td>80 mg IM</td>
<td>Miscarriage</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>6</td>
<td>Ultrasound plus laparoscopy</td>
<td>50 mg IM</td>
<td>Miscarriage</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>4</td>
<td>Ultrasound</td>
<td>50 mg IV</td>
<td>Surgical abortion</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>6</td>
<td>Ultrasound</td>
<td>85 mg IM</td>
<td>Surgical abortion</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>8</td>
<td>Ultrasound</td>
<td>92 mg IM ×2 doses</td>
<td>Surgical abortion</td>
<td>9</td>
</tr>
</tbody>
</table>
152 were ectopic) by emergency physicians reported 99.3% sensitivity and a negative predictive value of 99.96%. However, many practicing emergency physicians in the community did not receive formal ultrasound training, and are left to catch up. The diagnostic challenges and serious risks of ectopic pregnancies, and the relative ease of methotrexate administration compared with surgical abortion may lead to exposure of intrauterine pregnancies to methotrexate, before additional confirmatory imaging, to delineate the precise location of the embryo is conducted. In addition, with the increasing prevalence of assisted reproductive technologies the possibility of a heterotopic pregnancy should be considered and ruled out prior to administration of methotrexate. An additional ultrasound exam to verify the diagnosis or, alternatively, hospital admission of stable patients for observation and follow-up of serum β-hCG levels may prevent a proportion of these misdiagnosed intrauterine pregnancies.

In the current litigious climate, where medico-legal issues frequently impact physician’s decision-making, there is little incentive for clinicians to report these cases to regulatory agencies or in the medical literature, as suggested by the paucity of methotrexate embryopathy cases that have been published in this context worldwide. A comprehensive literature review yielded only 3 isolated case reports, all published within the last 7 years.

There are no formal published data on the proportion of intrauterine pregnancies misdiagnosed and managed erroneously as ectopic pregnancies. However, the following figures suggest that this may be a serious public health issue: an overall ectopic pregnancy rate of 2% (which translates to over 125,000 cases/y in the US); a 40% initial misdiagnosis rate; only up to 20% of pregnancies with unknown location that are ultimately diagnosed as ectopic; 15% failure rate of methotrexate to induce abortion; over 80% of women in an inner city population in the US treated with methotrexate for ectopic pregnancies are lost to follow-up; and nearly 50 years of methotrexate use in obstetrics. Put together, it is conceivable that this phenomenon may not be rare, and is likely under-reported in current literature, and hence unappreciated by regulatory agencies and professional societies. Moreover, when used continuously in lower doses, for cancer chemotherapy or rheumatologic conditions, methotrexate exposure in the first trimester was associated with a 29% anomaly rate among exposed offspring. Considering both the anomaly rate in first trimester methotrexate exposure, as well as the fact that some ectopic pregnancies resolve spontaneously and do not require methotrexate, clinicians must ensure that the correct therapeutic time window of methotrexate administration is thoughtfully considered and met, based on pregnancy viability and clinical picture.

Our cases also delineate that the significant teratogenic risk following methotrexate exposure can lead to pressure on exposed pregnant women to abort their child. This pressure by health care providers likely stems from fears of iatrogenically-induced congenital malformations, and is an attempt to circumvent the potential medico-legal consequences that leads to tremendous costs and suffering.

Effective, nonpunitive reporting mechanisms should be sought, to determine the true magnitude of this phenomenon and to facilitate improvement in point-of-care diagnostic accuracy of early ectopic pregnancies.

REFERENCES